Supporting Statement A for

The Atherosclerosis Risk in Communities Study (ARIC)

OMB Number: 0925-0281

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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. A total of four (4) examinations of the cohort occurred every three years over the period 1987-1998, and 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). In 2011, ARIC will increase 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. In addition, ARIC also conduct another clinical examination of the cohort over a 24-month period (May 2011 to April 2013).

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% person 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 next phase of the study involving re-examination of the ARIC cohort will focus on identifying risk factor associations that can help inform strategies for prevention and treatment at both the individual and population levels. The general approach will focus on long term risk factor trajectories and 25-year cardiovascular disease (CVD) prediction. Specific focus will be made on the occurrence, progression, and outcomes of clinical and subclinical heart failure, an increasing public health problem. The introduction of echocardiographic imaging and pulse wave velocity into the ARIC clinical examination is expected to result in the discovery 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 help understand 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.

The ARIC study has recently received the OMB approval on April 1, 2010 for continuation of annual follow-up telephone calls and ARIC surveillance activities through April 30, 2013. The following 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. 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.

This request for OMB approval will cover the following components that were added to the ARIC study through the recent contract extension for the next three years:

1. Re-examination of the surviving ARIC cohort (anticipated n = 8,220) in 2011-2013 for the following purposes: (a) characterize heart failure stages using echocardiography; (b) identify risk factors for ventricular dysfunction and vascular stiffness; (c) describe changes in pulmonary function; and (d) update risk factor status, medication use, and other relevant outcomes since their last examination in 1996-1998.
2. Continue telephone follow-up of the ARIC cohort, increasing the frequency of calls to twice a year, 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.

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
1998-1999	Analysis
1999-2010	Continued annual follow-up for morbidity and mortality
1999-2014	Analyses
2011-2014	Repeat visit Clinic examination 5 (Visit 5), continued follow-up (semiannual)
	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

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 nine times by OMB over the past twenty-four years. ARIC has recently requested and received OMB approval for continuation of annual follow-up telephone calls and ARIC surveillance activities through April 30, 2013. 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.

This request is seeking OMB approval for the activities related to: 1) another clinical examination (Visit 5) among surviving cohort participants (anticipated n = 8,220) in 2011-2013, and 2) increase in the frequency of follow-up calls (once to twice a year) to identify new cardiovascular events, update information about CVD risk factors, and obtain data on access to and use of medical care for heart failure risk factors and heart failure. These changes will be included in the ARIC study through the recent ARIC contract renewal.

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 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 91.0 percent of eligible participants for the contact year 21 (Table B.1.c.3 in Supporting Statement B).

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.

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 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 (see summary, **Attachment 1**). In December 2008, the ARIC Observational Studies Monitoring Board (OSMB) endorsed the continuation of the ARIC study with another clinical examination with a focus on heart failure. The members of the NHLBI Board of External Experts (BEE) and NHLBI Advisory Council also discussed future studies and provided an endorsement to continue the study with this participant cohort

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, much more needs to be learned about risk factors and disease progression. Atherosclerosis, or the hardening and narrowing of the arteries, is considered the primary abnormal condition that leads to heart attacks and strokes. Heart failure results from coronary atherosclerosis, hypertension, and other processes. However, the development and progression of atherosclerosis are not well understood

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

in the general population. ARIC will study subclinical heart failure by means of the echocardiogram. The study will examine a large number of new factors potentially related to the atherosclerotic and heart failure processes. Thus, ARIC fulfills a major research need to understand completely the determinants of cardiovascular disease and death.

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 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. As stated previously 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. 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 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 the opportunity to provide novel information about heart failure occurrence risk factors, and outcomes in the general population. Furthermore, ARIC has 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 650 publications (**Attachment 2**), 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 and stroke in apparently healthy individuals.

The ARIC contract renewal involves a 2-year clinical examination (Visit 5) of the cohort and increase the telephone follow-up of the cohort (from annual to semiannual) to obtain more reliable information on clinical events and outcomes measures. The study will generate information on epidemiologic profile of heart failure in the communities, basic mechanism of heart failure development, and quality and outcomes of medical care for patients with heart failure and heart failure risk factors. The findings from the study will be published in peer reviewed journals and presented at scientific conferences to advance CVD research. The information will be used by federal and state agencies for CVD prevention programs and policy making. The results will also be incorporated into national clinical practice guidelines to improve medical care for patients with heart failure and heart failure risk factors.

