Request for OMB Approval for

the Multi-Ethnic Study of Atherosclerosis (MESA)

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Table of Contents.....Page

Attachment 1

Minutes from Recent Outside Consultant Meetings

Working Group on Future Research Opportunities in the Multi-Ethnic Study of Atherosclerosis (MESA).....D

National Heart, Lung, and Blood Advisory Council meeting, June 2007.....E

Attachment 2

IRB Approvals

Attachment 3

Data Collection

Physician Questionnaire: Cardiac/PVD.....A

Physician Questionnaire: Cardiovascular Death.....B

Informant Interview.....C

Physician Questionnaire: Stroke/TIA……...……D

Letters

E.2.1 Hospital Release

E.2.2 Cover letter to Hospitals

E.2.3 Physician /Clinic Record Release form

E.2.4 Cover Letter to Physician/Clinic

E.2.5 Cover Letter to Next of Kin

E.2.6 Medical Examiner Record

E.2.7 Cover Letter to Medical Examiner

E.2.8 PQ Cover Letter to Physician

E.2.9 PQ Cover Letter to Attending Physician of Decedent

E.2.10 PQ Cover Letter to Medical Clinic

E.2.11 Letter to Informant/ Next of Kin Known Telephone Number

E.2.12 Letter to Informant/ Next of Kin Unknown Telephone Number

E.2.13 Reply Postcard from Informant/ Next of Kin

E.2.14 Letter to Neighbor of Decedent

E.2.15 Reply Postcard from Neighbor of Decedent

Attachment 4

Bibliography of MESA Publications

Attachment 5

Project Time Schedule

Attachment 6

Individuals Consulted on Statistical Aspects

Individuals Collecting and/or Analyzing Data

Summary of the Multi-Ethnic Study of Atherosclerosis Study (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and risk factors that predict progression to clinically overt cardiovascular disease and that predict progression of subclinical disease itself, in a population-based sample of 6,800 men and women aged 45-84 that is 38 percent white, 28 percent African-American, 22 percent Hispanic, and 12 percent Asian, of Chinese descent. The cohort was recruited from six Field Centers and characterized with respect to coronary calcification using computed tomography, ventricular mass and function using magnetic resonance imaging, flow-mediated endothelial vasodilatation, carotid intimal-medial wall thickness and distensibility using ultrasound, lower extremity vascular insufficiency using the ankle-brachial blood pressure index, electrocardiographic measures, standard coronary risk factors, sociodemographic factors, lifestyle factors, and psychosocial factors. Blood samples are assayed for putative biochemical risk factors and stored for case-control studies. DNA has been extracted and lymphocytes will be immortalized for study of candidate genes and genome-wide scanning. Selected repetition of subclinical disease measures and risk factors allows study of the progression of disease. Participants will be followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; mortality; and for cardiovascular disease interventions.

A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary

Approximately 12.2 million Americans are estimated to have coronary heart disease (CHD), approximately 4.4 million have had a stroke, and approximately 4.6 million have congestive heart failure. Cardiovascular disease (CVD) is responsible for approximately 950,000 deaths in the United States per year. Nearly all CVD that eventually manifests clinically begins as subclinical disease. As part of its events surveillance, the Multi-Ethnic Study of Atherosclerosis (MESA) is collecting information on cardiovascular events (myocardial infarction, angina, congestive heart failure, peripheral vascular disease, stroke, and transient ischemic attack), and is

adjudicating participants' deaths to determine if these are cardiovascular in nature. MESA will further understanding of the pathogenesis of CVD by (1) characterizing cardiovascular disease before it has become clinically manifest and, therefore, subject to interventions that disrupt study of the natural history and (2) optimizing the study of progression of subclinical disease. During the MESA clinical examinations under clinical exemption (CE-99-11-08), participants were evaluated for the presence and extent of subclinical disease through use of several non-invasive procedures used for the first time in a study of this size or in combination with each other. These procedures include computed tomography for determination of coronary calcium, cardiac magnetic resonance imaging to determine left-ventricular mass and other measures of cardiac structure and function, use of B-mode carotid ultrasound for measurement of intima-media thickness of the carotid arteries and plaque resolution, flow-dependent brachial artery vasodilation, and arterial wave forms to measure compliance of arteries. The proposed data collection for MESA Event Surveillance will continue to provide information on the number and specific types of CVD and other morbid events that occur in the cohort that has been clinically well-characterized with respect to putative and established risk factors and subclinical disease. The relationship between these measurements and subsequent clinical outcomes is a cornerstone of observational epidemiologic research, providing information on prediction of clinical disease.

