Atherosclerosis Risk in Communities Study: Community Surveillance and Cohort Morbidity/Mortality Follow-Up

Manual 1

General Description and Study Management

Version 5.0

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FOREWARD

This manual, entitled ***General Description and Study Management***, Version 4, is one of a series of protocols and manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study: Community Surveillance and Cohort Morbidity/Mortality Follow-Up. Manual 1 provides the background, organization, and general objectives of the ARIC Study. Manuals 2 and 3 describe the operation of the Cohort Follow-up and Surveillance Components of the study, respectively. Detailed Manuals of Operation for data collection during the 4 ARIC cohort examinations, including those of reading centers and central laboratories, are available on the ARIC WebSite at (http://www.bios.unc.edu/cscc/ARIC).

ARIC Study Protocols and Manuals of Operations

MANUAL	TITLE
1	General Description and Study Management
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Manual 1. General Description and Study Management

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1.0 INTRODUCTION AND BACKGROUND

CVD mortality continues to decline but remains the leading cause of death in the US. There are few long-term US studies monitoring CVD incidence and case fatality, and none other than ARIC are conducted as multicenter CVD surveillance studies in diverse communities. Information on the pattern of CVD trends is essential to guide public policy related to CVD. ARIC and other studies suggest, for example, that the incidence of MI has not decreased from the mid-1980's to mid-1990's, and thus, primary prevention may not have progressed.

Much is known about lifestyle risk factors and the pathogenesis of CVD. However, there are still significant gaps in knowledge related to African-Americans and women; about the relations of subclinical disease and its progression to clinical disease; about the role of genes and their interaction with environment in CVD causation, and about the role of chronic inflammatory precursors of atherosclerosis and its sequelae. The relation of these factors to incident CHD and stroke will be assessed through the additional follow-up data. ARIC's continued community surveillance and cohort morbidity/mortality follow-up will add ethnic and gender-specificity to our community surveillance trends and contribute precision; it will greatly increase numbers of cohort events permitting more extensive subgroup analyses and examination of interactions; it will allow us to extend or verify unusual or promising findings; and it will allow us to take advantage of new developments in the fields of biochemistry and genetics to contribute to investigation of new risk markers for CVD and gene-environment interactions.

2.0 STUDY DESIGN

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective study conducted in four US communities to 1) investigate the etiology and natural history of atherosclerosis, 2) investigate the etiology of clinical atherosclerotic diseases, and 3) measure variation in cardiovascular risk factors, medical care and disease by race, sex, place, and time. It includes a Cohort Component and a Community Surveillance Component.

Community surveillance planning began as a consequence of recommendations of the 1978 National Heart, Lung, and Blood Institute (NHLBI) Workshop on the Decline in Coronary Heart Disease (CHD) Mortality. A protocol for community surveillance was developed and pilot tested in the NHLBI Community Cardiovascular Surveillance Program (1980-1984).

The cohort component was subsequently created and added to the surveillance component to create the current ARIC Study for two reasons. First, cohorts can enhance the value of incidence rates derived from community surveillance by validating them using events ascertained by the standard methods of prospective studies and by providing information with which to interpret them, e.g. information on risk factors and out-of-hospital medical care. Secondly, community surveillance can enhance the generalizability of cohort findings by comparing incidence rates and the characteristics of clinical events in residents who do and who do not participate in cohort follow-up and by relating the study community CHD experience with that of other vital statistics reporting areas of the US.

Atherosclerosis was assessed in the ARIC Study by observing lesions through ultrasound imaging. This permits assessment of 1) the association of risk factors with the underlying arterial disease, 2) the association of the same factors with clinically recognized diseases and 3) the value of ultrasound diagnosis in predicting these diseases. The major atherogenic processes, lipid metabolism and thrombosis, are investigated by using laboratory procedures

only recently made available. Storage of blood for future prospective case-control analysis increases the chance of discovering unsuspected precursors of cardiovascular disease.

In the Cohort Component, four random samples, totaling 15,792 persons, ages 45-64 years, were selected for the baseline visit, one from each community. The four communities are Forsyth County, North Carolina; Jackson, Mississippi; Suburban Minneapolis, Minnesota; and Washington County, Maryland. The communities are clearly defined geographical entities, have well delineated medical care referral patterns, and provide an opportunity to study blacks and whites, males and females in urban and rural settings. The Jackson cohort is a sample of blacks, while the other field centers sampled from their entire defined communities. These same four geographical entities define the areas of community surveillance of coronary heart disease for all persons age 35-74 in the communities.

