Supporting Statement A

for

The Framingham Heart Study (FHS) NHLBI 0925-0216

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The Framingham Study

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Supporting Statement

A. Justification

This long-term, multigenerational study is designed to identify genetic and environmental factors influencing the development of cardiovascular and other diseases. The project examines the incidence and prevalence of cardiovascular disease (CVD) and its risk factors, trends in CVD incidence and its risk factors over time, and family patterns of CVD and risk factors. Other objectives include the estimation of incidence rates of disease, a description of the natural history of CVD, including the sequence of clinical signs and systems that precede the clinically recognizable syndrome, and the consequences and course of clinically manifest disease.

A.1. Circumstances Making the Collection of Information Necessary

The objective of this information collection is within the National Heart, Lung, and Blood Institute (NHLBI) mandate described in the Public Health Service Act, Section 421 (42 USC 285b-3) and specifies the 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."

Cardiovascular disease is a major public health concern because it is the leading cause of death and a major source of illness and disability. It has an adverse effect on the quality of life of patients and their families. Cardiovascular disease is the underlying cause of death for 32% of all deaths in the U.S. Other measures of the public health importance of cardiovascular disease are the major burdens it imposes on health care personnel, medical institutions and resources. One of the roles of the NHLBI, Division of Cardiovascular Sciences (DCVS) is to plan and direct epidemiological studies and projects for disease prevention and health

promotion in heart diseases. The Framingham Study is one of many ongoing studies that help to fulfill that role and address the public health concerns described above.

Despite substantial progress in understanding of pathological precursors of cardiovascular disease, there still exists a compelling need to utilize the prospective epidemiological design to improve methods of identifying the high risk individual at the youngest possible age. Over the last six decades, the Framingham Study has made major contributions to the knowledge and utility of cardiovascular disease risk factors. Beginning with the first paper in the 1950s that identified serum cholesterol, cigarette smoking, blood pressure and left ventricular hypertrophy as "factors of risk," the Framingham Study has expanded the scope and nature of cardiovascular risk factors. For example, because of protocol enhancements that permitted measurement of lipoprotein cholesterol beginning in 1969 in the original cohort and in 1971 in the offspring cohort, the limited scope of total cholesterol has been expanded to a more useful lipoprotein profile that includes knowledge of LDL-C and HDL-C as well as total cholesterol. The nature of the risk factors shown to be associated with cardiovascular disease has changed as technological development has presented new opportunities to study cardiac structure with non-invasive methods. For example, after the Framingham Study protocol included echocardiography in 1979, only four years of follow-up were necessary to demonstrate a strong relationship between left ventricular mass and the incidence of cardiovascular disease. In recent years, scientific advances in genetics technology have further allowed the Framingham Study to be in the forefront of investigating how genes contribute to the development of cardiovascular risk factors and the progression to clinical diseases.

Despite the rapid increase in knowledge about the etiology of cardiovascular disease that has resulted from these studies, there remain numerous opportunities to improve the identification of

high risk individuals. Further research into the underlying variation of platelet reactivity in populations may have clinical therapeutic implications in heart and blood disorders.

To our knowledge, The Framingham Heart Study (FHS) Offspring and Omni 1 cohorts comprise the largest known population sample of platelet reactivity worldwide. Framingham was the key population sample in the largest heritability and genetic studies to date of platelet reactivity traits

There is also a need to better understand the details of the mechanisms of cardiovascular pathophysiology for two reasons: (1) because earlier, more effective treatments might result from improved knowledge of mechanisms and (2) because good information about mechanistic connections between personal behavior and disease processes may increase the likelihood of beneficial behavior changes. For example, the distribution of a web-based 24-hour dietary recall questionnaire to the Third Generation & NOS and Omni Group 2 participants at examination 3 will afford the relation of dietary intake to body weight, binge eating behavior, the built environment, and diffusion of eating behavior through the FHS social network. The resources created through this application will be available to the entire scientific community for use in many different ancillary projects. Finally, there is a need to monitor all aspects of cardiovascular status in this genetically circumscribed sample over time.

