The Atherosclerosis Risk in Communities Study (ARIC)

OMB Number: 0925-0281

January 28, 2010

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Request for OMB Approval of Extension of the Atherosclerosis Risk in Communities Study (ARIC)

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Summary of the Atherosclerosis Risk in Communities (ARIC) Study

ARIC study was initiated in 1985 to examine the major factors contributing to the occurrence of and the trends for cardiovascular diseases among men, women, African Americans and white persons in four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The cohort in Jackson is selected to represent only African American residents of the city. The primary objectives of the study are to: 1) investigate factors associated with both atherosclerosis and clinical cardiovascular diseases and 2) measure occurrence of and trend in coronary heart disease (CHD) and relate them to community levels of risk factors, medical care, and atherosclerosis. In 2006, the ARIC study added community surveillance of heart failure beginning with the events occurring in 2005 for the residents aged 55 years and older. Operationally, ARIC study has two integrated components:

1. Surveillance for hospitalized myocardial infarction (MI) and fatal CHD covering a sample of all residents aged 35-74 of the four study communities, including record review, death investigation, and central standardized diagnosis, monitored under a comprehensive quality assurance program. Beginning in 2006, the community surveillance of CHD was expanded to include the age group 75-84 years. Additionally, ARIC began monitoring these four communities for hospitalized heart failure for the residents aged 55 years and older. Non-hospitalized heart failure cases aged 65 years and older are monitored by obtaining and analyzing the Medicare data.

2. Follow-up of cohorts consisting of approximately 4,000 participants aged 45-64 years at the enrollment from each community, including comprehensive examinations, triennial re-examinations, and annual telephone interviews for new cardiovascular events. In 2006, ARIC began to collect and verify the heart failure events in the cohorts.

Using a standardized protocol for investigation and uniform criteria for diagnosis, ARIC study has found that from 1987-2000, CHD mortality in the study communities declined on average slightly over 4% per year in white men and slightly under 1% in black men. In women, the decline was over 3% in both African Americans and white persons. Out of hospital CHD deaths without a prior history of MI declined 1.7% in men but there was no change in rates for women. Over the 14-year period there was a statistically significant decline in hospitalized definite MIs (>1%/year), but this decline was restricted to white men and women. Data from ARIC surveillance are used to validate and supplement coronary disease diagnosis from a community perspective measuring both true incidence, by distinguishing new and recurrent events, and total incidence, by including angina and silent infarction and tracking case-fatality. This information is needed to assess the separate contributions of primary prevention and medical care to community trends in mortality.

In order to evaluate factors associated with mortality decline, ARIC study measures in the community residents major potential determinants of the trend. These include most recognized cardiovascular risk factors, from biochemical to behavioral, the prevalence of the underlying disease process, i.e. atherosclerosis assessed by ultrasonography, and key components of medical care received for cardiovascular conditions. ARIC study addresses a continuing need to improve

identification of persons at risk for cardiovascular diseases by including measurements of major known risk factors as well as a large number of new, suspected factors. The large size of the study, prospective design, and age structure facilitate the search for unrecognized risk factors. The cardiovascular risk attributable to the hemostatic factors measured in ARIC is assessed adequately only in large prospective studies. These discoveries may suggest new approaches to disease prevention.

Specific activities for the ARIC in the next three years will remain to be the same as those in the previous three years:

1. Continue surveillance in the ARIC communities to provide reliable estimates of CHD morbidity and mortality rates and trends in the separate study communities for the residents aged 35-84 years;
2. Continue surveillance of heart failure in the ARIC communities for the residents aged 55 years and older beginning with the events occurring in 2005 and track out-patient heart failure using the Medicare data;
3. Conintue follow up of the ARIC cohort to document the occurrence of all manifestations of cardiovascular disease for comparison with community surveillance events, and for use as endpoints in the prospective study of risk factors for clinical and sub-clinical cardiovascular.

Timeline
Atherosclerosis Risk in Communities (ARIC) Study

Years	Activity
	Cohort Component (Approximately 4,000 men and women aged 45-64 at visit 1 in each community)
1985-1986	Protocol development and pilot tests of procedures
1987-1989	Baseline visit Recruitment of participants, clinic examination 1, annual telephone follow-up of participants
1990-1992	Repeat visit Clinic examination 2, continued annual follow-up
1992-1993	Analyses
1993-1995	Repeat visit Clinic examination 3, continued annual follow-up
1994-1995	Analyses
1996-1998	Repeat visit Clinic examination 4, continued annual follow-up
1998-1999	Analysis
1999-2012	Continued annual follow-up for morbidity and mortality
1999-2012	Analyses
	Surveillance Component (men and women in each community)
1985-1986	Protocol development
1987-1992	Community surveillance for MI and CHD death in men and women aged 35-74
1992-1993	Analyses
1993-1998	Community surveillance for MI and CHD death in men and women aged 35-74
1994-1999	Analyses
1999-2004	Community surveillance for MI and CHD death in men and women aged 35-74
2000-2004	Analyses
2005-2012	Community surveillance for heart failure in men and women aged 55 years and older as well as MI and CHD death in men and women aged 35-84
2005-2012	Analyses
2005-2012	Obtain Medicare data for out-patient heart failure monitoring for community populations