2.1 Cohort

Cohort members completed four clinic examinations, conducted three years apart, in 1987-1989, 1990-1992, 1993-1995, and 1996-1998. Each examination lasted about three hours. Table 1 lists the components of each visit. In addition to B-mode ultrasound, noninvasive measures of subclinical disease in the cohort component included the ankle-brachial index, retinal photography for the assessment of microvascular disease (Visit 3), cerebral magnetic resonance imaging (visit 3, Jackson and Forsyth only) and echocardiography (visit 3, Jackson only). The flexibility of the prospective design allowed changing components of clinic visits. The cohort was followed-up by annual phone interviews, and search of death certificates and hospitalizations, done in conjunction with community surveillance. Events (e.g., deaths, hospitalized MIs) have been ascertained through cohort and community surveillance activities. The combination of cohort and community surveillance resulted in an informative and cost-efficient process for the ascertainment and validation of coronary and cerebrovascular events.

2.2 Community Surveillance

In Community Surveillance, these four communities are investigated to determine the occurrence of hospitalized myocardial infarction and coronary heart disease death in men and women age 35-74 years. Samples of hospital records are reviewed for age-eligible residents of each community with a discharge diagnosis of myocardial infarction or one of several related screening diagnoses. Samples of age- and residence-eligible death certificates with various manifestations of coronary heart disease coded as the cause of death are also reviewed. For deaths not occurring in a hospital, the decedent's physician and next-of-kin are queried about the circumstances around the time of death.

The aim of the community surveillance component is the assessment of geographic and time variation in incidence rates of fatal CHD and of hospitalized (fatal or nonfatal) myocardial infarction, proportions receiving various treatments, and case fatality in the four communities. Monitoring of events in 35-74 year old persons in the ARIC communities started in January 1, 1987, and consistent methods have been used for surveillance and endpoint classification. The surveillance process has three components: 1) identification of possible events; 2) investigation by abstraction, interviews, or other means; and 3) endpoint classification. Event classification is performed by computer algorithm at the Coordinating Center or by the Morbidity and Mortality Classification Committee (MMCC), comprised of physicians from each field center. The surveillance protocol also identifies possible cohort events. In addition to fatal CHD and hospitalized MI, cohort events of interest include stroke and congestive heart failure.

Table 1. The ARIC STUDY: Interviews and Procedures by Examination

PROCEDURES	VISIT 1	VISIT 2	VISIT 3	VISIT 4
ANTHROPOMETRY				
HEIGHT				
Sitting Height	X			
Standing Height	X		X	X
FRAME SIZE				
Elbow		X		
Wrist	X			
GIRTHS				
Calf	X			
Hip	X	X	X	X
Waist	X	X	X	X
SKINFOLDS				
Subscapular	X	X		
Triceps	X	X		
WEIGHT	X	X	X	X
MALE BALDNESS				X
BLOOD PRESSURE				
SITTING	X	X	X	X
SUPINE	X		S	S
STANDING	X		S	S
ANKLE	X		X	X
ECHOCARDIOGRAPHY				
Jackson			X	
ELECTROCARDIOGRAMS				
2 MINUTE RHYTHM STRIP	X			
12 LEAD	X	X	X	X
HEART RATE VARIABILITY	X			A
GLYCEMIC LOAD				X
MEDICAL DATA REVIEW	X	X	X	X
MRI, CEREBRAL				
Forsyth County			X	
Jackson			X	
PERIODONTAL EXAMINATION				A
PHYSICAL EXAMINATION				
Walking/Standing	X			
Neck	X			
Cardio/pulmonary	X			
Breast	X			
Lower extremities	X			
Urine collection				X

PROCEDURES	VISIT 1	VISIT 2	VISIT 3	VISIT 4
PULMONARY FUNCTION				
FEV_1	X	X		
FVC	X	X		
Max. Inspir. Pressure		X		
RETINAL PHOTOGRAPHY			X	
ULTRASOUND, B-MODE				
CAROTID ARTERIES	X	X	S	S
DISTENSIBILITY	X	X		
POPLITEAL ARTERY	X			
VENIPUNCTURE				
CHEMISTRIES				
Glucose	X	X		X
Creatinine	X	X		X
Insulin	X	X		X
Total Protein	X			
Albumin	X			
Uric Acid	X	X		X
Urea Nitrogen	X			
Calcium	X			
Phosphorous	X			
Magnesium	X	X		
Sodium	X	X		
Potassium	X	X		
Glucose Tolerance				X
HEMATOLOGY				
Hematocrit	X	X		
Hemoglobin	X	X		
White Blood Cell Count	X	X		
Platelet Count	X	X		
Neutrophil Count	X	X		
Neutrophil Bands	X	X		
Lymphocytes	X	X		
Monocytes	X	X		
Eorinophils	X	X		
Basophiles	X	X		
Mean Corpuscular Volume		X		
HEMOSTASIS				
Factor VIII	X		S	
Factor VII	X			
Activated PTT (aPTT)	X			
Fibrinogen	X		S	
Von Willebrand Factor	X			
Protein C	X			
Antithrombin III (AT-III)	X			