A.2. Purpose and Use of the Information

This request is for a revision; the current approval expires on 10/31/2016. The purpose of this information collection for the Framingham Study is to continue to collect medical and lifestyle information on a long-term cohort in order to pursue the objectives described above. There are five existing study cohorts funded by NHLBI contracts which comprise the Framingham Study.

- Original Cohort (originating in 1948)
- Offspring Cohort (children of Original Cohort and their spouses originating in 1971)
- Generation Three Cohort and New Offspring Spouses-NOS (Children of Offspring cohort

and some Spouses of the Offspring, Originated in 2002)

- Omni Group 1 cohort (minority residents of Framingham, under contract in 2009)
- Omni Group 2 cohort (offspring of OMNI Group 1, under contract in 2009)

During the last OMB renewal, the Framingham Study completed re-examinations of the Original Cohort (cycle 32), as well as Generation Three Cohort and Omni Group 2 (cycle 2); completed a computerized tomography (CT) examination on the subsets of the Offspring Cohort and Generation Three Cohort; conducted an examination of the Offspring Cohort (cycle 9) and Omni Group 1 Cohort (cycle 4); and continued monitoring the morbidity and mortality in all five Framingham Cohorts.

This proposal is to extend the Framingham Study to examine the Generation Three Cohort, New Offspring Spouses and Omni Group 2 Cohort, as well as to continue to monitor the morbidity and mortality which occurs in all five Framingham Cohorts. The contractor, with the collaborative assistance of NHLBI Intramural staff, will invite study participants, schedule appointments, administer examinations and testing, enter information into computer databases for editing, and prepare scientific reports of the information for publication in appropriate scientific journals. All participants have been examined previously and thus the study deals with a stable, carefully described group.

Data are collected in the form of an observational health examination involving such components as blood pressure measurements, venipuncture, electrocardiography and a health interview, including questions about lifestyles and daily living situations. The data collection instruments for re-examination of the Third Generation Cohort and New Offspring Spouses, and Omni Group 2 Cohort are attached **(Attachment 1)**.

Individuals who are either unwilling or unable to participate in an in-person examination or are between examination cycles for more than two years are sent Medical History Update Forms **(Attachment 2)**.

The National Heart, Lung, and Blood Institute uses the results of the Framingham Study to: characterize risk factors for cardiovascular and lung diseases so that national prevention programs can be designed and implemented; 2) evaluate trends in cardiovascular diseases and risk factors over time to measure the impact of overall preventive measures; and 3) understand the etiology of cardiovascular and lung diseases so that effective treatment and preventive modalities can be developed and tested. Most of the reports of study results have been published in peer reviewed medical journals and books. The majority of these publications have appeared in the cardiology or cardiovascular epidemiology literature. More than 3,000 articles have been published from the Framingham Study since 1952. Framingham Study articles published during 2014-2015 are listed in the attached file **(Attachment 3)**. The variety of titles in the listing suggests the wide range of hypotheses that have been tested using data collected at previous examination cycles. The results of Framingham Study will continue to be published in scientific and medical literature. Results which will appear in the literature will continue to be used by the medical community to improve their understanding of the mechanisms of cardiovascular diseases as they occur in a general population setting. Their understanding will help health care providers treat patients by recommending preventive measures for future disease among healthy individuals, as well as those with cardiovascular disease. This information also will be used by the Federal government and health professionals to design and target cardiovascular disease prevention and education program.

A.3. Use of Information Technology and Burden Reduction

The Framingham Study will use state-of-the-art data entry and computer management systems which maximize data accuracy. Data from anthropometric measurements, blood pressure, questionnaires, and venipuncture collection and processing will be recorded directly into data screens or, in some cases, on paper forms by clinic personnel and then key entered into the database. Electrocardiography will be collected electronically on separate, procedure-dedicated computers. There will be a new pilot project using smartphone technology to obtain information outside of the clinical assessments.