Supporting Statement

A. Justification

A.1. Circumstances Making the Collection of Information Necessary

ARIC is an epidemiological study of atherosclerosis and cardiovascular disease that has been previously approved eight times by OMB for a total twenty-one year period ending May 31, 2010. Since the study as designed and as approved by OMB calls for contact of the selected cohort, informants, and physicians for the out-of-hospital CHD deaths and outpatient heart failure diagnosis in the four study communities, we are requesting continuation of OMB approval through May 31, 2013. The annual follow-up, already in progress, will carry over through January 31, 2012. The surveillance of community events will continue to include events through December 31, 2009.

In ARIC, a random sample of 15,792 persons aged 45-64 years was selected in 1987 from four communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD). Participants are providing medical, social, and demographic information and are currently participating in the annual telephone follow-up to study the etiology and overt clinical sequelae of atherosclerosis. The four communities are clearly defined geographical entities, have well delineated medical care referral patterns, and provide an opportunity to study African Americans and whites, men and women, in urban and rural settings. Operationally, the study has progressed in the following steps: 1) definition of the sampling frames and procedures for each community; 2) enumeration of identified households to determine the study eligibility of each household member; 3) interview in the household of all study eligible members; 4) recruitment of eligible household members to participate in clinical visit 1; 5) participation in the first clinical visit at the examination center in each community; 6) interview of participant annually after the first visit to determine health status; 7) contact of health care providers and family members review of medical records of participants who are hospitalized or die in the follow-up period; 8) and participation in a clinical visit every three years for four clinical visits. The fourth visit of the 15,792 participants was completed in January 1999. The return rate was 93 percent for the second visit, 86 percent for the third visit, and 81 percent for the fourth visit. Annual contact has been completed on 92 percent of eligible participants for the contact year 19.

These four communities are also under surveillance for the occurrence of hospitalized MI and CHD in men and women aged 35-84 years. A review of hospital records is being done on a sample of all age-eligible residents of each community with a discharge of myocardial infarction or one of several related screening diagnosis codes. Additionally, a review is being done on a sample of all age- and residence-eligible death certificates with various manifestations of CHD coded as the cause of death. For deaths not occurring in a hospital, the decedent's physician and next-of-kin are being queried about the circumstances around the time of death. Hospitalized heart failure in the four communities for men and women over 55 has become a part of the community surveillance, for events occurring in 2005 onwards.

The background for ARIC was stated in our original OMB application. The Subcommittee on the Departments of Labor and Health, Education, and Welfare of the Committee on Appropriations of the House of Representatives requested a Working Group to advise the Director of the National Heart, Lung, and Blood Institute (NHLBI) on the needed areas of epidemiologic cardiovascular research. Its report[1] in 1979 recommended studies in diverse U.S. communities that select and follow a general population sample to identify key factors predictive of the occurrence of cardiovascular diseases. These factors included nutrition, serum lipids, lipoproteins, blood pressure, cigarette smoking, physical activity, and measures of blood clotting. The Working Group advised NHLBI to conduct epidemiologic studies to understand cardiovascular "trends in the population, their precursors and causes, and consequently, the optimal approaches to furthering the control effort." ARIC with its 1) total population surveillance in four diverse communities, and 2) risk factor assessment and follow-up in representative samples of those communities is clearly responsive to each of these recommendations.

As we stated, cardiovascular disease continues as the leading cause of death in the United States. Despite many advances in identifying the causes of this disease, less than half of the occurrences can be accounted for by known factors. Atherosclerosis, or the hardening and narrowing of the arteries, is considered the primary abnormal condition that leads to heart attacks and strokes. However, the development and progression of atherosclerosis are not well understood. ARIC studies atherosclerosis by direct visualization of the process using ultrasound. The study examines a large number of new factors potentially related to the atherosclerotic process. These include an array of cholesterol and other fats in the blood that are hypothesized to cause accumulation or removal of cholesterol deposits in the arterial wall. Blood clots may also contribute to the initial narrowing of the arteries. Measurement of coagulation factors in the blood is done in ARIC to better understand these processes. Thus, ARIC fulfills a major research need to understand completely the determinants of cardiovascular disease and death.