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. Data from the examination component of ARIC are keyed directly as the interview is being administered to the participant or measurements are taken. 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 tests the consistency and generality of the findings.

b. ARIC investigates the relationship of blood lipid, lipoprotein, coagulation, 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) 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 diversities, 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 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 study assesses trend 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. After completion of the fourth examination in 1999, annual interviews were continued 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 ARIC cohort participants have not received a physical examination since the Visit 4 (1996-1998). Another exam in ARIC provides opportunities to phenotype heart failure stages using echocardiogram and novel biomarkers, and update crucial missing pieces on heart failure risk factors (e.g., dyslipidemia, hypertension, diabetes, renal insufficiency, and obesity). With risk factor and biomarker data from the previous examinations, ARIC will be able to study how the entire trajectory of mid-life to old-age risk factors and their control affects development and progression of ventricular dysfunction and vascular stiffness.

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 will be 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 would allow identification of a broad spectrum of determinants for CVD prevention and control. Semiannual phone calls will improve the reliability and accuracy of self-reported information from the aging cohort, and ensure the unbiased 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

On October 12, 2010, page 62544, the **Federal Register** published NHLBI's notice, wherein public and affected agencies' comments were solicited. No comments were received during the 60 day period.

Recent approval of the ARIC contract renewal involving a 2-year clinical examination was given by the NHLBI Advisory Council in June 2009. The NHLBI Advisory Council is 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. In December 2008, the Board endorsed the extension of ARIC with another clinical examination with a focus on heart failure (**Attachment 3**). The members of this committee are:

C. Morton Hawkins, ScD, Professor Emeritus: Policy Board Chair (920-206-7084)
Cashell Jaquish, PhD, NHLBI, Executive Secretary (301-435-0447)
Robert J. Goldberg, Ph.D., University of Massachusetts Medical School (508-856-3991)
Karen L. Kaplan, M.D., Sinai Hospital, Elmhurst, NY (212-452-2386)
Jose Ordovas, PhD, Tufts University (617-556-3102)
Veronique Roger, MPH, MD, Mayo Clinic: Dept. of Internal Medicine (507-284-0519)
Jerome Rotter, MD, Director, Division of Medical Genetics, Cedars-Sinai Medical Center (310-423-6467)
Jeremiah Stamler, M.D., Professor Emeritus, Northwestern University Medical School (312-908-7914)
Marvin C. Ziskin, M.D., Professor of Radiology/Medical Physics, Temple University Medical School (215-707-4259)

The details of ARIC design and data collection are developed within several committees that began meeting in September 1985 and continue to meet as needed. Committees that continue to meet regularly are the Steering Committee, Executive Committee, Annual Follow-up Committee, Laboratory Committee, Surveillance Committee, Morbidity and Mortality Classification Committee, Heart Failure Committee, Quality Control Committee, and Publications Committee. These ARIC committees are currently composed of the following persons:

David Aguilar, MD, Baylor College of Medicine (713-798-2545)
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)
Aurelian Bidulescu, MD, MPH University of North Carolina (919-966-3168)
Eric Boerwinkle, PhD, University of Texas (713-500-9816)
Ebony Boulware, Johns Hopkins University (413-287-2582)

