**Multi-Ethnic Study of Atherosclerosis**

 **(MESA)**

 **Exam 6 Protocol**

 **Version 1.5 March 22, 2017**

 **Modified on 2/15/17 to add MESA Air Monitoring**

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 **MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS**

 **PROTOCOL – Exam 6**

# **Summary of the Multi-Ethnic Study of Atherosclerosis**

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 diverse, population-based sample of 6,814 men and women aged 45-84. Some 38.5 percent of the cohort is white, 27.7 percent African-American, 22 percent Hispanic, and 11.8 percent Asian, predominantly of Chinese descent.

The cohort was recruited from six Field Centers and characterized with respect to coronary calcification, ventricular mass and function, flow-mediated endothelial vasodilation, carotid intimal-medial wall thickness and presence of echogenic lucencies in the carotid artery, lower extremity vascular insufficiency, arterial wave forms, electrocardiographic measures, standard coronary risk factors, sociodemographic factors, lifestyle factors, and psychosocial factors. Selected repetition of subclinical disease measures and risk factors allowed study of the progression of disease. Blood samples were assayed for putative biochemical risk factors and stored for case-control studies. DNA was extracted and lymphocytes immortalized for study of candidate genes and genome-wide scanning. Participants have been 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.

In addition to the six Field Centers, the study involves a Coordinating Center, a Central Laboratory, and Reading Centers for Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound, Retinal Photography, and Electrocardiography. Protocol development took place in the first 18 months, and staff training, and pilot testing occurred prior to each exam. The first examination took place over 25 months, followed by four follow-up exams: a 17-month examination period, an 18-month examination period, a 21-month examination period, and a 22-month examination period. Participants have been contacted every 9-12 months throughout the study to assess clinical morbidity and mortality.

The study was originally funded for 9.5 years and contracts to the Field Centers, Coordinating Center, MRI Reading Center, and Central Laboratory were renewed for an additional seven years, until August 2015. A second renewal extends MESA to August 2020 and funds a basic core sixth examination beginning September 2016. The core exam will be enhanced by clinic procedures funded by ancillary studies. The final 12 months will be dedicated to close out and data analysis and publication.

# **Objectives and Research Questions of MESA**

In a population of men and women aged 45 to 84 from four race/ethnic groups, the Multi-Ethnic Study of Atherosclerosis is designed to meet the primary and secondary objectives shown in Table 1 below and to address the research questions in Table 2.

**Table 1**

**ORIGINAL OBJECTIVES OF THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS**[[1]](#footnote-2)

Primary Objectives

1. To determine characteristics related to progression of subclinical to clinical cardiovascular disease.

2. To determine characteristics related to progression of subclinical cardiovascular disease.

Secondary Objectives

1. To assess race/ethnic, age, and gender differences in subclinical disease prevalence and risk of progression and clinical cardiovascular disease.
2. To describe the interrelationships of newly identified factors, established risk factors, and subclinical disease and determine the incremental predictive value for clinical cardiovascular disease of newly identified factors and subclinical disease measures above that of established risk factors.
3. To develop population-based methods, suitable for application in future screening and intervention studies, for characterizing the risk of asymptomatic persons.

**Table 2**

**KEY RESEARCH QUESTIONS OF THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS**

What are the risk factors for clinical coronary heart disease and stroke?

1. What is the relationship between subclinical cardiovascular disease (CVD) and future risk of clinical CVD?
2. What are the risk factors among persons with varying levels of subclinical atherosclerosis (for example, among those with the greatest burden of atherosclerosis) and other forms of subclinical CVD?
3. Does the risk associated with subclinical CVD vary among different gender and race/ethnicity subgroups?
4. Are there new CVD risk factors that are important predictors after accounting for the effects of traditional risk factors?

What are the risk factors for progression of subclinical atherosclerosis and other forms of subclinical CVD?

1. Are there new risk factors that are important predictors after accounting for the effect of traditional risk factors?
2. Does the risk associated with these factors vary among different gender and race/ethnicity subgroups?

c. What are the risk factors for progression of subclinical CVD, particularly atherosclerosis, among those with different levels of baseline subclinical CVD?