PROCEDURES	VISIT 1	VISIT 2	VISIT 3	VISIT 4
LIPIDS				
HDL Subfractions	X			
Apo AI	X	X		
Apo B	X	X		
Total Cholesterol	X	X	X	X
Total Triglyceride	X	X	X	X
HDL Cholesterol	X	X	X	X
LDL Cholesterol	X	X	X	X
Lipoprotein [a]	X			
INTERVIEWS				
Blood Transfusion				X
CHD Events/Procedures	X	X	X	X
Cognitive Function		X	MRI	X
Dietary Intake	X	S	X	S
Family History of CHD		X		
Fasting Status	X	X	X	X
Health History	X	X	X	X
Home Interview	X			
Identification	X	Updated	Updated	Updated
Inflammation				X
Informed Consent	X	X	X	X
Medication Survey	X	X	X	X
Personal History	X	X	X	X
Physical Activity	X		X	
Reproductive History	X	X	X	X
Respiratory Symptoms	X	X		
Social Support	X	X	X	X
Socioeconomic Status	X	X	X	X
TIA/Stroke	X	X	X	X
Trait Anger		X		
Vital Exhaustion			X	
Vitamin Survey			X	

S=Sample of the cohort; A=Ancillary study mechanism

2.3 Central Agencies

In addition to the four Field Centers, the ARIC study includes a coordinating center and several other central agencies. The protocols for the procedures performed by each of these agencies are contained in separate manuals from the ARIC cohort examinations: echocardiography (Manual 15), retinal photography (Manual 14), magnetic resonance imaging (Manual 13), clinical chemistry (Manual 10), hemostasis (Manual 9), lipids (Manual 8), electrocardiography (Manual 5), pulmonary function (Manual 4), ultrasound (Manual 6), and quality control (Manual 12). The roles of the agencies which continue in the study are summarized in this section.

2.3.1 Central Hemostasis Laboratory

Atherosclerosis, long recognized as a disease of lipid deposition into arterial walls, is increasingly believed to involve the hemostasis system. Hemostasis may be critical both for the onset of clinical disease (thrombotic occlusion leading to cerebral or myocardial infarction) and

for initiation and progression of the underlying atherosclerotic lesions. Since the hemostasis system is highly reactive, prospective studies, rather than studies of clinical cases, are necessary to test hypothesis related to hemostasis. The Central Hemostasis Laboratory, at the University of Texas, evaluates each component of the hemostasis system in ARIC cohort participants: coagulation proteins and platelets (which promote arterial clot formation) and coagulation inhibitors and the fibrinolytic system (which prevent or lyse clots). The Lab remains an active ARIC Central Agency, in analysis of frozen samples in a case-cohort design and in publication activities.

2.3.2 Central Lipid Laboratory

Central Lipid Laboratory at Baylor University measurements of lipids, cholesterol, cholesterol in lipoprotein fractions, and glucose permitted ARIC to maintain a characterization of study participants during the course of the study. Now, newer lipid measurements are made on selected cases and controls, using stored plasma. The Lab remains an active ARIC Central Agency, in analysis of frozen samples in a case-cohort design and in publication activities.

2.3.3 The DNA Laboratory

The DNA Laboratory at the Human Genetics Center, University of Texas-Houston evaluates the ability of novel, functional genetic variation to predict the occurrence and progression of atherosclerosis and onset of clinical CVD. It uses genomic laboratory and statistical methods to identify and localize novel gene regions contributing to the occurrence and progression of atherosclerosis. The Lab remains an active ARIC Central Agency, in analysis of frozen samples in a case-cohort design and in publication activities.

2.3.4 Central Clinical Chemistry Laboratory

The clinical chemistry measurements were performed at the first and second exams by the Central Clinical Chemistry Laboratory at the University of Minnesota. The determinations were made on frozen sera for all cohort participants. The analytical methods and quality control programs (both internal and external) followed those of the University of Minnesota Hospital Laboratories. In addition, blind replicate samples were submitted by the Field Centers as an additional means of monitoring laboratory performance. Frozen serum remains available at the Clinical Chemistry Lab for future analysis, but the Lab is no longer an active ARIC Central Agency.

2.3.5 ECG Reading Center

Hospital electrocardiograms (ECGs) continue to be collected in the ARIC cohort and community surveillance. The ECG Reading Center is at the University of Minnesota Division of Epidemiology.

2.3.6 Coordinating Center

The Coordinating Center provides centralized administration, planning, and management for all components of the ARIC Study. Its administrative functions include supporting the Project Office and the chairman of the Steering Committee and Executive Committee in convening meetings, documenting decision and action items, preparing and distributing meeting minutes and coordinating the work of the various subcommittees. Technical support for the installation, use and maintenance of local equipment and software is provided by in-house staff. The Coordinating Center serves as the official repository for all ARIC Steering Committee records, manuals of operations, data collection instruments, research data and publications.