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

There is no duplication of effort because the Original Cohort, Offspring Cohort, and Third Generation Cohort, as well as the Omni Groups 1 and 2 Cohorts, are unique. No other study of free-living adults has a comparable database on the cardiovascular experience of parents and offspring. No other group of free-living adults has been so extensively tested using non-invasive cardiology methods because these methods are usually applied to symptomatic patients. No other large group of parents, children, and grandchildren has undergone longitudinal studies of risk factor quantification. Because of the dynamic features of cardiovascular diseases, it is necessary to update previous findings related to earlier examinations and assess the consequences of the collected information from prior examinations in terms of the impact on cardiovascular disease incidence. A key feature of the Framingham Study is that it is monitoring the same community-based sample over time. This will permit an assessment of secular trends in cardiovascular disease that are not likely to be biased by changes in sample composition over time.

The NHLBI supports a study titled The Atherosclerotic Risk in Communities (ARIC) Study (OMB# 0925-0281, expiration date 5/31/2017 This study, however, is different from the

Framingham Study because the ARIC Study is measuring different risk factors while using different approaches to assessing cardiovascular disease status.

Since cardiovascular disease is a dominant health problem among older populations, the NHLBI initiated the Cardiovascular Health Study (OMB# 0925-0334, expiration date 03/31/2011: note: OMB clearance is no longer required because the contract is supporting only the study's basic infrastructure, which includes no direct participant contact). This study of four elderly cohorts focuses on factors thought to induce clinically overt disease. It was designed to assess the prediction of clinical disease from non-invasive measures of preclinical disease such as carotid atherosclerosis, left ventricular impairment, and arrhythmias or transient ischemia. It also aimed to assess the associations between clinical disease and recent changes in health or life circumstances such as concurrent disease, social support, stressful life situations, diet, physical activity and functional status.

The NHLBI also supports the Multi-Ethnic Study of Atherosclerosis (MESA) study; this study is clinically exempt from OMB review. Its main focus is to study the characteristics of subclinical cardiovascular diseases (disease detected non-invasively before it has produced clinical signs and symptoms) and risk factors that predict the progression to clinically overt diseases. The MESA study differs from the Framingham Study in that they were recruited from six different communities and that people with clinical cardiovascular diseases were excluded from the study at the outset. The participants have also undergone high-technology imaging procedures, including cardiac magnetic resonance imaging.

Each of these studies has its own particular strength and major focus. The dominant strength of the Framingham Study is the long term follow-up and multi-generational design. A major focus

of the Framingham Study is the detailed cardiovascular and pulmonary assessment of each participant and the identification of the genetic contribution to disease. There is no similar information available. The unique features of this study, described above, preclude the use of modification of similar data. The information from the Framingham Study will further our understanding of the development of cardiovascular disease and will be used to recommend cardiovascular disease prevention approaches.

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

Physicians, health care providers, and nursing homes constitute the only small businesses which may receive requests for information for this study. The study requests medical records from participants' regular medical care providers such as private physicians and clinics in order to track medical events that occur in study participants. These requests are limited only to essential information needed to determine the presence of disease events. The response of these small businesses is only 25 minutes per event and the estimated number of events requiring inquiry is 2300 events per year throughout all of the five cohorts. The data collection forms have been reduced to the essential information necessary to validate the disease diagnoses. In addition, 160 copies death certificates are requested annually from local and state offices of vital records. The study is dependent on this information because it is not readily or accurately available from any other sources. The participants' medical care providers have been responsive to these requests in the past and it is not anticipated that the current request will pose any problems for these respondents **(Attachment 4).**

A.6. Consequences of Collecting the Information Less Frequently

The Generation Three and NOS participated in clinical examination about 6 years prior to this planned examination. Morbidity and mortality assessment is done in all cohorts though an

annual telephone contact to the participant. A six year interval is appropriate to identify change in risk factors, and to take advantage of new technology to measure new ones. A one year interval to identify morbidity and mortality is appropriate since these cohorts are aging and a longer interval will results in missed identification of illnesses and hospitalizations. Due to the dynamic features of cardiovascular disease, it is important to update information in an appropriate time frame toidentify the course of cardiovascular disease development. Furthermore, theories concerning mechanisms of disease development can be developed and will help describe revised approaches to cardiovascular disease prevention. The Framingham Study and its findings have left no doubt concerning the dynamic nature of cardiovascular disease. The continuation of The Framingham Study is essential for describing how changes in lifestyle and metabolic factors are related to cardiovascular disease development.