The objectives of this study are clearly within the National Heart, Lung, and Blood Institute (NHLBI)'s mandate, and the Institute is uniquely capable of coordinating this complex study. 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." MESA proposes to continue to collect data that will impact the knowledge of the epidemiology, etiology and prevention of cardiovascular disease through the measurement of subclinical cardiovascular disease and newly-defined risk factors. The results of this study are particularly important as they will increase understanding of this disease in several ethnic groups. MESA developed its sampling design and methodology to include data collection from individuals of four different ethnicities: Caucasian (38% of cohort), African-American (28%), Hispanic (23%), and Asian-

American (Chinese) (11%). Inclusion of these groups will allow study results to be generalized to populations other than white Americans and to investigate more thoroughly cardiovascular disease and its precursors in these previously under-studied groups. While it is clear that smoking, diabetes, hypertension, obesity, hyperlipidemia, low socioeconomic status and psychosocial stress are detrimental in all groups, the distributions of several risk factors and, arguably, their associations with disease differ among groups. While some of these differences may be biological, evidence of true biological differences in disease pathogenesis among racial/ethnic groups is limited. Differences in environmental, behavioral and psychosocial conditions have been inadequately examined in relationship to subclinical disease and its progression to clinical events.

A.2 Purpose and Use of the Information

MESA will provide important new information about the pathophysiology of subclinical disease development and progression and its role in clinical cardiovascular disease. The study has the potential to identify new risk factors and, therefore, increase the ability to predict cardiovascular disease and, ultimately, to design new interventions to prevent cardiovascular disease. The ethnic diversity of the cohort is a major strength of the study, allowing comparisons that may provide unique insights about new risk factors and subclinical disease and allowing the possibility of ethnic-specific preventive strategies to be explored.

It is the mandate of the NHLBI to bring the knowledge of new risk factors to the attention of health professionals and the public. As new information regarding subclinical cardiovascular disease is revealed, it will be disseminated by publication of results in appropriate scientific journals (e.g., *New England Journal of Medicine*, *Journal of the American Medical Association*, *Circulation*, and *Stroke*). In addition, presentations at scientific meetings (e.g., American Heart Association, American College of Cardiology, American Public Health Association) will be made to provide data quickly to other investigators and to stimulate discussion. After full scientific evaluation, results may be incorporated into policy recommendations by the NHLBI using public education and prevention programs. NHLBI-sponsored studies have excellent records for publication of manuscripts in well-respected scientific journals. For example, since their respective inceptions the Cardiovascular Health Study (CHS) has published over 500

manuscripts and the Atherosclerosis Risk on Communities (ARIC) has published nearly 600 manuscripts in peer-reviewed journals. MESA has published 93 manuscripts to date.

A.3 Use of Information Technology and Burden Reduction

MESA uses a number of state-of-the-art applications of information technology to reduce burden on proxies/informants and physicians and help ensure accuracy throughout collection and processing of the data. These include: 1) use of a scanning software to increase accuracy; 2) local printing of forms to include automatic coding of the participant ID on each page of every form to ensure that data are scanned into the database accurately; 3) use of sophisticated tracking systems to reduce duplication of effort and assure that technicians have necessary available information on hand when contacting a proxy; 4) use of direct data entry systems and computer-assisted programs for data collection of surveillance and events information; 5) use of internet transmission of data from the Field Centers to the Coordinating Center for increased ease and speed; and 6) development and maintenance of a web site to increase communication among MESA investigators as well as to keep the public informed of events and results of the study in a timely manner. As technology develops, new applications to improve efficiency for the study will be evaluated for incorporation into study procedures. MESA, including its event surveillance, will be a model study for demonstrating many of the efficiencies that modern technology can provide to multi-site research studies.

