Supporting Statement A for

The Atherosclerosis Risk in Communities Study (ARIC)

OMB Number: 0925-0281

Revised: April 24, 2014

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Request for OMB Approval of Revision 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. Operationally, the 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 Medicare billing claims data (available through the Centers for Medicate and Medicaid Services [CMS]).

2. Follow-up of the ARIC cohort, which originally comprised approximately 4,000 participants from each community aged 45-64 years at the enrollment. Four (4) examinations of the cohort occurred every three years over the period 1987-1998, and a fifth exam was conducted in 2011-13. Participants have been contacted annually by phone to update contact information, identify new cardiovascular events and hospitalizations, and update selected risk factors. In 2006, ARIC began to collect and verify the heart failure events in the cohorts (now aged 62-83 years) and in 2011, ARIC increased the frequency of calls to twice a year, allowing for a more fine-grained characterization of cardiovascular events, particularly for heart failure and associated medical care outcomes.

Using a standardized protocol for investigation and uniform criteria for diagnosis, ARIC study has found that from 1987-2007, CHD mortality in the study communities declined on average slightly over 3.1% per year in black men, 6.6% in white men, 3.9% in black women, and 5.5% in white women. During the same period, the average annual percent change in incidence of hospitalized definite or probable MI changed little in black men and women. Statistically significant declines in hospitalized MI incidence were seen for white men and white women. In 2005, incidence of hospitalized acute de-compensated heart failure was 8.8 per 1,000 persons, with a higher rate in black persons than in white persons. 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 CHD mortality.

The 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 ARIC cohort is used to examine long term risk factor trajectories and 25-year cardiovascular disease (CVD) prediction, and outcomes of clinical and subclinical heart failure, an increasing public health problem. The data on echocardiographic imaging and pulse wave velocity allow detailed investigation of novel risk factors involved in arterial and cardiac structural disease. Inclusion of measures on medical care for heart failure and heart failure risk factors can improve our understanding of current practice patterns in community settings and their associated outcomes, and help generate evidence for "best practices" from which quality improvement measures may be developed. These discoveries may suggest new approaches to cardiovascular disease prevention and treatment.

Specific activities for this revision of ARIC are as follows:

1. Continue telephone follow-up of the ARIC cohort, with twice yearly calls to identify new cardiovascular events and hospitalizations, update information about risk factors, and obtain information on access to and use of medical care for heart failure risk factors and heart failure.
2. 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.
3. 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.
4. Continue 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 disease.

Time Line

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 (Visit 1), annual telephone follow-up of participants
1990-1992	Repeat visit Clinic examination 2 (Visit 2), continued annual follow-up
1992-1993	Analyses
1993-1995	Repeat visit Clinic examination 3 (Visit 3), continued annual follow-up
1994-1995	Analyses
1996-1998	Repeat visit Clinic examination 4 (Visit 4), continued annual follow-up
1996-1999	Analysis
1999-2010	Continued annual follow-up for morbidity and mortality
1999-2014	Analyses
2011-2013	Repeat visit Clinic examination 5 (Visit 5), continued semiannual follow-up
2014-2017	Analyses
2014-2017	Continued semiannual follow-up for morbidity and mortality
	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
2005-2014	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
2005-2014	Analyses

2005-2014	Obtain Medicare data for out-patient heart failure monitoring for community populations
2014-2017	Analyses
2014-2017	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
2014-2017	Obtain Medicare data for out-patient heart failure monitoring for community populations

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 ten times by OMB over the past twenty-seven years. ARIC has previously requested and received OMB approval for continuation of annual follow-up telephone calls and ARIC surveillance activities through March 31, 2014. These activities include contact of the selected cohort, informants, and physicians for information about out-of-hospital CHD deaths and outpatient heart failure diagnosis in the four study communities.