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

Two weeks prior to the Generation Three and NOS Cohort and Omni Group 2 Cohort Exam 3 visit, an appointment letter will be sent that includes a request for a list of healthcare contacts **(Attachment 6)** which they are asked to bring with them to the clinic**.** A bag is also sent with a request that all the participant's current medications be placed into the bag and brought to the clinic as well. Collection of this information is required in advance of the clinic visit since names of health care contacts are available in the home, and the dietary questionnaire can be completed with fewer time constraints in the home. Bringing in the medications to the clinic also helps to ensure that a complete list and spelling of the medications are captured correctly.

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

A Federal Register notice, wherein public and affected agencies' comments were solicited, was

published on December 31, 2015 (Pages 81830-81832). No comments were received during the 60 day period. The future direction of the study was discussed at meeting of the National Heart, Lung, and Blood Advisory Council on June, 2013.

The Framingham Executive Committee meets regularly to advise on policy and operations. This committee addresses issues relating to data collection, clarity of instructions, record keeping, and frequency of collection. The members of this committee are:

Daniel Levy, M.D., Framingham Study, NHLBI, 508-935-3458

Vasan Ramachandran, M.D., Boston University School of Medicine, 503-935-3450

Emelia Benjamin, M.D., Boston University School of Medicine, 617-638-8468

Caroline Fox, M.D., Framingham Study, NHLBI, 508-935-3439

Joanne Murabito, M.D., Framingham Study, Boston University, 503-935-3461

L. Adrienne Cupples, Ph.D., Boston University School of Public Health, 617-638-5172

Andrew Johnson, Ph.D., Framingham study, NHLBI, 508-663-4082

Paul Sorlie, Ph. D., NHLBI, 301-435-0456

Phyliss Sholinsky, MSPH, NHLBI, 301-435-0703

An Observation Studies Monitoring Board meets annually and advises the NHLBI regarding study progress and performance and on participant safety and privacy; the minutes are attached **(Attachment 6).** The members are:

Russell Luepker, M.D., University of Minnesota, Division of Epidemiology, 612-624-6362

George Papanicolaou, PhD., NHLBI Executive Secretary, 301-435-0453

Pamela Douglas, M.D., Duke University, 919-681-2690

Philip Greenland, M.D., North Western University, 312-908-7914

James Neaton, Ph.D, University of Minnesota, Division of Biostatistics, 612-626-9040

Svati Shah, M.D., Duke University, 919-681-6197

Lewis J Smith, M.D., Northwestern University, 312-503-2615

Jason Umans, M.D., MedStar Health, 301-560-2959

Alexander F. Wilson, Ph.D., National Institutes of Health, NHGRI, 443-740-2918

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

There is no payment or gift to respondents in return for their participation.

A.10. Assurance of Confidentiality Provided to Respondents

A.10.1 Human Subjects

Participation in this study is voluntary. The contract stipulates that research involving human subjects is subject to an annual review to be submitted each year. A copy of the letters from the Boston University Institutional Review Board Coordinator indicating approval of the study is attached **(Attachments 7).** The consent forms describe the study to participants, inform them of the risks and benefits of procedures, and indicate where to obtain information about the rights of research subjects.

A.10.2 Privacy Act

The information obtained by The Framingham Study will be included in the Privacy Act system of records 09-25-0200, Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD **(Attachment 8)**.

Individuals will be informed that they may refuse to participate in the examination and that their refusal will not result in any loss of benefits to which they might otherwise be entitled, nor will it adversely affect any medical care. Consent forms are attached **(Attachment 9).**

Except as permitted by the Privacy Act, or in accordance with routine uses established for this system, the data from this study may be used only to evaluate epidemiological determinants of health, cardiovascular disease, and risk factors and mortality by cause of death.