Heart failure remains highly lethal. In the 1990s, 59% of men and 45% of women were dead 5 years after diagnosis. Because heart failure is such a profoundly costly condition, both in human and fiscal terms, it is important to understand its incidence, prevalence and mortality, and study the effects of treatment on disease outcomes. Such knowledge will help project future needs in terms of both health care resources and research priorities. Expanding our understanding of the relations of heart failure risk factors and the underlying cellular processes to the development of heart failure will provide insight into approaches for the primary prevention and treatment of this dreaded disease. ARIC began conducting surveillance of inpatient and outpatient heart failure for the residents living in the four U.S. communities in 2006;, the surveillance provides valuable information on the epidemiologic profile of heart failure, secular trend in its incidence, prevalence and mortality, and clinical outcomes of heart failure care.

To identify with assurance the factors that cause and predict cardiovascular disease, it is necessary to measure the factors in individuals before disease is manifested and to follow the individuals until disease occurs. This is the reason for the prospective design of ARIC. Prospective studies are definitive but require a large number of participants and long-term

[1] Report: National Heart, Lung, and Blood Institute; Working Group on Heart Disease Epidemiology. (NIH pub No 79-1667) Public Heath Service, June 1979.

follow-up. The use of multiple communities will test the generalizability of findings for diverse population groups. The study objectives are clearly within NHLBI mandate and the Institute has the unique capability to coordinate this complex study within four different communities and over an extended period. The NHLBI mandate is described in the PHS Act, Section 421 (42USC 285b-3) and specifies provision of "investigation into the epidemiology, etiology and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases."

A.2. Purpose and Use of the Information

ARIC uses the information for publication of study results in appropriate scientific journals, presentation of results at scientific meetings, and after full scientific evaluation, will be presented as policy recommendations by the NHLBI using public education and prevention programs. During the past three years, The study has been extremely productive and has produced over 300 publications. Many of the findings are unique and original contributions to understanding the etiology of atherosclerosis and clinical cardiovascular disease, and have been used to develop evidence-based clinical practice guidelines for coronary heart disease, diabetes, stroke, and chronic kidney disease. Some major contributions of the ARIC study include: 1) identification of carotid IMT as a subclinical marker of atherosclerosis, providing a basis for considering IMT in health screening and as an end point in anti-atherosclerotic drug clinical trials; 2) identification of two distinct loci on chromosome 9p21 that are attributed to increased risk for coronary heart disease and diabetes among Caucasians, a finding that may help early identify persons at risk and better manage patients with coronary heart disease and diabetes; 3) identification of the contribution of low neighborhood socioeconomic status to increased risk of incident coronary heart disease, indicating a need to combine person-centered approaches with approaches aimed at changing residential environments; 4) identification of association between retinal arteriolar narrowing and the development of coronary heart disease in women but not in men, suggesting an important clinical implications in prevention and treatment of coronary heart disease in women; and 5) development of prediction equations for coronary heart disease and stroke in apparently healthy individuals for cardiovascular disease prevention programs. ARIC community surveillance data on coronary heart disease rates and trends have been used extensively by Center for Disease Prevention and Control (CDC) and NHLBI to identify public health and research priorities, evaluate the impact of cardiovascular disease prevention programs, and allocate research resources. In addition, ARIC has contributed valuable data to the yearly American Heart Association (AHA) Statistical Update and is one of the major sources of data used to monitor the reduction in coronary heart disease incidence and mortality for the AHA goals for 2020.

ARIC will continue to provide research information of the relationships between person attributes, physiological measurements, the progression of atherosclerosis and subsequent development of clinical cardiovascular disease. Since half of the cardiovascular disease cannot be explained by currently identified risk factors, expansion of the knowledge of the etiology of atherosclerosis and cardiovascular disease is needed. Many of these relationships can be evaluated only with the prospective design of ARIC. Prospective studies require larger numbers

of participants and a relatively long follow-up period thus requiring a major commitment from NHLBI for their implementation.

As new risk factors are identified, it is the mandate of the NHLBI to bring this knowledge to the attention of the health profession and the public. The NHLBI currently has programs and recommendations concerning high blood pressure and high cholesterol and ARIC can confirm and test the consistency of these recommendations for each of the diverse populations being studied (blacks, whites, men, women, rural, urban). Most importantly, ARIC is using the information as the study investigates new risk factors for cardiovascular disease development and these results will be translated into preventive strategies and recommendations.

A.3. Use of Information Technology and Burden Reduction

ARIC uses and will continue to use state-of-art data entry and management systems which maximize data accuracy and minimize respondent burden. The data entry system displays screens that resemble paper forms. The data collector reads the items from the screen, performs the measurement or queries the participant, and keys the response into the computer. As data for a field are entered, they are edited by the system. The values failing the edit checks cause an error message to be displayed and prevents further entry until the problem is resolved. The data collector can correct the value, confirm it, or flag it as "questionable" and in need of further investigation. In addition to collecting and editing the data, the system permits users to enter text into an electronic "post-it notes" attached to any field as needed. This computer assistance can rapidly direct the interviewer to the relevant sections of the interview for the particular respondent and provides for very rapid interviewer action, thus lessening the respondent burden. The privacy and security of the information systems developed by the Coordinating Center was assessed through the Privacy Impact Assessment (PIA).