**Table 3**

**UPDATED OBJECTIVES OF MESA CONTINUATION**

1. To identify factors related to progression from subclinical to clinical CVD
2. To identify predictors of decline in ventricular function
3. To further understanding of the basis for racial/ethnic differences in CVD
4. To provide a platform for in-depth ancillary studies of CVD and other areas

# **Background and Rationale of MESA**

## 3.1 Overview

Prospective epidemiologic studies have traditionally relied on the occurrence of clinically overt events, such as myocardial infarction, stroke, and CHD death, to identify factors predicting development of disease. This design has served well to identify the major cardiovascular disease (CVD) risk factors in the general population, but risk factors defined by these methods fail to predict a considerable proportion of future CVD events. The planned study is intended to improve risk prediction and further understanding of the pathogenesis of atherosclerosis and other cardiovascular diseases by (1) providing more accurate and quantifiable measures of cardiovascular disease; (2) characterizing cardiovascular disease before it has become clinically manifest and, therefore, subject to interventions that disrupt study of the natural history; (3) studying progression of subclinical disease; (4) including multiple ethnic populations to provide information about specific ethnic groups; and (5) allowing comparisons among groups at different levels of risk that may provide clues to pathogenesis. Each of these issues is discussed below.

## 3.2 Utility and Advantages of Measuring Subclinical Cardiovascular Disease

An inherent shortcoming of traditional studies of CVD morbidity and mortality is that identification of clinical events requires: (1) recognition of symptoms by the study participant; (2) relatively rapid access to sources of medical care; and (3) proper diagnostic assessment by a treating physician. These aspects all vary in unpredictable ways by characteristics of study participants, their sources of medical care, and community, and all are prone to significant biases. Fully one-third of myocardial infarctions in the Framingham Heart Study, for instance, are unrecognized by participants and their physicians and are detected only on routine biennial ECGs, even though they confer an increased risk of subsequent events. In addition, unrecognized MIs are not randomly distributed (occurring more frequently in women and the elderly, for example), thereby biasing ascertainment of infarction. Reliance solely on clinical events thus leads to weakening or distortion of risk relationships because of under-detection, biased ascertainment, and misclassification of cases.

Subclinical disease measures can enhance studies of CVD risk by examining the early stages of CVD in an objective manner free of biases related to severity, diagnostic suspicion, or completeness of medical investigation. Because subclinical disease is asymptomatic and previously unknown to participants, it is unlikely to have any direct impact on health behavior, such as lifestyle modification or medication use, which may limit the detection of risk relationships with disease. Finally, the continuous nature of most subclinical measures greatly increases power to detect risk associations compared to discrete measures -- presence or absence of clinical events.

For these reasons, more objective and less biased measures of CVD have been introduced in recent epidemiologic studies of CVD etiology. Two well-developed examples include echocardiography and carotid ultrasound, both of which allow detection of important underlying subclinical disease processes and predict clinical CVD.

Findings from the study of risk factors for subclinical CVD have implications for prevention beyond that of clinical CVD. Risk associated with subclinical disease measures has been shown to be graded and continuous, similar to risk associated with conventional CVD risk factors such as blood pressure and serum cholesterol, rather than demonstrating a threshold level at which risk increases sharply. This suggests that interventions yielding even modest reductions in levels of subclinical disease should be explored for their potential impact on reducing CVD risk. To design such interventions, factors contributing to the development and progression of subclinical disease must be identified.

Recent developments in measurement of cardiovascular structure and function make the imaging of subclinical disease and measuring functional aspects of the vasculature in population-based studies feasible and accurate, providing specific, detailed information that relates more directly to pathology. Improved gray-scale ultrasound imaging of the carotid arteries and aorta, for example, can identify plaque characteristics related to rupture and thrombosis, such as echolucency and heterogeneity, associated with a 4-6-fold increased risk of acute myocardial infarction. Cardiac MRI is capable of providing precise measures of left ventricular mass, diastolic and systolic function, and aortic distensibility. Magnetic resonance imaging of the carotid wall may provide an opportunity for improved assessment of plaque characteristics and their relationship to clinically overt disease in the carotid arterial bed. Coronary calcium quantified by computed tomography (CT) has correlations of >0.90 or greater with histological coronary plaque area and is able to identify persons with increased risk for CHD events. Vascular stiffness and other aspects of arterial mechanics and endothelial function are additional noninvasive measures of “early” functional changes in the vasculature that are related to existing disease, risk factor exposure, and risk factor alteration. Some measures of arterial dynamics may be obtained relatively quickly, inexpensively, and non-invasively, and could thus have clinical application as screening and monitoring tools.

## 3.3 Plaque Rupture and Newly Proposed Risk Factors

The recognition that plaque rupture is a key event in coronary thrombosis and that plaque ruptures often occur in vessels with subcritical stenoses associated with lipid-laden lesions has shifted the focus of etiologic research to factors leading to formation and rupture of unstable plaque, such as inflammation and impaired endothelial function. Inflammatory and infectious factors have long been known to be associated with CVD in epidemiologic studies, and recognition of the importance of plaque rupture provides a plausible mechanism for this relationship. Continued research on inflammation and CVD risk in populations thus provides a promising avenue for elucidating mechanisms of plaque rupture.