A.10.3 Clinic and Data Security

Access to the data will be restricted to protect the rights of individuals involved.

Physical controls: All records, including individually identifiable records, will be kept in locked files. The information obtained by The Framingham Study will be established and maintained in computer data files and also stored in paper record files. All outer doors of the Framingham Study facility are locked and admission is only by pass key or release by reception personnel. The landlord maintains perimeter surveillance of the building.

Technical Controls: Data stored in computers will be accessed through the use of key words known only to principal investigators or authorized project personnel. The Framingham Study computer network is housed on secure servers in a locked room, with a secure back-up system. Password protection and firewalls are in place.

Administrative Controls: Each participant will be provided with written assurance on their consent forms that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act and in accordance with routine use established for this system.

Data will be given only to NHLBI employees and contract personnel associated with the project on an as needed basis, unless otherwise provided by law. Access to files which link identification numbers with names will be restricted and made available only to authorized project personnel. Access to the data will be controlled by the Principal Investigator and the Project Officer. Additionally, all contract personnel, including physicians, are made aware of

and bound by the Privacy Act clause in the contract.Some well-established clinical measurements obtained by the Framingham Study will be reported to the individual participant and/or to the personal physician/healthcare provider designated by the participant to be the recipient during the informed consent interview. Novel research measurements of uncertain value to individuals will not be routinely reported.

A.11. Justification for Sensitive Questions

During the Generation Three, New Offspring Spouse and Omni Group 2 Examination, the Framingham Study is collecting information which is sensitive, as listed below. The steps which are being taken to safeguard the documents and files containing potentially sensitive information are the same as those described in Section A.10. Respondents are being fully informed in writing about the nature of the study, the voluntary aspects of their participation, benefits from participation, risks associated with participation, and the extent to which confidentiality of identifiable information can be assured.

Informed consent is obtained from all participants; the forms are attached **(Attachment 9)**. The participants are fully informed of the content and procedures in the examination. They are informed that they can refuse any or all of the examination without any penalties. The reasons for the collection of the information and the study's use of the information are described below and are verbally given to the participant if he/she has any questions. To provide information about Framingham Study research activities to the participants directly during the intervals between their scheduled examination, a newsletter **(Attachment 10)** is mailed to every participant annually.

Social Security Number was provided by participants at earlier examinations and it will be asked again. Social security number was requested to facilitate tracking of events,

especially deaths with the National Death Index.

Alcohol consumption was determined in the Offspring Cohort and Omni Group 1 and will be determined in the Third Generation, NOS and Omni Group 2 Cohorts cycle 3 since studies have suggested that moderate levels of alcohol use may be protective for coronary heart disease. Because alcohol consumption may change over time, particularly with the onset of illness, this information collection is a repeat of that from earlier examinations.

The Center for Epidemiologic Studies Depression (CES-D) Scale is a depression scale that was administered to the Original Cohort, Offspring Cohort, and Omni Group 1 Cohort and will be administered in the Third Generation, NOS and Omni Group 2 Data from this instrument will be collected to investigate the relationship between depressive symptomatology and clinical cardiovascular events. Data on depression will also be used to assess the impact of clinical events and to determine short- and long-term disability following events.

Current medication use was determined in the Original, Offspring, and Omni Group 1 Cohorts and will be determined in the Third Generation, NOS and Omni Group 2, as many 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. In addition, several medications are modifiers of onset and progression of clinical events (e.g., aspirin, beta blockers), and will be used as covariates in analyses. Information on use of anti-hypertensive and diabetic medications are necessary to assess whether a participant has either of these conditions.

Ages at menopause and oral contraceptive use were assessed in the Offspring and Omni Group 1 Cohorts' female genitourinary disease form, and will be assessed in the Third Generation, NOS and Omni Group 2 Examination 3. Oral contraceptives contain estrogen and/or progestin which have effects on lipid levels, glucose metabolism, and coronary disease risk.