A.4. Efforts to Identify Duplication and Use of Similar Information

ARIC contains many research components that do not exist in any epidemiologic studies and thus ARIC does not duplicate research effort done elsewhere. The new features of ARIC are described below.

a. Using highly standardized techniques, ARIC studies four diverse population groups (African Americans in Jackson, Mississippi; suburban whites around Minneapolis, Minnesota; rural and urban whites in Washington County, Maryland; rural and urban white and African Americans in Forsyth County, North Carolina). The diversity of the populations tests the consistency and generality of the findings.
b. ARIC investigates the relationship of blood lipid, lipoprotein, coagulation, genetic determinants, and other factors to cardiovascular disease. Many of these factors have not previously been included in prospective population studies.
c. Using stored blood, urine, and DNA samples, ARIC studies biomarker and genetic factors for the diagnosis and progression of heart failure. The role of biomarkers and genetic factors in the development of heart failure has remained unclear.

d. ARIC determines the occurrence of MI, CHD death, and heart failure using surveillance procedures in a sample of all adults in the four communities. This information will be validated using detailed information from the cohort sampled from the community.

While there are other cohort studies (e.g. The Framingham Study, OMB Clearance 0925-0216) and other surveillance studies (e.g. Minnesota Heart Heath Program, NIH Grant, study not directed by NIH, no OMB number), these do not include the population diversity, the measurement of new risk factors, the direct measurement of atherosclerosis, and the community surveillance and cohort linkage which will allow ARIC to expand the knowledge of cardiovascular disease etiology. The Cardiovascular Heath Study (OMB Clearance 0925-0334), started in 1989 and operated under contract from the NHLBI, is similar in some study components to ARIC but is conducted among the participants iniatially aged 65-84 year old. This study in the elderly does not duplicate ARIC, because it focuses on the major differences in the expression and prognosis of cardiovascular disease among older persons. Adding heart failure to both the ARIC cohort follow-up and the community surveillance is a major advantage of having this study in place. ARIC study uniquely combines community-wide cardiovascular disease surveillance with in-depth assessment of population-based cohorts from each of four communities in the US, permitting the direct application of cohort data to clinical cases in the community at large. The study collects and validates heart failure events in cohorts and communities, providing unique data to study epidemiology, etiology and treatment of heart failure. Additionally, ARIC study assesses trend in incidence of MI, CHD and heart failure in the 4 communities, and determines factors associated with any secular changes using data from the cohort and communities such as changes in treatment patterns, CVD risk factors, comorbidities, and disease severities.

The unique nature of this study precludes the use or modification of similar data. ARIC will continue to collect new information on precursors to atherosclerosis and cardiovascular disease which will be used to develop cardiovascular disease prevention policies and strategies.

A.5. Impact on Small Businesses or Other Small Entities

Physicians constitute the only small business burdened by ARIC. They are requested to provide medical information on selected patients identified by the study. To determine whether deaths in the entire community that do not occur in a hospital are cardiovascular deaths, a questionnaire is sent to the decedent's physician and next-of-kin. This information is collected only once, after the death has been identified from vital statistics or hospital records. These requests are limited only to essential information needed to determine the presence of cardiovascular conditions. This information collection will not have a significant economic impact on a substantial number of small entities.

A.6. Consequences of Collecting the Information Less Frequently

ARIC conducted a sampling of the communities for identification and recruitment of participants into the cohort study only once. Because of the size of the population this

recruitment took three years, ending in 1989. These individuals in the general population were burdened only once.

Once the sampled cohort population agreed to participate in the study, they were given repeat clinic examinations three years apart with annual interviews between visits and until the end of the study. The examinations were complete, but annual interviews are required to monitor the morbidity and mortality experience, to update contact information, and to obtain interim information from questionnaires. The prospective data collection and follow-up is required to determine the change in measured characteristics over time, to determine accurately the occurrence of cardiovascular events, and to analyze risk factors as precursors to disease development.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

Since there are no more clinical examinations in the ARIC extension through 2012, compensation for participation in the cohort study does not apply. The current protocol designed for the ARIC does not include any special circumstances that would cause information collection to be conducted in a manner outside of the guidelines of 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside Agency

On November 16, 2009, page 58962, the *Federal Register* published NHLBI's notice. The Project Officer received one comment from the public that stated there was no need to continue collecting data from the ARIC study, as there is already 40 years of existing data. The Project Office acknowledged receipt of the comments.