The Coordinating Center supports the Morbidity and Mortality Classification Committee in monitoring the status of each study endpoint, preparing documentation of events to be verified and creating a final diagnosis file.

The Coordinating Center also supports the design, management, and analysis of case control studies, and the publication of results of the collaborative study.

The Coordinating Center's responsibility for the centralized management of the study includes the provision and tracking of training and certification; monitoring protocol adherence in the Field Centers and Central Agencies; the design, implementation and monitoring of quality assurance programs in the field centers, laboratories and reading centers; and data management, including the development of a computerized data collection system, on-site and centralized data processing and data analysis. The specific procedures for the distributed data management systems and data analysis are described in the following section of this manual.

The CC implements closure of the data. The closed data files are prepared in SAS transport format for distribution to Field Centers, Central labs and NHLBI. Documentation of the distributed data files are sent with the data.

The CC prepares study data in SAS transport format for use by the public (without revealing confidential information). Public use data are available five years after the closing date of an examination abstraction cycle.

3.0 STUDY MANAGEMENT

3.1 Introduction

The ARIC Study is funded by the National Heart, Lung, and Blood Institute, and directed by the Epidemiology and Biometry Program of the Division of Epidemiology and Clinical Applications. The operations of the study are directed by the ARIC Study Steering Committee whose members are the Principal Investigators of the Field Centers, Coordinating Center, the Lipid, DNA, and Hemostasis Laboratories, and the NHLBI Project Officer.

The Steering Committee is supported by committees responsible for the details of study design and implementation, and a Morbidity and Mortality Classification Committee (MMCC). These committees report and make recommendations to the Steering Committee. The committees and their charges are listed in the section below.

3.2 ARIC Study Committees and Charges

3.2.1 Executive Committee

The Executive Committee is comprised of the Field Centers and Coordinating Center PIs and the NHLBI project officer. The committee meets regularly to manage the study, review ancillary study requests, and etc.

3.2.2 Surveillance Committee

The Surveillance Committee is comprised of a Field Center PI, a representative of NHLBI Project Office, and two members from the Coordinating Center. The Committee meets monthly to discuss progress toward meeting annual closure deadlines, quality control, changes in medical care and diagnostics, and trends in disease rates.

3.2.3 Publications Committee

The Publications Committee is described in Section 3.5.

3.2.4 Cohort Follow-up Committee

The Cohort Follow-up is comprised of a Field Center PI, a Coordinating Center representative, and follow-up coordinators from each field center. The Committee meets quarterly to discuss follow-up operations, quality control, and certification.

3.2.5 Laboratory Committee

The Laboratory Committee is comprised of Laboratory PIs and pertinent staff, Coordinating Center PI and staff, NHLBI project officer and interested Field Center PIs. The Committee proposes and monitors laboratory analyses using ARIC's stored specimens and the appropriate study design. It also reviews ancillary proposals to use stored specimens.

3.2.6 Quality Control Committee

The Quality Control (QC) Committee is comprised of a Field Center PI, a CC representative, a representative of the Annual Follow-up Interviewers, a representative of the Surveillance Abstractors and a representative of the NHLBI Project Office. The Committee meets quarterly to discuss protocol adherence and quality control issues for the lab, AFU, and surveillance operations.

3.2.7 Morbidity and Mortality Classification Committee

The Morbidity and Mortality Classification Committee (MMCC), comprised of physicians from the Coordinating Center and each Field Center, is responsible for the process of assigning all medical events of interest in the ARIC Study into diagnostic classes defined by the study.

The MMCC operates by assessing medical information received from each Field Center. In most cases this involves independent assessment by two committee members with differences adjudicated by the full committee. Problems in classification may result from lack of clarity in the study diagnostic criteria. Under these circumstances the committee recommends appropriate modifications to the criteria.

3.3 Communications

3.3.1 Periodic Reports

The Field Centers and Central Agencies prepare routine periodic reports to the ARIC Study Project Office which document the progress to date in each major activity, administrative matters, staffing changes, and current or anticipated problems. The Coordinating Center also provides reports on the data collection at the Field and Laboratory Centers, quality control findings on examinations, reabstracted records, recertification, laboratory determinations, and protocol adherence. Status reports on recruitment and centers. Quality control reports are likewise sent to the Central Laboratories and Reading Centers.

3.4 Publication Policy

Overall responsibility for manuscript and abstract generation and approval for the ARIC Study lies with the Steering Committee and Publications Committee. The Steering Committee and Publications Committee have developed procedures for generating manuscripts and abstracts as well as the formal requirements for manuscript approval prior to submission for publication or prior to abstract submission for presentation.

The overall aim of this process is to encourage the preparation of manuscripts and abstracts while also providing appropriate control over their quality and content. The process also serves to avoid inappropriate duplication.