Informant interviews for cardiovascular disease deaths are being conducted with informants previously designated by the participant to determine the circumstances surrounding a participant's death. The information from these interviews is critical in determining whether or not a death was due to cardiovascular causes, which is the primary endpoint of the study. While these interviews conceivably have the potential for exacerbating grief or producing anxiety or guilt in the respondents, they have been well accepted to date in The Framingham Study Staff are experienced in allowing the informants to discuss their feelings openly and at length as needed. They also emphasize the value of this information to the research goals of The Framingham Study, in which the decedent was an important member, in the hope that some comfort may be derived from this knowledge.

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

The estimate for respondent burden for the Original Cohort is presented in Table A.12–1.1, for the Offspring and Omni Group1 Cohorts in Table A.12-1.2, and for the Generation Three & NOS, and Omni Group 2 Cohorts in Table 12-1.3 below. These tables cover the three-year period from 3/1/2016 to 12/31/2019, with all values annualized. Combined annualized totals are shown in Table 12-1.4. Detailed descriptions of the components listed in tables 12.1.3 can be found in **Attachment 11**

Table A.12-1.1
ESTIMATE OF RESPONDENT BURDEN, ORIGINAL COHORT
ANNUALIZED

Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Time per Response (in hours)	Total Annual Burden Hour
I. PARTICIPANT COMPONENTS				
ANNUAL FOLLOW-UP				
a. Records Request (Attach #5)	30	1	15/60	8
b. Health Status Update (Attach #3)	30	1	15/60	8
SUB-TOTAL:PARTICIPANT COMPONENTS	30*	----------	----------	15
II. NON- PARTICIPANT COMPONENTS				
A. Informant Contact (Pre-exam and Annual Follow-up) (Attach #3-pages 3-7)	15	1	10/60	3
B. Health Care Provider Records Request (Annual follow-up) (Attach #5)	30	1	15/60	8
SUB-TOTAL:NON-PARTICIPANT COMPONENTS	45	----------	----------	10
TOTAL: PARTICIPANT AND NON-PARTICIPANT COMPONENTS	75	75		25

*** Number of participants as reflected in Row I.b. above**

Table A.12-1.2
ESTIMATE OF RESPONDENT BURDEN, OFFSPRING COHORT and OMNI GROUP 1 COHORT
ANNUALIZED

Type of Respondent	Number of	Number of	Average Time	Total Annual

	Respondents	Responses per Respondent	per Response (in hours)	Burden Hour
I. PARTICIPANT COMPONENTS				
ANNUAL FOLLOW-UP				
a. Records Request (Attach #5)	1500	1	15/60	375
b. Health Status Update (Attach #3)	1700	1	15/60	425
SUB-TOTAL: PARTICIPANT COMPONENTS	1700*	----------	----------	800
II. NON- PARTICIPANT COMPONENTS				
A. Informant contact (Pre-exam and Annual Follow-up) (Attach #3-pages 3-7)	150	1	10/60	25
B. Health Care Provider Records Request (Annual follow-up) (Attach #5)	1500	1	15/60	375
SUB-TOTAL:NON-PARTICIPANT COMPONENTS	1650	----------	----------	400
TOTAL: PARTICIPANT AND NON-PARTICIPANT COMPONENTS	3350	3350		1200

*** Number of participants as reflected in Row I.b. above**

Table A.12-1.3
ESTIMATE OF RESPONDENT BURDEN, GENERATION 3 COHORT, NOS and OMNI GROUP 2 COHORT
ANNUALIZED

Type of Respondent	Number of Respondents	Number of Responses per Respondent	Average Time per Response (hours per year)	Total Annual Burden Hour
I. PARTICIPANT COMPONENTS				
A. PRE-EXAM				
1.Telephone contact for	1,450	1	10/60	242