Longitudinal epidemiologic studies such as ARIC requires long term follow-up of the participants to collect information on development of conditions and diseases, as well as changes in risk factor exposures, in order to identify the determinants of morbidity and mortality. Trends in cardiovascular incidence are difficult and expensive to obtain, are not available on a national basis, but are critical in monitoring a primary mission of NHLBI to reduce the burden of the disease in the population. ARIC provides the needed estimates of the trends in hospitalized MI and CHD deaths since 1987 and heart failure since 2005 in diverse US communities. As cardiovascular disease (such as CHD and heart failure) remains a public health problem resulting in enormous morbidity, mortality, and health care costs, continued monitoring of the trends through this well established infrastructure is most cost effective and should provide NHLBI with a primary data source for assessing the impact of prevention and medical treatment of this disorder.

Recent approval of the extension of ARIC was given by the NHLBI Advisory Council during the meeting of June 10, 2009. The NHLBI Advisory Council is also composed of non-government health professionals and researchers and provides final review of NHLBI research.

An ARIC Observational Study Monitoring Board (OSMB) meets periodically to review the progress and to advise on study design, procedures, data analyses, and participant burden. The members of this committee are:

Cashell Jaquish, PhD, NHLBI (301-435-0447) (Executive Secretary)
Robert J. Goldberg, Ph.D., University of Massachusetts Med. School (508-856-3991)
C. Morton Hawkins, Ph.D., University of Texas at Houston (713-729-4401)
Karen Kaplan, M.D., Sinai Hospital, Elmhurst, NY (718-334-3951)
Jose Ordovas, PhD, Tufts University (617-556-3102)
Veronique Roger, MPH, MD, Mayo Clinic: Dept. of Internal Medicine (507-284-0519)
Jerome Rotter, MD, Cedars-Sinai Medical Center (310-423-6467)
Jeremiah Stamler, M.D., Northwestern University Med. School (312-908-7914)
Marvin C. Ziskin, M.D., Temple University Medical School (215-221-4259)

The details of ARIC design and data collection are developed within several committees that began meeting in September 1985 and continue to meet throughout the study. Committees that are functional in this extension are the Steering Committee, Executive Committee, Annual Follow-up Committee, Laboratory Committee, Surveillance Committee, Morbidity and Mortality Classification Committee, Quality Control Committee, and Publications Committee. In 2006, a Heart Failure Committee was added to the ARIC committees. These ARIC committees are currently composed of the following persons:

Sunil Agarwal, University of North Carolina (336-716-0843)
Alvaro Alonso, MD, MPH, PhD, University of Minnesota (612-626-8597)
Gina Andrews, MPH, University of North Carolina (919-962-1176)
Chris Baggett, University of North Carolina (919-966-7825)
Christiane Ballatyne, PhD, Baylor College of Medicine (713-798-4168)
Alain Bertoni, MD, Wake Forest University (336-716-2824)
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Eric Boerwinkle, PhD, University of Texas (713-500-9816)
Ebony Boulware, Johns Hopkins University (413-287-2582)
Patricia Chang, MD, University of North Carolina (919-843-5214)
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Pat Crowley, Johns Hopkins University (301-791-1847)
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Aaron Folsom, MD, MPH, University of Minnesota (612-626-8862)
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Ron Hoogeveen, PhD, University of Texas (713-798-3407)
Laura Loehr, University of North Carolina (919-966-1937)

Edgar (Pete) Miller, Johns Hopkins University (410-502-6444)
Alanna Morrison, PhD, Health Sciences Center of Houston (713-500-9913)
Tom Mosley, PhD, University of Mississippi Medical Center (601-984-2763)
Hanyu Ni, National Institute of Health (NHLBI) (301-435-0448)
Mona Pandey, National Institute of Health (NHLBI) (301-435-0704)
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Moyses Szklo, MD, DrPH, Johns Hopkins University (410-955-3462)
Herman Taylor, University of Mississippi (601-368-4644)
Gina Tritle, University of Minnesota (612-626-8876)
Kelly Volcik, PhD, University of Texas (713-500-9891)
Lynne Wagenknecht, DrPH, Wake Forest University (336-716-7652)
Evelyn Walker, MD, Jackson State University, (601-368-4654)
Stanley Watkins, MD, Alaska Heart Institute, (410-955-3462)
Eric Whitsel, MD, MPH, University of North Carolina (919-966-3168)
Pamela Williams, Wake Forest University (336-716-6181)
Kelly Volcik, PhD, University of Texas (713-500-9891)

The following individuals provided consultation in the initial development of the study design and the protocol in specific scientific areas:

Ultrasound: Marvin C. Ziskin, M.D. (215-221-4259)
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A.9. Explanation of Any Payment or Gift to Respondents

There are no clinic visits in this extension of ARIC. There are no payments or gifts to respondents in this extension.