Central to all of these activities is the Publications Committee referred to above. The latter is composed of four members, all of whom are active in the ARIC Project. One member serves as chairman and another as the Committee's editor. The Committee holds conference calls an average of once every four weeks. If an abstract needs urgent approval between calls, this is usually accomplished through fax or electronic messages. Other urgent business is similarly transacted.

Periodically, the Committee checks on the progress of previously approved manuscripts. For this purpose, it has developed a series of tracking tables, generated by the Coordinating Center, using the Committee's database stored there. The Publications Committee also maintains through the Coordinating Center a list of abstracts/presentations. These materials are updated and distributed to the Steering Committee and are available on the ARIC Web site. To guide it in dealing with out-of-the-ordinary circumstances related to manuscripts or abstracts, the Committee has developed a series of special policies. These are available through the Coordinating Center.

The Publications Committee oversees all aspects of study publications and presentations, from the formation of writing groups and approval of proposals for publications through final ARIC approval of final manuscripts and ready for submission to journals. The approval of manuscripts is delegated to the committee editor who assigns reviewers and communicates all decisions to the authors.

3.4.1 Types of Publications and Presentations

The types of publications and presentations for which approval procedures are established include:

a. Major descriptions of the design and conduct of the ARIC Study.
b. Major descriptions of results, based on data from all Field Centers, addressing the main objectives of the ARIC Study.
c. Descriptions of results, based on data from all Field Centers, addressing issues other than the main objectives of the ARIC Study. These include ancillary studies unless specifically exempted by the Steering Committee.
d. Descriptions of results based on data collected from a single Field Center.
e. Descriptions of methodological developments required to meet the needs of the ARIC Study.
f. Articles to appear in proceedings of meetings for which no abstract was required.
g. Manuscripts/abstracts generated collaboratively between ARIC and other studies.
h. Invited presentations for which no abstract is submitted and for which there are to be no published proceedings.

i. Press releases or discussions with the media.
j. Lectures or other informal presentations.

The Publications Committee is responsible for resolving any uncertainties as to which category a specific presentation or publication belongs.

3.4.2. Outline of the Preparation and Approval Process

a. Publications and presentations usually arise from individual investigators.
b. The Steering Committee occasionally designates a topic and selects a writing group and its lead author.
c. Lead authors prepare a list of co-authors and obtains their willingness to participate. ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (can be the same as the first author but must be an ARIC investigator).

Name:_____

d. The manuscript proposal including the lead author and list of writing group members is submitted to the Publications Committee for approval. The study has a standardized form that is used to submit all manuscript proposals (an electronic copy is available on the ARIC Web site). Manuscript proposals, however, when approved by the Publications Committee are passed on to the Steering Committee for final approval. Abstracts require Publications Committee and NHLBI approval before submission to a scientific meeting. Abstracts should be submitted to NHLBI via email to: EBPDOCS@NHLBI.NIH.gov.
e. The writing group prepares and communicates computational specifications to the Coordinating Center, or it prepares statistical computations using the data set distributed by the Coordinating Center.
f. The Coordinating Center, when requested, prepares statistical computations according to priorities specified by the Publications Committee.
g. The working group prepares, reviews internally, and submits the completed document to the Steering Committee for review and approval.
h. ARIC primary and statistical reviewers are assigned, respectively, by the ARIC editor and by the Coordinating Center to review this manuscript and to convey to the editor the results of the review.
i. Members of the Steering Committee review the manuscript and send comments to the editor.
j. NHLBI review occurs concurrently with Steering Committee review. The ARIC editor's office submits final manuscripts for review to NHLBI.
k. The manuscript is sent to the Coordinating Center for final data verification, if the analysis was done at the Coordinating Center.
l. The manuscript/abstract is formally submitted to a journal or scientific meeting selection process. However, upon receiving Steering Committee approval to submit a manuscript to a journal, the lead author must first complete a final checklist of items to ensure all appropriate procedures have been followed.

The overall responsibility for managing the entire process lies ultimately with the Steering Committee; however, for some steps a subgroup may be given responsibility. Further, the nature of the approval process varies according to the type of document. These issues are outlined below.

3.4.3 Authorship

The authorship policy varies according to the type of publication or presentation being

considered. For some publications, the author is listed as the "The ARIC Study Investigators," with the preparers clearly indicated. In other cases, the persons preparing the manuscript are listed as authors followed by the words, "for the ARIC Study Group." Similarly, for some presentations, the paper is listed as presented by someone for the ARIC Study. In other cases the individual is listed as the lead author. In all cases, however, the person who assumed the lead responsibility for a particular publication or presentation is to be listed as the first author or preparer. In addition, the phrase "ARIC Study" is to be included in the title and listed whenever possible.

The Steering Committee is responsible for resolving any conflicts or confusion that occur with respect to appropriate recognition of authorship.