appointment				
2. Exam appointment, scheduling, reminder and instructions **(Attach #6)**	1,270	1	35/60	741
B. EXAM CYCLE 3				
1. Exam at study center **(Attach #1)**	1,200	1	90/60	1,800
2. Consent **(Attach #10)**	1,200	1	20/60	400
3. Home or nursing home visit **(Attach #1 – partial as respondent is capable)**	35	1	1	35
C. ANNUAL FOLLOW-UP				
1. Records Request **(Attach #5)**	1,200	1	15/60	300
2. Health Status Update **(Attach #3)**	1,400	1	15/60	350
SUB-TOTAL: PARTICIPANT COMPONENTS	**2,850***	**----------**	**----------**	**3,860**
II. NON- PARTICIPANT COMPONENTS – ANNUAL FOLLOW-UP				
A. INFORMANT CONTACTS (Attach #3 – pages 3-7)	180	1	10/60	30
B. Health Care Provider RECORD REQUEST (Attach #5)	1,155	1	15/60	289
SUB-TOTAL:NON-PARTICIPANT COMPONENTS	1,335	----------	----------	319
TOTAL: PARTICIPANT AND NON-PARTICIPANT COMPONENTS	4,185	28,890		4,179

*** Number of participants as reflected in Rows I.A.1 and I.D.2 above**

Estimates of annualized total hour burden are summarized in Table A.12 – 1.4 below.

Type of Respondent	Number of Respondents	Number of Responses Per Respondent	Average Time per Response (in hours)	Total Annual Burden Hour

Participants	4580	1	90/60	4,675
Non-Participants	3030	1	15/60	729
Totals	7610	14,045		5,414

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

The annualized cost to the participants consists of the cost of their time for which no remuneration is given, and transportation costs. The Occupational Employment Statistics Query System of the Bureau of Labor Statistics listed the hourly mean wage of $27.29 for Massachusetts in 2015 for all occupations; the same system listed $102.58 as the hourly wage for Internists, General. Assuming $27.29 per burden hour for participants and informants and $102.58 per burden hour for physicians and other professional health care respondents, the annual cost for time is $279,302. The average travel distance for participants coming to the Framingham clinic is 10 miles round trip; the cost per mile is estimated at $1.50. Participants needing transportation (15% of the original cohort and 12% of the offspring cohort) are provided with taxis; the taxi service is paid directly by the study. The total annual cost for transportation is $1,780.65. The respondent cost burden is summarized in Table A.12-2 below.

A.12 - 2 ANNUALIZED COST TO RESPONDENTS

Type of Respondents	Number of Respondents	Annual Hour Burden	Hourly Wage Rate	Respondent Cost

Individuals (Participants and Informants)	4925	4,733.0	$27.29	$129,164
Physicians	2685	671.5	$102.58	$ 68,882
				Total: $198,046

(Note: reported and calculated numbers differ slightly due to rounding. Hourly Wage Rates information can be found at http://data.bls.gov/oes/datatype.do)

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 in The Framingham Study. There are no Capital Costs, Operating Costs, or Maintenance Cost to report.

A.14. Annualized Cost to the Federal Government

The Framingham Study is largely being run by a contractor. At the same time, there are NHLBI Intramural staff on the site contributing to the conduct of the study and NHLBI contributes directly to some of the costs of the study. The total annualized cost to the U.S. Government for information collection is $6,553,562 per year.

Table A14 -1 presents total costs for 12/01/13-11/30/16 and average annual costs, broken down by whether the costs are part of the contract or not.

TABLE A.14-1 ANNUALIZED COSTS TO THE GOVERNMENT FOR INFORMATION COLLECTION, THOUSANDS OF DOLLARS

Staff	Grade/Step	Salary	% of Effort	Fringe (if applicable)	Total Cost to Gov't
Federal Oversight					
Contracting Officer	14-5	133,264	10		13,326

Contracting Officer's Representative	12-5	82,359	10		8,236
Contractor Cost					
Salary					3,326,000
Materials, Supplies, and Equipment					291,692
Travel					10,610
Consultants					23,580
Other Direct Costs					
Fringe					2,880,118
Total					6,553,562

A.15. Explanation for Program Changes or Adjustment

During the last OMB approval period, the Original Cohort completed its 1st 32nd examination cycle; the Offspring Cohort and Omni Group 1 Cohort also completed Examinations 9 and 4, respectively, and there was continued surveillance on the five Framingham Cohorts (Original, Offspring, Generation Three & NOS, Omni Group 1, and Omni Group 2). Table A.15-1 lists a timeline of the exams and surveillance activities for time periods 2014-2016 and 2016-2019.