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 have provided medical, social, and demographic information and are currently participating in the semiannual telephone follow-up to study the etiology and overt clinical sequelae of atherosclerosis and heart failure. 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 fifth visit of the 15,792 participants was completed in June 2013, with a period of twelve years between the fourth and fifth visits. The return rate was 93 percent for the second visit, 86 percent for the third visit, 81 percent for the fourth visit, and 65 percent for the fifth visit. Annual contact has been completed on 86 percent of eligible participants for the contact year 24 (**Table B.1.c.3**).

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 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 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 queried about the circumstances around the time of death. Hospitalized heart failure in the four communities for men and women over 55 is a part of the community surveillance, for events occurring from 2005 forward.

The background for ARIC was 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.

Heart failure remains highly lethal. In 2008 1 in 9 death certificates mentioned heart failure and hospital discharges for heart failure among persons 45-64 years old increased from 122,000 to 196,000 between 1990 and 2000 and are estimated at 254,000 in 2009-2010 . 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 both in terms of 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.

In July 2008, NHLBI convened a working group of independent investigators to discuss the need for future research in the ARIC study. The Working Group acknowledged that the ARIC study is a valuable resource for research on the progression of subclinical to clinical cardiovascular disease and heart failure. The group endorsed another clinical examination with major topic areas, including heart failure diagnosis and screening, triggers and modifiers in heart failure development, and outcomes associated with heart failure. Most recently, the November 2013, the ARIC Observational Studies Monitoring Board (OSMB) endorsed the continuation of the ARIC study.

To identify with assurance the factors which 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 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 of time. 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

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

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 research evidence by the NHLBI supporting policy recommendations for public education and prevention programs. As stated in previous submissions to OMB, ARIC will provide research information of the associations between personal attributes, physiological measurements, the progression of atherosclerosis and subsequent development of clinical cardiovascular disease. Expansion of the knowledge of the etiology of atherosclerosis and cardiovascular disease is needed and many of these associations 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.

ARIC was the first general population study of the atherosclerotic condition as actually visualized in the arteries leading to the head and lower extremities using ultrasound imaging. We now have information about heart failure occurrence risk factors, and outcomes in the general population and the ability to conduct a detailed investigation of each of the primary processes leading to atherosclerosis and cardiac failure: hypertension, cholesterol and other blood lipids, endothelial damage, diabetes, and the tendency of the blood to clot readily. These primary processes, as well as lifestyle factors (diet, smoking and physical activity), and a number of risk factors (blood pressure, insulin, obesity, renal deficiency, cognitive impairment, postmenopausal hormone usage, etc.) are studied in four geographic areas, urban and rural, women and men, and blacks and whites. The study has been extremely productive and has produced over 1,107 publications (**Attachment 7**), and has more than 30,000 citations. Many of the findings are unique and original contributions to understanding the etiology of atherosclerosis and clinical cardiovascular disease. Some major contributions of the ARIC study include: identification of carotid IMT as a subclinical marker of atherosclerosis, identification of traditional and novel risk markers and genetic variants for CHD, and development of prediction equations for CHD, stroke, and heart failure in apparently healthy individuals. In 2011 a clinical exam was conducted (a) to characterize heart failure stages using echocardiography; (b) to identify risk factors for ventricular dysfunction and vascular stiffness; (c) to describe changes in pulmonary function; and (d) to update risk factor status, medication use, and other relevant outcomes since their last examination in 1996-1998. The exam components included echocardiographic imaging and pulse wave velocity measurement to assess the occurrence, progression, and outcomes of clinical and subclinical heart failure and identifying risk factor associations to help inform strategies for prevention and treatment at both the individual and population levels. Also frequency of phone calls was increased to twice per year in 2011 to allow more fine-grained characterization of cardiovascular events, particularly for heart failure and associated medical care outcomes.

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, high cholesterol, and obesity. 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 a state-of-art system for data collection and management that maximizes data accuracy and minimizes respondent burden (centrally managed system on Dell PowerEdge servers using operating systems consisting of Netware, Windows 2000/2003/2008 Server, SuSE, Linux, and VMWare ESXi). Data from the cohort follow up interviews are keyed directly as the interview is being administered to the participants. This direct (paperless) data entry approach has become the gold standard in research today because of the possibility of identifying errors in real time. Values failing field-specific validation checks trigger error messages. Further entry is restricted until the data collector corrects the value, confirms it, or flags 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.