3.4.4 Manuscript and Abstract Generation

Under normal circumstances, the lead author of the writing group will be listed as the first author for those manuscripts where individual recognition is appropriate or as the first preparer for those where the ARIC Study is listed as the author. The lead author also has the responsibility for listing the co-authors in the appropriate order. As indicated above, the Steering Committee serves as final arbitrator of any conflicts.

Individuals interested in preparing a manuscript or abstract on a specific topic must submit their proposals, which must include the names of the writing group members, to the Publications Committee for approval. The proposal must include a clear statement of the nature of the publication, the hypotheses to be addressed, and the types of statistical computations or data summarizations likely to be required.

The Steering Committee has the responsibility for reviewing and approving these proposals, both for appropriateness and for a priority designation. The Steering Committee also ensures that the different participating centers and groups are appropriately represented and that appropriate recognition is provided.

Once the specifications for the manuscript have been approved, the requirements for statistical computing can be formally communicated to the Coordinating Center. Requests will be processed according to the priorities specified by the Publications Committee. The Coordinating Center has representation on the writing group whenever possible and this person serves as the liaison to the writing group, both for communications about computing issues and for providing or obtaining appropriate statistical input.

The Publications Committee reviews the progress that each writing group is making toward the completion of its task and makes changes required for the timely completion of each manuscript or abstract.

3.4.5 Approval Procedures

A manuscript stemming from the ARIC study is submitted to the ARIC editor, who sends copies of the manuscript to a primary reviewer, a coordinating center's statistical reviewer and Steering Committee members for their critiques. A detailed critique is expected from the primary reviewer(s). Upon receiving the critiques, two courses of action are possible: (1) If the editor deems the reviewers' suggestions to be mainly editorial in nature, he may approve the manuscript and request that the authors incorporate suggested changes to the final version, or submit in writing reasons for not doing so. No further action is needed from the Steering Committee; or (2) If, in the editor's judgement, critiques entail substantive changes, the revised manuscript must be further reviewed by the primary reviewer, the Coordinating Center's reviewer and the Steering Committee before approval is granted.

The approval procedures are presented separately for each type of publication or presentation listed in section 3.4.2.

3.4.5.1 Publication types a., b., and f.

The procedures described here are to be followed prior to submitting for publication any document describing the design and conduct of the ARIC Study or including results, based on data from all field centers and addressing the main objectives of the study. All such documents are to be processed through each of the preparation and approval steps listed above. This includes the data verification step. Abstracts are a special case of this procedure and are discussed separately later.

All papers meeting the conditions of this section (publication types a., b., and f.) are to be published under the by-line "The ARIC Study Investigators." In addition, a statement that the article was "prepared by (writing group lead author, then other members, listed in order specified by the chairperson)" is also to be included.

The above specifications for authorship apply also to abstracts submitted for presentations, whether or not they are to be published. They also apply to articles to be published in the proceedings of meetings (type f). In this case the presenter can also be identified.

3.4.5.2 Presentation types a. and b.

The same conditions apply to abstracts for presentations of type a. or b. as apply for manuscripts for these publication types except that the Publications Committee has full authority to give approval or to reject, i.e., no Steering Committee action is required.

3.4.5.3 Publication or presentation type c.

The preparation and approval procedures for publications and presentations of results based on data from all field centers which do not address one of the main objectives of the ARIC Study are identical to those which do address one of these objectives. However, the listing of the authors can be different. For these publications, it is permissible for individual investigators to be listed as authors. The order of this listing follows guidelines consistent with those for other papers. Namely, the working group chairperson is listed as the lead author with the other authors listed in the order that the lead author designates. Following the name listed, the words "for the ARIC Study Group" are added.

3.4.5.4 Publication or presentation type d.

The ARIC Study discourages the publication or presentation of results based on data from a single field center, other than those from a single field-center based ancillary study, and from a collection of field centers that is less than the full data set. Should this appear desirable for some reason, the nature of what is to be prepared and presented or published will be submitted to the Publications Committee by way of manuscript proposal, clearly indicating therein, that the proposal incorporates plans for a manuscript using less than a full data set. The Publications Committee will accept or reject the proposal or pass it on to the Steering Committee for decision if this is felt to be the best course of action. However, even if approved by the Publications Committee, the proposal (as with all manuscript proposals) will still require Steering Committee ratification.

3.4.5.5 Publication or presentation type e.

Publications or presentations describing methodology developed to meet the needs of the ARIC Study are to be prepared and approved by the same procedures as those based on data collected by the study.

3.4.5.6 Presentation type g.

For those presentations for which the formal submission of an abstract is not required and for which no proceedings are to be published, the invited or otherwise designated presenter is to submit a letter containing information equivalent to that of a typical abstract to the Publications Committee for review and approval. The Publications Committee will treat the letter in the same way that it treats an abstract.