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

MESA is the only longitudinal epidemiologic study to focus on progression of subclinical cardiovascular disease in four different ethnicities using the selected imaging modalities, lab tests and other procedures. Several non-invasive high technology procedures are being used for the first time in a cohort of this size. Many other hypotheses, for example involving psychosocial risk factors, will be used to assess specific concepts that may help differentiate rates of disease by race/ethnicity. Other more traditional risk factors, such as elevated blood pressure and dyslipidemias, will be used to investigate their impact on subclinical disease prior to the onset on clinical symptoms. Combined, these characteristics make MESA a unique study utilizing innovative methodology and procedures.

MESA has incorporated information learned from other major cardiovascular studies to develop the events surveillance techniques to be utilized here. Many of the Principal Investigators and sites were/are active members of other large-scale epidemiologic studies funded by NHLBI and other agencies of NIH. Many of the events criteria and questionnaires to be applied to the goals of MESA are those previously tested and used in other major studies. Thus, rather than be sources of duplication, results from these other studies have been used to design and enhance the MESA protocol. Of greatest influence to MESA have been the following studies: Framingham Heart Study (0925-0216, expiration 12/31/07); Atherosclerosis Risk in Communities (ARIC) (0925-0281, expiration 05/31/2010); the Cardiovascular Health Study (CHS) (0925-0334, expiration 09/30/07); CARDIA (CE 94-10-01); Systolic Hypertension in the Elderly (SHEP) (CE 85-03-02); and the grant-funded studies Family and Genetic Study of Cardiovascular Disease and the Insulin Resistance Atherosclerosis Study (IRAS). Use of established procedures helps ensure standardization of data and allows comparisons of results across studies.

A.5 Impact on Small Businesses or Other Small Entities

Physicians constitute the only small businesses burdened by MESA. They are requested to provide medical information on patients identified by the study as having died or experienced non-hospitalized cardiovascular events. Limited information is requested from these physicians' offices, primarily to gather information on symptoms, procedures and tests, and medications involved so that incident disease may be classified. Questionnaires, modeled after those used successfully in the Cardiovascular Health Study (CHS: 0925-0334, expiration 09/30/07), have been utilized to gather this information. Providing the requested information is estimated to take ten minutes or less. While these questionnaires are mailed to physicians' offices, they are allowed the option to respond by telephone or to send office notes in lieu of returning the completed questionnaire.

A.6 Consequences of Collecting the Information Less Frequently

Data collection relevant to this request includes follow-up contacts with proxies or informants and with physicians. Four clinical examinations of MESA participants took place in the study over 7 years, between 18-24 months apart, through April 2007. Contacts with participants continue to be made at intervals of 9-12 months. At these phone contacts, participants are asked

to identify any hospitalizations or procedures/diagnoses of interest to the study they may have experienced/received since their last MESA contact. On occasion, a proxy will be asked to provide this information.

Proxy contacts will also occasionally be necessary to ascertain information on all potential CVD events, in cases where the participant is unable or unavailable to provide information about circumstances surrounding events. Physicians are contacted in cases where the participant was not hospitalized for a potential CVD event. Contacts will only occur when a potential CVD event has occurred. Less frequent contact would compromise the quality of the data collection, as it becomes more difficult to identify and contact informants and physicians, and recall of events becomes less accurate with time.

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

The MESA Event Surveillance protocol 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 agency's 60-day notice in the Federal Register soliciting comments on the information of this submission was published on 08/21/07, comments due by Oct 20, 2007. No comments have been received.

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A Special Emphasis Panel (SEP) was convened on September 5-6, 1995 on Longitudinal Cohort Studies that recommended further observational studies of subclinical CVD. Another SEP was convened on June 28, 1996 on Use of Cardiac EBCT and MRI in Epidemiologic Studies of Cardiovascular Disease that recommended methods for further utilization of these technologies. These recommendations led to the Request for Proposal for the Subclinical Cardiovascular Disease Study, which was later renamed MESA. The Request for Proposals was presented to the National Heart, Lung, and Blood Advisory Council in May 1997. A Working Group on Future Research Opportunities in the Multi-Ethnic Study of Atherosclerosis (MESA) was convened on

March 5, 2007, that identified as highest priority continued follow-up of the cohort for surveillance for clinical CVD events to better understand progression and predictive value of subclinical disease and other measures. Most recently, the initiative to renew the MESA contracts was proposed to the NHLBI Board of Extramural Experts and the Request for Proposals was presented to the National Heart, Lung, and Blood Advisory Council, both in June 2007. Summaries from the 2007 Working Group and NHLBI Council meetings are included in Attachment 1. Since the study's inception, an Observational Studies Monitoring Board has been convened annually.