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 improves the consistency and generalizability of the findings.
b. ARIC investigates the relationship of blood lipid, lipoprotein, coagulation, novel biomarkers (e.g., troponin T, NT-proBNP) 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.
e. ARIC uses echocardiography, biomarker, and medical history to define heart failure stages in the cohort selected from the communities under surveillance. This is the first biracial population study that uses imaging, biomarkers, and clinical results to early identify and predict heart failure in the general population.

While there are other cohort studies (e.g. The Framingham Study, OMB Clearance 0925-0216, 10/31/2016) 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 and geographic diversity, the measurement of new risk factors, the direct measurement of atherosclerosis and imaging technology, and the community surveillance and cohort linkage which will allow ARIC to expand the knowledge of cardiovascular disease etiology. The Cardiovascular Health Study, started in 1989 and operated under contract from the NHLBI, is similar in some study components to ARIC but is conducted among 65-84 year old participants. This study in the elderly does not duplicate ARIC, because it represents a different birth cohort in which treatment of heart failure and its risk factors were different at comparable ages, with a much smaller group of African American participants and a less complete definition of heart failure. Adding heart failure to both the 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 assesses trends in incidence of MI, CHD and heart failure in the four 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, coronary heart disease, heart failure, and other cardiovascular disease which will be used to develop cardiovascular disease prevention policies.

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 underwent four clinic examinations three years apart with annual interviews between visits. The fifth examination was completed in 2013 and provided valuable data from echocardiogram and novel

biomarkers used to ascertain cardiovascular disease in the participants since they have transitioned to older age. Semiannual interviews were begun in 2011 to monitor the morbidity and mortality experience, update contact information, and obtain limited risk factor information. The prospective data collection and follow-up is required to determine the change in participant characteristics over time, to determine accurately the occurrence of cardiovascular events, and to analyze risk factors as precursors to disease development.

The purpose of conducting the cohort telephone follow-up semiannually is to obtain more reliable information on clinical events and outcomes measures, because the cohort has transitioned from middle age to old age and CVD morbidity becomes prevalent. The cohort is followed by phone calls to obtain information about access to and use of medical care, medication compliance, satisfaction of care, and outcomes of treatment. Along with medical records abstraction, the study will evaluate patterns of treatment, elucidate factors contributing to those patterns, and assess short and long term outcomes. Combined information from cohort follow-up, physician surveys, linked Medicare data, hospital and outpatient records, and death certificates allows identification of a broad spectrum of determinants for CVD prevention and control. Semiannual phone calls improve the reliability and accuracy of self-reported information from this aging cohort, and improve the quality of the study results that will be used to provide recommendations and guide the programs in CVD prevention and treatment.

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

The ARIC study will comply with the guidelines of 5 CFR 1320.5. 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

The 60 day FRN was published on December 20, 2013 (Vol. 78, No. 245, page 77138). 0 comments were received.

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. In December 2013, the Board endorsed the continuation of ARIC (**Attachment 8**). The members of this committee were:

Chair: Veronique Roger, M.D., M.P.H., Department of Internal Medicine, Mayo Clinic (507-284-0519)
Executive Secretary: Cashell Jaquish, PhD., Division of Cardiovascular Sciences, NHLBI (301-435-0447)
Julie Buring, Sc.D., Department of Epidemiology, Brigham and Women's Hospital Division of Preventive Medicine (617-278-0863)
Robert J. Goldberg, Ph.D., University of Massachusetts Medical School (508-856-3991)
Mary Haan, Ph.D., Department of Epidemiology and Biostatistics, University of California-San Francisco (415-514-8291)
Oscar Lopez, M.D., Department of Neurology, University of Pittsburgh (724-935-1500)
Jose Ordovas, PhD, Tufts University (617-556-3102)