A revision to the previous OMB submission is requested because the 3rd examination of the Third generation and the Omni Group 2 participants is planned for the 2016-2019 time period. The numbers of participants to be examined will be different than those during the last OMB approval period because they are drawn from different cohorts. In addition, morbidity and

mortality (surveillance) on all of the Framingham Cohorts including the two Omni Cohorts will be monitored, by means of the Medical History Update Form **(Attachment 2),** the annual newsletter mailings and requests for permission to release medical records for ascertainment of outcomes **(Attachment 4).**

Table A.15-1 Time Line of Examinations	
YEARS of Examination Cycles	
2010-2014	**2016-2019**
Original Cohort Exams	
Offspring Exam 9 and Omni Group 1 Exam 4	Third Gen & NOS and Omni Groups Exam 3

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

Framingham will analyze the collected information in a timely manner after the necessary data editing has been done. The timetable for data collection and analysis, in terms of the time elapsed following OMB approval, is presented in Table A.16 - 1.

Table A.16 - 1 Time schedule for three-year Framingham Study continuation	
Activity	**Time elapsed after OMB approval**
Participant contact	1 to 36 months
Data collection	1 to 36 months
Analysis	1 months to 5 years
Publication	1 months to 5+ years

To achieve the ultimate goal of determining policy recommendations for cardiovascular disease prevention, the intermediate goal of analyzing data and presenting results needs to be met. Numerous examples of the statistical analyses used by the Framingham investigators are

available in the published literature; publications are attached **(Attachment 3)**. Data to be collected will be merged with that from previous examinations and analyzed in a longitudinal fashion to gain better understanding of the dynamic features of cardiovascular disease. At the same time, cross-sectional analysis of the newly collected data will also occur. Results of both types of analyses will be presented to the public by publishing in scientific journals such as New England Journal of Medicine, Journal of the American Medical Association, Circulation, and Annals of Internal Medicine; by oral and poster presentation at scientific meetings (e.g. American Heart Association, Council on Cardiovascular Epidemiology, American College of Cardiology); and by publishing book chapters.

The extent and complexity of The Framingham Study necessitates that future statistical analyses will cover many topics using past and proposed content, and will be ongoing. Examples of analytic topics which will be expanded upon using future Framingham data can be found in the titles of some of the recent publications. A list of some other topics to be addressed in possible future publications follows:

Common genetic variation and diabetes traits

Exceptional aging across the life span

Genome-wide association study (GWAS) of total and specific IgE

Genome-wide association study of QT interval duration

Energy density, adoption of healthy lifestyle behaviors and metabolic disease

Determinants of skeletal fragility in diabetes

Progression of radiographic abdominal calcification and risk of heart disease

Volumetric bone density and vascular calcification

Role of mitochondrial genes in hypertension

Cloning a blood pressure gene on chromosome 2q

GWAS of dementia, Alzheimer's disease, and related imaging and cognitive phenotypes

Endothelial progenitor cells: clinical correlates and prognosis in the community

An investigation of vitamin D status, structure, and function in middle aged adults

Natriuretic peptides, the renin-angiotensin system, and metabolic risk in obesity

Metabolomic predictors of insulin resistance and diabetes

Longitudinal predictors of chronic kidney disease

Pleiotropy and phenomics of musculoskeletal aging

Plasma GGT fractions as predictors of metabolic syndrome and cardiovascular disease

Testing genes that may affect lifespan

Vitamin D and volumetric bone mineral density

Lycopene and cardiovascular health

The NHLBI Human Exome Project

Genetic and lifestyle factors of obesity

Developing a lifestyle risk profile score for predicting risk of Alzheimer's disease

The thyroid in aging

Targeted resequencing for chronic kidney disease

Myocardial dysfunction in the community: spectrum, correlates, and prognosis

Population based reference ranges for estradiol in men

Whole genome sequencing

Genetics of Platelet function

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

The OMB Expiration Date will be displayed as required.

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

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