If an abstract is subsequently required, it should be submitted for review as other abstracts are. In a similar fashion, if it should be decided later to publish the proceedings, then the document detailing the presentation is to be submitted for review as are other publications.

3.4.5.7 Press releases and media discussions type i.

In general, scientific findings from ARIC made available to the media will involve those findings being presented at scientific meetings and being published in the scientific literature. Such presentations and publications require prior clearance as noted above. In some circumstances, media discussions and press releases may be appropriate to clarify scientific findings for the lay public, but they should not be used as forums to release new information. Investigators are requested to keep the Project Office informed of contacts with representatives of the major national media and of major national media coverage of information that they have supplied. If a situation arises in which it appears desirable to release to the media new information not otherwise cleared for presentation or publication, or if such has been cleared for scientific presentation or publication, but this has not yet transpired, prior clearance from both the Steering Committee and the Project Office is required.

Release of general descriptive information about the ARIC Study for local use (such as a local newspaper, university newsletter or state medical society journal) does not require prior approval. Use of centrally prepared materials for such purposes is encouraged. A copy of any resultant article should be sent to the Project Office.

3.4.5.8 Lectures and other informal presentations type j.

No formal approval is required for lectures and informal presentations so long as they do not constitute the initial release of ARIC results. Otherwise, the rules for presentation type g. apply.

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 Chair of the Steering Committee, currently Aaron Folsom [folsom@epi.umn.edu]; procedural questions can be sent to Sandy Irving [Sandy_Irving@unc.edu] at the coordinating center.

To apply for approval of an ancillary study, a written request on the ARIC Ancillary Study Proposal Form (http://www.cscc.unc.edu/aric/forms/) should be submitted to the Steering Committee (by email via the Chair of the Steering Committee, currently Aaron Folsom [folsom@epi.umn.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 may be asked to first approve ancillary studies using stored biological samples. 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 and by NHLBI 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 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:

1. security of these study materials,
2. completion of our ARIC "Data Distribution Agreement" or a "Materials Distribution Agreement" (http://www.cscc.unc.edu/aric/datadist/)
3. documentation of IRB approval, and
4. final disposition of study materials at the conclusion of the ancillary study.

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 http://www.nhlbi.nih.gov/resources/deca/default.htm. 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. Left-over 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 Federal Express 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. A file copy with all required signatures will be retained by the Coordinating Center and copies distributed to the Ancillary Study Principal Investigator.

ARIC Ancillary Study Update-Central Receiving
Department of Biostatistics, Collaborative Studies Coordinating Center
137 East Franklin Street, Suite 400
Bank of America Center, CB #8030
Chapel Hill, NC 27514
Phone: (919) 962-2073 Fax: (919) 962-3265
Email: ARICupdate@mail.cscc.unc.edu4.7 **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.

4.7.1 Sample availability

A list of samples originally collected by ARIC is shown below. 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.

<u>DNA Lab Stored Samples</u>

DNA and buffy coat stored on almost all ARIC participants.
Frozen transformed white cells on 2000 participants in the ARIC MRI study.

<u>Minnesota Stored Samples—Original Amounts by Type</u>

Visit 1	SERUM – Green 1.5 ml*
	SERUM – Red 1.1 ml
	DNA aliquot extracted by DNA lab
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*
*Thawed and refrozen.

Atherosclerosis Lab Stored Samples—Original Amounts by Type (Status 9/06)

Visit 1 EDTA PLASMA—4 aliquots 1.0 ml (1-2 vials remain for most)

Visit 2 EDTA PLASMA—4 aliquots 1.0 ml (2-3 vials remain for most)

Visit 3 EDTA PLASMA—4 aliquots 1.0-2.0 ml (3-4 remain for most)

Visit 4 FASTING EDTA PLASMA—4 aliquots 1.0-2.0 ml (4 remain for most)
2-HOUR OGTT EDTA PLASMA—5 aliquots 1.0 ml (3 remain for most)
BUFFY COAT—2 aliquots 1.0 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

4.7.2 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 identify 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.

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 theses 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 plates. The amount of DNA will be determined at the time of ARIC Laboratory Committee approval. In general, 50 ng will be provided for typing six to ten polymorphisms. It is suggested that investigators wanting to type one or two polymorphisms carry this work out collaboratively with an ARIC central laboratory. In this way, the work can be carried out quickly and efficiently without wasting DNA and time spent on the aliquotting, shipping and genotyping process. The resulting genotype 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.

4.7.3 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-aliquotted and returned to the ARIC laboratory providing the sample. Alternatively, ARIC may decide that realiquotting 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, aliquotting and shipping.

4.7.4 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.

4.8. 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 .