Jerome Rotter, MD, Director, Division of Medical Genetics, Cedars-Sinai Medical Center (310-423-6467)
Thomas Wang, M.D., Division of Cardiovascular Medicine, Vanderbilt University (615-936-1720)

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-Genetics Committee, Surveillance Committee, Morbidity and Mortality Classification Committee, Quality Control Committee, Publications Committee, Heart Failure Committee, Operations Committee, Outcomes Research Committee and the Analysis Committee. These ARIC committees are currently composed of the following persons:

Sunil Agarwal, Johns Hopkins University 301-791-1847
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Alvaro Alonso, Tulane Medical Center 612-626-8597
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Christie Ballantyne, Baylor College Of Medicine and VA Center 713-798-5034
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Wayne Rosamond, University of North Carolina 919-962-3230
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A.9. Explanation of Any Payment or Gift to Respondents

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

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) completed Form HHS-596 certifying Institutional Review Board (IRB) review and approval of the protocol (**Attachment 9**).

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 Cohort Follow-up phone call and medical records of the participants are in secure storage. When they are no longer useful, they are discarded based on center-specific security protocol. The data management system provides a high level of confidentiality including features such as user authorization (i.e., requirement of username and password to access the system) and encryption of sensitive data.

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 NIH Privacy Act Systems of Records Notice 09-25-0200, entitled, "Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD," published in the Federal Register, Volume 67, No. 187, September 26, 2002 (**Attachment 10**).

Participant data are primarily collected using the computerized data management system (see below). In the rare case where data are collected on paper forms, the forms are handled like confidential medical records. Access to the files or forms is restricted to study staff. Original data do not leave the Field Centers without a complete backup (electronically or by paper copy).

A.10.b. Field Center Data Management System

Data management systems for collecting data from the examination, telephone follow-up, and surveillance allow data to be keyed by field center staff using any computer with a Windows-based operating system and web browser. Often the computers are laptops that can be used in hospitals or in other remote locations. If the computer has Internet access, the ARIC databases will be updated immediately upon data entry, thereby eliminating the need for separate data transfers. If there is no internet connection or the connection is lost, the data are automatically uploaded to the central ARIC database when connectivity is re-established.

The data management systems have a mechanism for automatically saving the content of an active form at frequent intervals to prevent data loss. Thus, a system failure will only result in

partial data loss on 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. These data can then be entered when the data management system becomes operational.

As participant information is entered at a workstation it is stored in the ARIC database which resides on a study server that is managed centrally on Dell PowerEdge servers using operating systems consisting of Netware, Windows 2000/2003/2008 Server, SuSE, Linux, and VMWare ESXi. Standard transaction validity checks are applied to all updates to the database (e.g., to prevent the addition of records with duplicate keys). Updating of the consolidated ARIC database by any means other than the study data management system is disallowed. Thus, audit logs from the data management system, and processing logs produced by the update program provide complete documentation for changes to the ARIC database. Backups of the consolidated database as well as imported files and processing reports are made daily.

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.

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 (**Attachment 11**). 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 local network of microcomputers was used for data management.

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 de-identified datasets of closed data to Study Principal Investigators. 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 revised 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 estimates of respondent burden is presented in **Table A.12.1** covers the 3-year period from 4/1/2014-3/31/2017. Time estimates are based on the experience of prior follow-up phone calls. The follow-up interviews are designated as a) annual follow-up interview occurring on or

near the anniversary of the participant's baseline exam; and b) semi-annual follow-up interview occurring approximately six months after the annual follow-up interview. For ease of administration in the automated data collection system the interview questions have been formatted as separate forms.