In recent years, roles have been suggested for a host of factors in the etiology of atherosclerosis and of clinical events, including hemostatic factors, factors related to lipoprotein metabolism (e.g., cholesteryl ester transfer protein, apoC-III variants, lipoprotein(a) and lipoprotein size), homocysteine, infectious agents (e.g., cytomegalovirus and *Chlamydia pneumoniae*), immune or inflammatory markers, specific fatty acids, and circulating markers of endothelial function such as cellular adhesion molecules and thrombomodulin. Investigation of potential risk factors should permit distinction of possible direct etiologic roles from confounding, as well as suggesting pathophysiologic mechanisms likely to be involved.

Advances in techniques for identifying genetic markers and sequencing genes and in statistical methods for analyzing genetic epidemiology data have opened opportunities for estimating gene frequencies in populations, exploring the relationships between genes and phenotypes, and understanding gene‑gene and gene‑environment interactions. Careful measurement of the components of vascular pathology will result in more precise phenotypic characterization than in past studies, enhancing the ability to relate specific genes or chromosomal regions to phenotypes. Proper collection and storage of genetic material for future studies has become routine procedure for population‑based studies of cardiovascular disease.

## 3.4 Study of Minority Race/Ethnic Groups

The incidence and prevalence of coronary heart disease differ among racial and ethnic groups in the United States. The study will include a substantial proportion of previously understudied minority groups whose prevalence of risk factors and CHD risk related to specific risk factors has been shown or hypothesized to differ from that of the majority population. African Americans, composing approximately 12% of the U.S. population, tend to have higher CHD rates than whites, particularly among women. Prevalence of coronary calcification has been suggested to differ in blacks and whites, though population-based data are sparse. Hispanic populations, composing about 8% of the U.S. population, tend to have lower rates of clinical disease despite high risk factor levels, although data are not consistent in this regard. Pacific Asians (particularly Chinese- and Japanese-Americans and immigrants from Southeast Asia), composing about 3% of the U.S. population, have lower morbidity and mortality rates than whites. This group, particularly Pacific Asian women, has not been well-represented in population-based studies to date. Study of relatively low risk populations, especially those with comparable levels of subclinical disease, may provide clues to prevention of disease in other ethnic groups.

In addition, levels of risk factors for cardiovascular disease differ among racial or ethnic 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 their associations with disease differ among groups. Notable examples of differences in distributions include higher blood pressure and rates of hypertension in blacks, higher levels of HDL-cholesterol in black men, higher levels of Lp(a) in blacks, and higher rates of obesity and diabetes in Hispanics and blacks compared to whites.

Although data on subclinical disease in minorities are much more limited, some data suggest greater carotid atherosclerosis in blacks than whites; limited data in Hispanics suggest slightly less carotid atherosclerosis than whites. Such data in American Pacific Asians are virtually nonexistent. The marked excess of end-organ disease among black hypertensives, which remains unexplained by differing levels of blood pressure or treatment, suggests that subclinical disease indicators may be useful in distinguishing racial/ethnic variations related to vascular and end-organ biology from those due primarily to psychosocial and cultural differences.

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 may be at least as important in disease development and progression, but have been inadequately examined in relationship to subclinical disease and its progression to clinical events. Substantial differences in use of invasive procedures, which have consistently been shown to be less frequently utilized in minority than majority populations, have not been explored in relationship to objective subclinical disease measures rather than subjectively measured symptoms or signs. For these reasons, adequate racial/ethnic diversity in studies of subclinical disease is essential.

## 3.5 Summary

MESA has provided 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 race/ethnic-specific preventive strategies to be explored.

Results of the study will be applicable to clinical practice by identifying noninvasive subclinical disease measures that best predict risk and by suggesting new approaches to intervention to prevent progression of subclinical disease and prevent conversion of subclinical to clinical disease. Some findings may be directly applicable to clinical practice, others may be used to design clinical trials or optimize interventions, and still others may lead to research resulting in new methods of intervention.

Pertinent references are provided in Appendix A.