Appendix A
Atherosclerosis Risk in Communities (ARIC) Ancillary Study Proposal Form

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 (NA=not applicable)

Center	Enroll or examine participants (N)	Assay samples (N participants)	Provide samples (N participants)	Analyze data (yes/no)
Forsyth Co. Field Center (Forsyth Co, North Carolina)		NA	NA	NA
Jackson Field Center (Jackson, Mississippi)		NA	NA	NA
Minnesota Field Center (Minneapolis, Minnesota)		NA	NA	NA
Washington Co. Field Center (Washington Co, Maryland)		NA	NA	NA

DNACentral Lab	NA			NA
Lipid Central Lab	NA			NA
Hemostasis Central Lab	NA			NA
ECG Reading Center	NA			NA
Coordinating Center (UNC)	NA			

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, or examined? 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 (http://www.cscc.unc.edu/aric/ancilary.htm) in consideration of your description of the following:

      i. Study year(s) for which samples are to be used
      ii. Sample type (eg. Serum, EDTA, citrate, DNA)
      iii. Requirement for frozen vs. previously thawed samples
      iv. Sample volumes
      v. Efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles.

   C. ARIC Field Centers:
   Describe effort (and estimated time) required of ARIC staff at each participating center.

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

      i. 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?

      ii. 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)?

      iii. 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?

      iv. How many papers do you estimate will be written from the Ancillary Study?

6. Variables/measurements from the ARIC main study database to be analyzed:

7. 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 8) ___ Yes (see question 7B)

   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.

8. Proposed starting and ending dates:

9. Estimated cost by year; number of years:

10. Source of funding; date of submission:

11. 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?

12. What is the advantage, both to ARIC and yourself, of conducting the study within the ARIC cohort versus another population?

13. Impact on ongoing ARIC studies (main study or other Ancillary Studies):

14. Provide the following assurances (answer each):

   (1) Who (name and position) will report progress of the study in the fall of each year? (Ancillary Study PI or designate preferred)

   (2) How will confidentiality of ARIC participants be maintained?

(3) Data collected by the Ancillary Study, with 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), will be provided to the ARIC Coordinating Center for integration into the main database. 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 some compromise will be worked out.

II. Abbreviated Ancillary Study Proposal

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

Purpose:

Background:

Hypothesis(es):

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

Please send (electronically and by surface mail) the completed proposal to:

Aaron R. Folsom, M.D. (Principal Investigator) folsom@epi.umn.edu
University of Minnesota :: School of Public Health
Division of Epidemiology
1300 South Second St., Suite 300
Minneapolis, MN 55454-1015
Phone: (612) 626-8862 Fax: (612) 624-0315

For Coordinating Center Use Only

Approved? _____ **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 2005
Due November 1, 2006

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.

Send the completed report to: ARIC Ancillary Study Update -Central Receiving
Department of Biostatistics, Collaborative Studies Coordinating Center
137 East Franklin Street, Suite 400
Bank of America Center, CB #8030
Chapel Hill, NC 27514
Phone: (919) 962-2073 Fax: (919) 962-3265

Preferred method of submission is via email, as an attachment sent to: ARICupdate@mail.cscc.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, which ever 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.

5.0 STRATEGY FOR ORGANIZING AND MANAGING ARIC DATA SETS

5.1 Data

Create a directory called “ARIC”.
Create the following sub-directories under the ARIC directory:

SUBDIRECTORY	DESCRIPTION
V1FINAL	Visit 1 data
V2FINAL	Visit 2 data
V3FINAL	Visit 3 data
V4FINAL	Visit 4 data
C_CNTRL1	Visit 1 case/control data
C_CNTRL2	Visit 2 case/control data
INCIDENT	Incident CHD and stroke data
SURVALL	Surveillance data

The CSCC will send ARIC data in the format of SAS transport files.

Transport files should be converted to SAS data sets that are formatted appropriately for a user’s operating system. For example, if you are using Windows, transport files should be converted to SAS data sets for Windows.

The SAS data sets created should be stored in the relevant subdirectory. For example, all visit 1 files should be stored in the V1FINAL subdirectory, visit 2 files should be stored in the V2FINAL subdirectory and so on.

If you received an updated version of a file that you already have:

a) You can move the older version of the file to tape or CD or
b) Create a subdirectory called “OLD” under each of the subdirectories listed above. Move the old version of the data set to the appropriate “OLD subdirectory. For example, if you receive an updated version of the visit 1 HOM file, move the older version of HOM to \V1FINAL\OLD. Files in the “OLD” subdirectories can be stored in compressed format to conserve space.

5.2 Documentation

A notebook should be created to maintain documentation for ARIC data. The notebook should be divided into sections similar to the ARIC data (visit 1, visit 2, ……) . When data is distributed by the CSCC, we will also provide documentation. The documentation will be in the form of file contents, listing of the first 10 observations, and descriptive statistics. When documentation is received it should be stored in the appropriate section of the ARIC data notebook.