Table A.12.1 Estimate of Respondent Burden, Year 2014-2017

Type of Response	Number of Respondents	Frequency of Responses	Time per Response (minutes)	Burden (hours)
Participant				
Annual Follow-up Form (**Attachment 1**) Semiannual Follow-up Form (**Attachment 2**)	10,049	6	15/60	15,074
Subtotal (participant)	**---**	**-**	**-**	**15,074**
Non-Participant				
a. Coroner/Medical Examiner Form (**Attachment 3**)	690	1	10/60	115
b. Informant Interview Form (**Attachment 4**)	570	1	10/60	95
c. Heart Failure Survey (**Attachment 5**)	1200	1	10/60	200
d. Physician Questionnaire Form (**Attachment 6**)	2760	1	5/60	230
Subtotal (non-participant)	**5,220**	**-**	**-**	**640**

The respondent cost burden is summarized in **Table A.12.2**. The annualized cost to the participants consists of the cost of their time, for which no remuneration is given, and transportation costs. Assuming $17.00 per burden hour for participants and informants and $92 per burden hour for physicians and coroner respondents, the annual cost for time is $319,965. Estimates of hourly wages are based on the U.S. Bureau of Labor Statistics May 2013 National Occupational Employment and Wage Estimates for all occupations ($16.87) and for Physicians and Surgeons ($92.25).

Table A.12.2 Annualized Cost to Respondents

Type of Respondents	Number of Respondents	Frequency of Response	Average Time (hr) per Respondents	Hourly Wage Rate	Respondent Cost
Participants	10,049	6	15/60	$17.00	$256,250
Physician (or coroner) (for CHD)	3,450	1	10/60	$92.00	$52,900
Physician (for heart failure)	1,200	1	5/60	$92.00	$9,200

Participants' next of kin	570	1	10/60	$17.00	$1,615

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

There are no other total annual costs which apply to respondents or record keepers. There are no capital costs, operating costs, or maintenance costs to report.

A.14. Annualized Cost to the Federal Government

The average annualized cost of monitoring the project by NHLBI is estimated at $204,000. This estimate is itemized in the following table.

Table A.14.1 Average Annualized Cost for Monitoring the Project

Personnel	GS Grade and Step	% Time	Cost
Contracting Specialist	11-5	0.50	$35,752
Contracting Officer	13-5	0.30	$30,574
Program Analyst	13-5	0.10	$10,191
Deputy Project Officer	12-1	0.30	$22,686
Project Officer	14-5	0.75	$90,322
Branch Chief	15-5	0.10	$14,166
Total cost			$203,691

The average annualized cost for contracts for collecting the information is estimated at $11,086,000. This is itemized in the following table.

Table A.14.1 Average Annualized Cost for Information Collection, ARIC Field and Coordinating Centers

Personnel	Equipment	Subcontracts	Other	Overhead	Total
$5,431,000	$35,000	$1,746,000	$881,000	$2,993,000	$11,086,000

The average annualized cost (contracts and monitoring by NHLBI) to the U.S. Government for information collection is $11,290,000 per year.

A.15. Explanation for Program Changes or Adjustments

During the last OMB approval period (March 1, 2011 –March 31, 2014) there was a re-examination of cohort participants by clinical exam in 2011-2013 and follow-up contacts occurred twice yearly. This revision does not include a clinical exam and thus represents a decrease in the burden, but does request continued cohort follow-up in the form of telephone calls and continued morbidity and mortality surveillance of the ARIC Cohort and ARIC Communities. Follow-up forms have been reformatted to facilitate automated administration in the data management system.

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

The ARIC staff will collect the information after obtaining OMB approval. The Coordinating Center staff will the 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 operated properly. The following timetable for data collection and analysis, in terms of time elapsed following OMB approval, is presented in **Table A.16.1**.

Table A.16.1. Time Schedule for Cohort Follow up and Surveillance

Activity	Time elapsed after OMB approval	
	Start	*Finish*
Data Collection	0 month	36 months
Analysis	18 months	60 months
Publication and Secondary Additional Analysis	24 months	60 + months

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 1,107 manuscripts using ARIC data have been published (**Attachment 7**) 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 5

- 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.
- 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 which predict atherosclerosis and cardiovascular diseases.

Case-control Studies of Frozen Blood Samples

- 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 cellular 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.

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

The data encompassed by this study will fully comply with all guidelines of 5 CFR 1320.8(b)(3) and no exception is requested to certification for Paperwork Reduction Act Submission.