A.9 Explanation of Any Payment or Gift to Respondents

Respondents are not paid for their participation.

A.10 Assurance of Confidentiality Provided to Respondents

Confidentiality of information obtained is maintained in several ways. These include certification of each site's Institutional Review Board (IRB), written assurance provided in the informed consents, the NHLBI Certificate of Confidentiality, and procedures used at the sites and Coordinating Center to maintain security. Each of these is briefly described below.

A.10.1 IRB Certification

All MESA contracts stipulate that research involving human subjects must be submitted for annual review with a properly completed certification of IRB approval of the protocol in accordance with 45 CFR 46. A copy of the most recent certification from each contract is included in Attachment 2.

A.10.2 Informed Consent

The consent form signed by the MESA participant provides written assurance that all individual data collected in the study are kept confidential to the extent provided by the Privacy Act of 1974. Each Field Center maintaining data with personal identifiers secures files so that confidential data are not released. Specifically, participants are informed that: (1) only members of the research team know that they are research participants and, if permission is granted by the participant, the participant's physician or health care provider; (2) no information about them

will be disclosed to others without their written permission, except if required by law; and (3) when the results of the study are published or discussed in conferences, no information will be included that would reveal their identity.

A.10.3 Certificate of Confidentiality

On behalf of all investigators involved in MESA, the Coordinating Center has received a Certificate of Confidentiality from the NHLBI to provide protection from release of data requested under subpoena to the fullest extent of the law. Reference to this certificate has been made in the informed consent for participants.

A.10.4 Data Security

All Field Center consent forms include information for the participant about the Health Insurance Portability and Accountability Act (HIPAA), which addresses rules for sharing of health information. All Centers follow local HIPAA guidelines.

At the Coordinating Center, MESA participant data is stored without identifiers such as name or social security number (SSN) and identified only by a unique study number on a secure firewall and password protected server running an SQL Server 7.0 database. The database containing the study participant's SSN, name and MESA study number is similarly protected on a computer that is not accessible by the internet. In addition, the SSN and name is encrypted using 128-bit encryption. This separate database that matches the study number to a subject is only available to authorized Coordinating Center staff. Each Field Center has available to them on site a similar database that identifies only their own subjects for tracking and update purposes. Only staff members properly trained in issues of privacy and confidentiality are allowed access to identifying data. This is limited to two individuals at the Coordinating Center. All databases require a user name and password for access. Data for ultimate distribution and analyses do not include any identifiers.

All data or requests for information sent over the internet use only the participant's study ID number and are encrypted with 128-bit encryption and password protected. When the study must request information from the National Death Index or the Health Care Financing

Administration that utilizes the SSN, that request is also encrypted using 128-bit encryption and a password protection process. These requests are not associated with any medical data but only include required information for the requested search.

A.11 Justification for Sensitive Questions

During investigation of morbid and mortal events during MESA Event Surveillance, requests for answers to sensitive questions are often asked. Respondents are assured that all responses are voluntary and there are no consequences involved with refusing to answer any specific question. All staff interacting with proxies and informants are trained in interviewing techniques involving sensitive questions and reiterate to respondents the voluntary nature of the data collection. Many of the questions utilized in MESA Event Surveillance have been taken from other OMB-cleared studies or validated in the literature (see individual forms and questions in Attachment 3).

An Informant Interview for Cardiovascular Disease Deaths form is administered to a contact designated earlier by the participant as someone likely to be knowledgeable of details regarding the participant's health. The information collected in this form is critical in determining whether or not a death was due to cardiovascular causes. While it may seem that these questions may have the potential to exacerbate grief, the interviews have been well accepted in other studies that have previously used them, such as ARIC and CHS. All staff doing these interviews are trained in methods of handling grief and providing consolation, and no interview is held prior to one month following the death.