Diane Catellier, DrPH, University of North Carolina (919-966-1895)
Patricia Chang, MD, University of North Carolina (919-843-5214)
Lloyd E. Chambless, PhD, University of North Carolina (919-962-3264)
Barbara Cochran, University of Texas, (713-500-9833)
Josef Coresh, MD, Johns Hopkins University (410-955-0495)
David Couper, PhD, University of North Carolina (919-962-3229)
Richard Crow, MD, University of Minnesota (612-626-9678)
Pat Crowley, Johns Hopkins University (301-791-1847)
Jing-fei Dong, Baylor College of Medicine (713-798-5888)
Aaron Folsom, MD, MPH, University of Minnesota (612-626-8862)
Ervin Fox, MD, University of Mississippi Medical Center (601-984-2250)
Sherita Golden, Johns Hopkins University (601-984-2250)
Gerardo Heiss, MD, University of North Carolina (919-962-3253)
Ron Hoogeveen, PhD, University of Texas (713-798-3407)
Cheryl Jennings, Contracting Officer, NHLBI (301-435-0347)
Laura Loehr, University of North Carolina (919-966-1937)
Stephanie London, MD, MPH, NIEHS (919-541-5772)
Maria Mirabelli, PhD, Wake Forest University (336-716-1112)
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)
Jennifer Nettleton, University of Texas (713-500-9467)
Hanyu Ni, NHLBI (301-435-0448)
Mona Pandey, National Institute of Health (NHLBI) (301-435-0349)
Jim Pankow, PhD, University of Minnesota (612-624-2883)
Dee Posey, Wake Forest University (336-716-6667)
Naresh Punjabi, MD, PhD, Johns Hopkins University (410-550-5405)
Charlie Rhodes, Baylor College of Medicine (713-790-4351)
Wayne Rosamond, PhD, University of North Carolina (919-962-3230)
Stuart Russell, MD, Johns Hopkins University (410-955-5708)
Eyal Shahar, MD, University of Minnesota (612-624-8231)
Richey Sharrett, MD, DrPH Johns Hopkins University (443-287-6178)
Paul Sorlie, PhD, National Institute of Health (NHLBI) (301-435-0456)
Lyn Steffen, PhD, MPH, University of Minnesota (612-625-9307)
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)
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 have provided consultation in the development of the study design and protocol for new procedures at the next examination:

Pulmonary Function:

Paul L. Enright, M.D. (520-844-7587)
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Graham Barr, M.D., DrPH (212-305-4895)
Columbia University Medical Center - PH 9 East
630 W. 168th Street, Room 105
New York, New York 10032

A.9. Explanation of Any Payment or Gift to Respondents

As approved by OMB for prior examinations (Visits 1-4), ARIC will compensate participants for transportation expenses incurred and time involved in coming to the Visit 5 clinic examination. This compensation is being done because a) the participant is informed that there will be no financial cost for participation in the study, b) lack of transportation can be an impediment to clinic participation, and c) to ensure a high participation rate and therefore valid results. The amount of compensation was arrived at by careful consideration of the study participant requirements at each field center and is standardized across study sites and participants for equity. The compensation for transportation covers parking, gas reimbursement for average mileage driven or public transportation costs, and payment of taxi cost. Reimbursement for time is through gift cards or checks.

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 4**).

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 5)**

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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. This 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 a Novell Local Area Network (LAN). 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 6**). 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

ARIC Visit 5 will collect information which is sensitive. This information and a justification for inclusion in this study are as follows:

Social Security Number (SSN) is required for identifying deaths in the cohort using the National Death Index of the National Center for Health Statistics. The SSN is the key identifier in linkage. During the reception portion of the visit, the participant is asked to verify previously collected identifying information which is displayed on a computer monitor. SSN is one of the items of identifying information. All but 25 individuals have provided their SSN during a prior visit. If the SSN is missing, the interviewer requests it from the participant.

Alcohol consumption will be determined to allow assessment of patterns of alcohol consumption over 25 years. Several studies have suggested that moderate levels of alcohol use may be protective for CHD.

Annual household income is included as a valid and parsimonious indicator of socioeconomic status. Extensive epidemiologic evidence has related socioeconomic status to cardiovascular morbidity and mortality. Given the heterogeneity of the ARIC population, an

assessment of current socioeconomic status is required if an accurate evaluation of the importance of biological risk factors for disease is to be achieved.

Current medication use will be determined since most blood chemistry values are modified by pharmacologically active drugs. Thus, knowledge of the use of prescription as well as over-the-counter medications is required to interpret the blood chemistry values.

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

The estimates of respondent burden is presented in the table below covers the 3-year period beginning with the Cohort examination (Visit 5) from 5/1/2011 – 4/31/2014. Time estimates are based on the experience of prior examinations or follow-up phone calls and preliminary testing of new questionnaires or procedures.