A.10. Assurance of Confidentiality Provided to Respondents

All ARIC Principal Investigators and their institutions have agreed to comply with the Federal Privacy Act as part of their contractual agreement with NHLBI. The contract stipulates that research involving human subjects cannot be conducted until 1) the protocol has been approved by NHLBI, 2) written notice of such approval is provided by the Contracting Officer, and 3) each ARIC Contractor provides the Contracting Officer with a properly completed Form HHS-596 certifying Institutional Review Board (IRB) review and approval of the protocol (see Tab 10).

A.10.a. Field Center Security and Confidentiality

Field Center staff is trained in procedures for insuring confidentiality of participant information. Paper records of the Annual Follow-up phone call and medical records of the participants are in secure storage. When they are no longer useful, they will be discarded based on center-specific security protocol. The data management system provides a high level of confidentiality for the machine-readable information. Each user of the system has a password

that is required to access the system. All data files are encrypted to prevent access to the data using other software.

In publications, the individual identities of participants are not disclosed, and data are reported only in the aggregate. Information obtained from the study will be included in the Privacy Act System of Records 09-25-0126, entitled, "Clinical Research, National Heart, Lung, and Blood Institute Epidemiology, and Biometric Studies, HHS/NIH/NHLBI as published in the Federal Register, Vol. 60 FR p. 4264, January 20, 1995 (Tab 9).

HHS-596 certifying Institutional Review Board review and approval in accordance with 45 CFR 46 are included for each center under Tab 10. Participant data are collected and stored by two methods. In addition to the computerized data management system (see below), data may be collected on paper forms, and then stored in locked file cabinets, stored in locked rooms. Original data do not leave the Field Centers without a complete backup (either paper copy in the case of forms, or electronic in the case of diskette or tape files).

A.10.b. Field Center Data Management System

The annual follow-up and surveillance data management system will use a set of computers – one primary computer and one or more secondary computers. All computers run the same data management system interface. The primary computer holds the field center's comprehensive database. On a secondary computer, the user runs a program to move the data collected on the secondary computer to the primary computer. Often the secondary computers are laptops that allow them to be used in hospitals or in other remote locations.

Data records corresponding to each form will be written to multiple hard disk files as the data are collected. Thus, a system failure will only affect the current form being entered. If, for some reason, such as power failure, the data management system is not functioning, data are collected on paper forms. This data can then be entered when the data management system becomes operational.

As participant information is entered at a workstation, the local database will be updated and automatically encrypted. In addition, a copy of participant record will be written to an encrypted ASCII file on the workstation hard disk. This file will serve as a backup from which the local database can be restored, if necessary. At the end of each data entry session, a copy of the local database will be made to another device – either a second hard drive, in the case of a primary machine; or removable storage media, in the case of a secondary machine.

The data management system requires users to have an ID and password for access. A user's ID determines which functions he is permitted to perform. Using this system, study data can be entered, reviewed, or edited only by those staff whose passwords permit that specific function. Transaction files containing an encrypted copy of every new, modified or deleted data record, will be sent to the Coordinating Center once every other week. These transaction files will be used to construct a field center database if it becomes corrupted. They are also used to update the study's consolidated database at the Coordinating Center.

A.10.c. Coordinating Center Security and Confidentiality

All Coordinating Center staff is instructed in procedures for maintaining data confidentiality and sign a form indicating their awareness of the necessity of maintaining confidentiality of data. Staff is informed that any inappropriate use or disclosure of confidential data will be cause for immediate termination of employment at the Coordinating Center.

The Coordinating Center maintains a "secure forms room", an interior room within the Collaborative Studies Coordination Center (CSCC) office suite. This room is used to store original paper forms from on-going studies. The room is locked at all times; only select members of the CSCC computing division have access to this room. In addition, the Coordinating Center leases an off-site data storage facility for paper archives. Archived tapes are stored off-site in the School of Public Health.

The CSCC also maintains procedures for disposal of confidential data, defined as "any table, graph or page that contains "blinded" (masked) information. . . and, any form or page that contains an individual's name, initials, address, telephone number, social security number, or other information that would identify a subject." Confidential data are disposed of by a University contractor.

A.10.d. Coordinating Center Data Management and Computing

The ARIC collaborative database for Visits 1 and 2 was managed using the Scientific Information Retrieval System (SIR) on the University's IBM 3090 computer system. For Visits 3, 4, and Post Visit 4, a CSCC local network of microcomputers is used for data management and most statistical computing.

Source data from field centers is received electronically and is copied to a designated area on the CSCC local area network. Files are backed up to tape overnight. At the end of the month, the data are copied to a permanent study tape. Similarly, the collaborative database is copied to tape nightly and to permanent tape monthly. The permanent tapes provide images of the database at all update levels. The permanent tapes are stored off site where proper conditions of temperature, humidity, and security are maintained.