# **Study Design**

## Sample Size and Power Calculations

### 4.1.1 Assumptions and Considerations in Determination of Sample Size

The following factors were considered in determining appropriate sample size and power:

* To provide adequate number of new events and to establish associations of risk factors with events and with progression of subclinical diseases, the recommended distribution of participants into the 10-year age groups 45-54, 55-64, 65-74, and 75-84 is 28.3%, 28.3%, 28.3% and 15% respectively.
* Fifty percent of the cohort should be females. The desired distribution of participants into ethnic groups is 40 percent white, 30 percent African‑American, 20 percent Hispanic, and 10 percent Asian, predominantly of Chinese descent.
* Event rates for whites and blacks and ages 45-74 were estimated from the seven-year follow-up data from the Atherosclerosis Risk in Communities (ARIC) study and for white and blacks ages 75-84 from the Cardiovascular Health Study (CHS). Based on the National Longitudinal Mortality Study and National Health Interview Study, the event rates for Hispanics were assumed to be 0.8 of the event rate for whites (within each gender and age subgroup) and the event rates for Asians were assumed to be 0.6 of the event rates for whites.
* To account for possible cardiovascular disease interventions, such as coronary artery bypass grafting (CABG) or percutaneous angioplasty (PTCA), it was assumed that in the upper quintile of calcium scores the event rates would be reduced by one third.
* A large proportion of the cohort was expected to have some coronary calcium, based on data collected primarily in white populations. The results of one previous study conducted in a group consisting of persons referred because of risk factors for coronary artery disease, industrial medicine patients as part of their annual physical examinations, and self-referred persons, are shown in Table 4a. Actual events rates in MESA are shows in Table 4b.

**Table 4a**

**Expected rate of CHD Death and Non-fatal MI in Six Years in Random Sample of 6,500 participants aged 45-84 free of CHD at baseline**[[2]](#footnote-3)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All |  | Men | Women |  | White | Black | Hispanic | Asian  |
| Event rate (%) | 5.1 |  | 6.7 | 3.5 |  | 4.9 | 6.7 | 4.3 | 3.2 |
|  |  |  |  |  |  |  |  |  |  |
| Number of events | 330 |  | 217 | 114 |  | 122 | 121 | 65 | 23 |

**Table 4b**

**Actual rate of CHD Death and Non-fatal MI in 11.1 Years in 6809 MESA participants**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | All |  | Men | Women |  | White | Black | Hispanic | Asian  |
| Event rate (%) | 5.0  |  | 6.6 | 3.5 |  | 5.5 | 4.6 | 5.4 | 3.4 |
|  |  |  |  |  |  |  |  |  |  |
| Number of events | 339 |  | 213  | 126 |  | 145 | 87 | 80 | 27 |

### 4.1.2 Hypotheses, Analyses, and Power Calculations for Exam 6

MESA papers cover a diverse range of topics, and each paper may have specific analytic challenges and features. We describe here some commonly used methods for the broad topic areas of interest.

(i) Further understanding of the basis for racial/ethnic differences in CVD.

As there are known differences in CVD rates between racial/ethnic groups, it is important to understand the role of traditional or novel risk factors in “explaining” these differences. As CHF and stroke event rates will be increasing with the aging of the cohort, the additional events will make it possible explore the race/ethnicity difference for these endpoints. Additionally we will explore gender differences by race/ethnicity in the major endpoints. Including such candidate mediator variables in the model we will examine whether the racial effects are attenuated, and if so to what extent. Of particular interest will be differences in subclinical disease burden. That is, can the difference in CVD rates be explained entirely by differences in atherosclerosis, or do racial/ethnic differences persist even conditional on amount of subclinical disease? Differences in lifestyle factors such as diet or physical activity will also be examined as potential mediators.

The risk of incident cardiovascular disease is typically modeled using Cox proportional hazards regression. Often baseline exposures have been used, however with the longer follow-up in MESA we can now focus on changes in exposure over time. These may be incorporated via time-varying covariates, for example. Most commonly a staged approach to modeling is used, whereby unadjusted models are examined first, followed by age, gender, and race/ethnicity adjusted models, followed finally by one or more models adjusting for potential confounders and/or mediators. Proportional hazards assumptions are checked via Schoenfeld residuals and/or time-by-exposure interaction terms. Competing risk of death is generally handled using the approach of Fine and Gray.

The role of racial/ethnic group in prediction of incident CVD will be evaluated by including the race/ethnic group as a predictor in the Cox models described above. Interaction terms between race/ethnicity and other risk factors will be examined to determine if the effect of these risk factors differs by race/ethnicity. Models stratified by race/ethnicity will also be examined, to detect qualitative differences that may be hypothesis-generating despite not being statistically significant.