Occasionally, surveillance questions or questions regarding circumstances leading up to a morbid event are asked of a proxy designated earlier by the participant to provide information on his/her health when he/she is unable to. It is estimated these interviews take no longer than 15 minutes.

A.12 Estimates of Hour Burden Including Annualized Hourly Costs

A.12.1 Respondent Burden

Respondent burden has been calculated utilizing number of projected responses and time per response. All time estimates were done from actual use of these procedures in MESA. The estimate for the next three years of MESA data collection is presented below.

Estimates of Hour Burden				
Type of Respondent	**Number of Respondents**	**Frequency of Response**	**Average Time per Response (Hours)**	***Annual Hour Burden**
Physicians	250	1	0.20	16.7
Proxies	300	1	0.20	20
Total	550	1	0.20	36.7

* Divided over a three year period

Event rates and estimated contacts for each type of disease outcome were calculated based on MESA's events surveillance to date.

A.12.2 Annualized Cost to Respondents

Annualized Cost to Respondents				
Type of Respondents	**Number of Respondents**	**Frequency of Response**	**Hourly Wage Rate**	**Annual Respondent Cost**
Physicians	250	1	$75.00	$1,253
Proxies	300	1	$18.65	$373
	550			$1,626

The annualized cost to the physicians and proxies consists only of the cost of their time. To estimate cost to those agreeing to provide physician or proxy information to the study, wage rates

from the 2000 U.S. Census and information accessed on the American Medical Association website (www.ama-assn.org) were used.

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

There are no operating, maintenance, or capital costs to respondents.

A.14 Annualized Cost to the Federal Government

The average annualized cost to the U.S. Government for the information collection in the proposed period of MESA Events Surveillance study is $216 thousand. This includes all Field and the Coordinating Center. The annualized cost of monitoring the project by the NHLBI is estimated at $298 thousand.

A.15 Explanation for Program Changes or Adjustments

MESA Event Surveillance is an ongoing collection of information. No substantial program changes have been made since the 2004 Supporting Statement submission. The estimated number of respondents has been adjusted slightly from the previous submission based upon actual experience in the study to date. The annualized cost to respondents has been adjusted upward based upon more realistic current hourly wage rate estimates. Average annualized costs to the U.S. government have been adjusted to reflect inflation.

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

The ultimate goals of MESA are to provide data on subclinical CVD and its progression to the scientific community and to provide data for developing policy recommendations for cardiovascular disease prevention. To achieve these goals, the MESA Publication and

Presentations Subcommittee was established to develop policy, promote preparation of manuscripts and presentations, and to monitor quality and timeliness of the results. This subcommittee also recommends to the Steering Committee directions for publications and presentations. A bibliography of MESA papers published to date appears in Attachment 4.

Use of morbidity and mortality data have only recently become feasible because sufficient numbers have been collected to provide adequate statistical power to address some research questions of interest. Event rates are compared between groups using Kaplan-Meier plots for unadjusted data. Cox proportional hazards models are used to assess strength and independence of risk factors for CHD and stroke outcomes as well as assessment of subclinical disease.

A timeline for implementation of the various MESA components utilizing data solicited from non-participants are provided as Attachment 5. The schedule of data collection, analyses and publication activity time based on number of months after the first OMB approval is presented below:

Project Time Schedule	
Activity	**Time Schedule**
Collection of events data from physicians and proxies	Beginning 1-2 months after initial OMB approval
Events data analyses for publication	Beginning 5 years after initial OMB approval
Submission of publications to journals	Beginning 6 years after initial OMB approval

Note that publication of analyses of events data did not occur until a sufficient number of events had accrued. This was not expected to occur until approximately 5 years into data collection. Thus, no published analyses of these data were expected during the first period of OMB clearance. Published analyses have begun during the current period of OMB clearance and are expected to continue during the proposed period of OMB clearance.

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

According to 5 CFR 1320.8(b)(1), the expiration date will be displayed.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submissions," of OMB Form 83-1.