In addition, all files on the CSCC network are backed up nightly. Once a month all files are put on tape and stored permanently. These system backups provide additional backup protection for the collaborative database and all source data.

A.10.e. Distributed Data Tapes

Under the direction of the ARIC Steering Committee, the Coordinating Center has distributed data tapes of closed data, except confidential identifiers to Study Principal Investigators. The data on the tapes contain no identifying information. Each Principal Investigator will maintain data security and confidentiality in accord with their Institutional Review Board agreements.

A.11. Justification for Sensitive Questions

There are no sensitive questions in the Annual Follow-up, informant contact, or physician contact questionnaires. However, personally identifiable information (PII), such as participant name, education, medical history, social security number (SSN), and date of birth, is collected from the cohort members at the ARIC Field Centers. Use of the SSN by the study is explicitly authorized in the ARIC study informed consent. At induction into the cohort the ARIC study requested disclosure of the participant's SSN, after presenting the participant with a statement that this disclosure was voluntary and failure to disclose the SSN would not affect his/her rights, participation in the study, nor the individuals' relation to the study agency.

Field centers may use the PII to trace study participants who are lost to follow-up and search for deaths of cohort members through the National Death Index (e.g., SSN), investigate social-economic factors in their relation to the development of cardiovascular disease (e.g., education), and conduct risk stratification and prediction of cardiovascular disease (e.g., medical history). No private companies are used to trace participants lost to follow-up through these means. The PII may also be used by authorized ARIC personnel at a field center to verify the identity of decedents among our study participants who have the same first and last names as other members of the ARIC cohort, and may have changed their address.

Personally identifiable information are stored as confidential information at each of the four ARIC field centers, under privacy and HIPAA regulations that cover the academic institution the field center is affiliated with. All data and PII are encrypted upon data entry into the ARIC Data Entry System on the laptops used by staff; the decryption code is only available at the ARIC Coordinating Center at the University of North Carolina, where these records are sent. No hard copy forms are used for interview.

A.12. Estimates of Hour Burden Including Annualized Hourly Costs

The following data are estimated for Post Visit 4 from Year 2010 to 2013, based on the data collected in the past years. The annual estimate of respondent burden for the proposed collection is presented in Table A.12.1 whereas the estimate for the entire period from 2010-2013 is in Table A.12.2. Table A.12.3 provides the annualized cost to respondents, which consists only time from the participants.

Table A.12.1 Annual Estimate of Hour Burden

Annual number of respondents	11,992 persons
Annual number of responses	11,992 responses
Average responses per respondent	1.00 responses per respondent
Annual total burden hours	2,877.4 hours
Annual hours per response	0.2399 hours per response

Table A.12.2 Information Collection, Year 2010-2013

Study Component	Number of Respondents	Number of Responses	Time per Response (minutes)	Burden (hours)
Follow-Up Interview (tabs 2 and 6)	10,735	32,205	15	8,051.3
Physician Contact for CHD Deaths	701	701	10	116.8
Coroner Contact for CHD Deaths	773	773	10	128.8
Informant Contact for Participant Deaths	1,726	1,726	10	287.7
Physician Contact for Out of Hospital Heart Failure	570	570	5	47.5
Total	**14,505**	**35,975**		**8,632.1**

Table A.12.3 Annualized Cost to Respondents

Type of Respondent	Annual Number of Respondents	Frequency of Response	Hourly Wage Rate ($)	Respondent Cost ($)
Participants	10,735	1	17.00	45,623.75
Physicians or Coroner (contacted for CHD Death)	491	1	75.00	6,141.67
Informant	575	1	17.00	1,630.11
Physicians (contacted for Out of Hospital Heart Failure)	190	1	75.00	1,187.50
Totals	**11,992**			**54,583.03**

A. 13. Estimate of Other Total Annual Cost Burden to Respondents or Record keepers

There are no Capital Costs, Operating Costs, and/or Maintenance Costs to report.

A.14. Annualized Cost to the Federal Government

The annualized cost of monitoring the project by NHLBI is estimated at $200,000. The average annualized cost (contracts and monitoring by NHLBI) to the U.S. Government for information collection is $6,905,000 per year. This is itemized in the following table.

Table A.14.1 Average Annualized Cost for Information Collection, ARIC Field and Coordinating Centers (in thousands of dollars)

Personnel	Equipment	Subcontracts	Other	Overhead	Total
$3,620	$35	$881	$1566	$1762	$6905

A.15. Explanation for Program Changes or Adjustments

The annual number of respondents has decreased, but the annual hours per response is similar to the previous submission (0.2399 vs. 0.2300 hrs). The decreased number of responses is due to: 1) some participants lost to follow-up or passed away; and 2) physician responses are adjusted based on the response rates and incidence/mortality during the past three years, as the numbers in the last submission were predicted estimates.