Estimate of Respondent Burden, Year 2011-2014

Type of Respondents	Number of Respondents	Frequency of Response	Time per Response (minutes)	Burden (hours)
Participant[¥]				
a. Recruitment	10,933	1	11.35	2068
b. Telephone contact to set up and confirm appointment	8,220*	2	5	1370
c. Clinic examination (**Attachment 7**)	6,836*	1	330	37598
d. Home or nursing home visit (**Attachment 7**)	1,334*	1	145	3,224
e. Biennial phone follow-up interview (**Attachment 8**)	10,933	6	15	16,400
Subtotal (participant)	---	-	-	**60,660**
Non-Participant				
f. Physician contact for CHD deaths (**Attachment 9**)	690	1	10	115
g. Coroner contact for CHD deaths (**Attachment 9**)	570	1	10	95
h. Informant contact (**Attachment 9**)	1200	1	10	200
i. Physician contact for out-of-hospital heart failure (**Attachment 9**)	2760	1	5	230
Subtotal (non-participant)	**5,220**	-	-	**640**
Total	**16,153**	-	-	**61,300**

[¥] See **Table A.12.3** for detailed breakdown of individual assessments.
* Participants included in item a.

The annual estimates of respondent burden are presented in **Table A.12.1**.

Table A.12.1 Estimates of Hour Burden

Type of Respondents	Number of Respondents	Frequency of Response	Average Time (hr) per Response	Annual Hour Burden
Participants	10933	3	0.6165	2022~~10~~
Physician (or coroner) (for CHD)	420	1	0.1667	70
Physician (for heart failure)	920	1	0.0833	76.6
Participants' next of kin	400	1	0.1667	66.7
Totals	12673			2043~~43~~

(Note: reported and calculated numbers differ slightly due to rounding.)

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 $75.00 per burden hour for physicians and coroner respondents, the annual cost for time is $355, 882.

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	10933	3	0.6165	$17.00	$343,749.92
Physician (or coroner) (for CHD)	420	1	0.1667	$75.00	$5251.05
Physician (for heart failure)	920	1	0.0833	$75.00	$5747.70
Participants' next of kin	400	1	0.1667	$17.00	$1133.56
Totals	12673	2.725	0.591	----	$355,882.23

Table A.12.3. Estimates of Administration Time Burden for Procedures and Questionnaires for the Cohort Examination (Visit 5)

Exam Component, home or nursing home visit specification (H)	Estimated time (minutes)
Fasting Block	**72**
Reception, informed consent, change clothes, urine specimen (H)	25
Anthropometry (H – height and weight only)	05
12-lead ECG	20
Seated Blood Pressure (H)	12
Phlebotomy (H)	10
Snack (H)	**10**
Procedures, sequence A	**80**
Ankle-brachial index (ABI)	20
Pulse wave velocity	30
Lung function	30
Blocks of interviews, sequence A	**28**
Dietary intake	20
Medication & Supplement use (H)	08
Procedures, sequence B	**75**
Echocardiography (H)	50
Physical function	15
Change clothes (H)	10
Blocks of interviews, sequence B	**55**
Access and quality of care	10
Anxiety questions derived from the Patient-Reported Outcomes Measurement Information System (PROMIS)	06
Minnesota Living with Heart Failure Questionnaire	06
Medical history (H)	05
Physical ability	06
Physical activity	08
Personal history	04
Respiratory history	05
SF-12 Health Status	05
Visit Termination	**10**
Exit interview (H)	10
Total Examination Time (Home Visit, n=1334)	**145**
Total Examination Time (Clinic Visit, n =6836)	**330**

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 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

During the last OMB approval period (April 1, 2010 - April 30, 2013) there was continued morbidity and mortality surveillance of the ARIC Cohort and ARIC Communities, and there was continued Cohort Follow-up in the form of annual telephone calls. A revision to the previous OMB submission is requested because (1) the Cohort will be re-examined over a two-year period, 2011-2013, and (2) the Cohort follow-up phone contacts will occur biennially rather than annually).

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 Visit 5, Cohort Follow up and Surveillance

Activity	Time elapsed after OMB approval	
	Start	*Finish*
Participant contact and appointment scheduling	1 week	26 months
Data Collection (Exams)	1 month	25 months
Primary 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 650 manuscripts using ARIC data have been published (**Attachment 2**) and over 900 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.
- 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 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.

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.