There is a slight difference in annual hours per response, due to decimal number round-up, differences in percent changes of number of respondents by study component, and varied time per response by study component.

A.16. Plans for Tabulation and Publication and Project Time Schedule

ARIC will analyze the collected information in a timely manner after the necessary data editing has been done and after the data quality control procedures have verified that collection procedures were operating properly. The timetable for data collection and analysis is shown in the Introduction. The schedule for annual follow-up and surveillance in terms of the time elapsed following PHS/OMB approval is presented in Table A.16.2.

Table A.16.2 Time Schedule for Annual Follow up and Surveillance

Full Study	Time elapsed after PHS/OMB approval
Data collection	0-36 months
Analysis	18 months – 5 years
Publication	24 months – 5+ years

To achieve the ultimate goal of determining policy recommendations for cardiovascular disease prevention, the intermediate goal of presenting statistical results by publishing in scientific journals (e.g. *New England Journal of Medicine, Journal of the American Medical Association, Circulation, Journal of Clinical Epidemiology*), by presentation at scientific meetings (e.g., American Heart Association, Council on Cardiovascular Epidemiology, American Public Health Association), and by compilation of special reports and monographs available to the scientific community. ARIC publication guidelines have been written to foster the analysis and publication of data.

The extent and complexity of ARIC necessitates that statistical analysis will cover many topics and will be ongoing. Based on the NHLBI past productivity with smaller prospective studies, hundreds of new scientific publications are expected to result from the analysis of ARIC data. Currently, over 900 manuscripts using ARIC data have been published and over 500 proposals are in process of being prepared for publication. A brief list of analytic topics follows:

Epidemiologic methods and procedures

- Analysis of data quality from results of quality control procedures.
- Assessment of non-response and loss-to-follow-up bias.
- The effects of sample design on analytic procedures.
- Comparison of the efficacy of recruitment procedures in different communities.
- Assessment of the ability and techniques to pool data from all four communities.
- Population distribution of measures of atherosclerosis by arterial ultrasound.

Cross-sectional analysis of information collected at Visit 1-Visit 4

- Determination of factors associated with pre-clinical atherosclerosis as determined by ultrasound imaging.
- Comparison of blood pressure (and other risk factors) relationships with covariates for the diverse populations studied (blacks, whites, men, women, rural, urban).
- Association of physical activity with physiological measurements and with atherosclerosis.
- Relationship of lipids and lipoprotein fractions with atherosclerosis and with cardiovascular risk factors.
- Estimation of means and variance of blood coagulation factors as they occur in a healthy population.

Analysis of Risk Factors for Cardiovascular Disease Incidence and Atherosclerosis

- Estimation of progression of atherosclerosis by ultrasound in population groups. Relation between atherosclerosis and future cardiovascular disease.
- Identification of lipid, lipoprotein and apolipoprotein predictors of clinical cardiovascular disease and atherosclerotic progression.
- Identification of genetic determinants and the role of gene-environmental interactions in development of clinical and subclinical cardiovascular disease.
- Determination of blood platelet, fibrinogen and coagulation factors and their role as precursors to cardiovascular disease development.
- Identification of socioeconomic variables as predictors of cardiovascular disease, both singly and in combination with other risk factors.
- Differences between women and men, blacks and whites in the factors that predict atherosclerosis and cardiovascular diseases.

Case-control Studies of Participants' Blood Samples that were Frozen

- Identify new cardiovascular disease cases occurring in follow-up, identify a sample of participants who did not develop cardiovascular disease, measure various special coagulation and lipoprotein values on the frozen blood collected at each visit and compare the measured values. (This technique reduces the cost of blood measurements since they are done on a small sample of the population.)

- Identify genetic variants and genomic factors associated with atherosclerosis and CVD events; evaluate genetic and genomic variation to correlate with carotid wall and plaque characteristics.
- Evaluate the ability of novel measures of celluar activation and aggregation and metabolism to correlate with atherosclerosis and clinical CVD events.

Analysis of Community Surveillance Information

- Validate CHD cases found in entire communities with those identified by more complete cohort procedures.
- Determine the trend in hospitalized CHD and fatal heart attacks over time for the four communities combined.
- Compare the four communities with respect to the incidence of fatal and nonfatal CHD.
- Compare the incidence of fatal and nonfatal CHD for the diverse population subgroups (blacks, whites, men, women, rural, urban).
- Determine rates of decompensated heart failure and chronic heart failure.
- Validation and classification methods of heart failure events.

The publications from ARIC to date are shown in Tab 12.

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

The OMB Expiration Date will be displayed as required.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to Certification for Paperwork Reduction Act Submissions.