(ii) Subclinical disease progression as a predictor of incident CVD

Of particular interest in MESA III will be examination of how progression of subclinical disease relates to incident CVD. For several measures of subclinical disease (e.g. MRI measures of LV mass and function, ultrasound measures of carotid IMT) this will necessitate restriction to events occurring after MESA exam 5. The additional five years of follow-up afforded by the renewal will allow these events to accumulate. For other measures, such as blood pressure and coronary artery calcium, which have been measured multiple times, we will be able to consider how trajectories over time relate to subsequent disease risk. Additionally we will also be able to use variables collected only at exam 5 as predictors of subsequent CVD, including measures of sleep quality by polysomnography, and myocardial scar by MRI with gadolinium contrast. These will be modeled as independent variables in traditional Cox proportional hazards models.

(iii) Identify novel factors related to progression of subclinical cardiovascular disease

MESA currently has a wealth of data, including many measures of subclinical disease that have been collected multiple times over the previous exam cycles. This allows the study of progression of subclinical disease over time, both overall and by gender and race/ethnic subgroups. For variables measured at two time points, such as LV structure and function or carotid IMT we would use a linear model for the change both with and without adjustment for baseline. There is some replicate information that will be used for measurement error adjustment in the adjusted model, via a regression calibration. For variables measured at multiple time points (e.g. blood pressure, coronary artery calcium) we will use a linear mixed model type approach, possibly allowing the slope to change with time since baseline. The longitudinal data also allows the opportunity to try to characterize cumulative burden, for example average blood pressure over a longer period. Finally we have noted in the coronary artery calcium data that there are “fast progressors”. That is, participants whose coronary calcium accumulates at a more rapid pace than can be explained by their risk factor profile. Study of this unique phenotype may lead to detection of novel risk factors, and have clinical implications. These analyses would primarily use logistic regression, in order to predict fast progression as a function of risk factors. Identification of fast progressors would be based on robust detection of outliers in models for calcium change over time.

#### 4.1.2.1 Power and Sample Size

**Projected Number of Events**

We estimated the expected number of events by the end of the renewal period (August, 2020). To calculate estimated event rates we used events accumulated through 2011, representing a median of 10.2 years of follow-up. For each event type an age-specific 10-year event rate was calculated using a Cox proportional hazards model with age as the only covariate. To obtain the projected number of events we use these rates (converted to an annual rate) and allow the cohort to age as time goes by. The **figure** illustrates the estimated age specific annual event rates for a set of endpoints of interest, including hard CHD (MI and CHD death), all CHD (hard CHD plus definite angina), hard CVD (hard CHD, stroke, cerebrovascular death), all CVD (all CHD, stroke, cerebrovascular death), heart failure (CHF) and stroke. Additionally we incorporate loss to follow-up, estimated at approx­imately 1.5% per year, based on our annualized retention through follow-up twelve, and an annual loss to death from non-cvd causes at slightly less than 1% per year. Table B.2.c.3 presents these projections overall and by race/ethnicity.

Table B.2.c.3. Estimated number of events by end of MESA III renewal period (2020) by race/ethnicity adjusted for aging of the cohort and loss to follow-up

|  |  |
| --- | --- |
|  | **Estimated Number of Events Accumulated by the end of MESA III****(adjusted for aging of the cohort and loss to follow-up)** |
|  | **White** | **Chinese** | **Black** | **Hispanic** | **Total** |
| Hard CHD | 300 | 50 | 195 | 175 | 720 |
| All CHD | 475 | 80 | 275 | 220 | 1050 |
| Hard CVD | 455 | 70 | 310 | 275 | 1110 |
| All CVD | 650 | 110 | 420 | 320 | 1500 |
| CHF | 270 | 40 | 220 | 140 | 670 |
| Stroke | 180 | 30 | 145 | 125 | 480 |

Hard CHD=MI, cardiac arrest, CHD death; All CHD=hard CHD, definite angina, probable angina if revascularized; Hard CVD=hard CHD, stroke, cerebrovascular death; All CVD=all CHD, stroke, cerebrovascular death; all projections rounded to the nearest 5 events.

With our current CVD event rates through a median of 10.2 years of follow-up, our minimally detectable hazards ratios within the Chinese subset (our smallest race/ethnic group) is approximately 2.0 with 80% power, and 2.25 with 90% power. The increase in events afforded by the renewal increases our power substantially. We estimate that the minimally detectable hazards ratios within the Chinese subset will now be 1.62 for 80% power, 1.75 with 90% power. Our other race/ethnic groups are much larger, and will have greater power.

More generally we consider here comparisons of two groups of equal size, representing exposed and unexposed participants, in terms of incident events. Examples of interest include comparing those above versus below median carotid IMT, gender comparisons, or those with and without coronary artery calcium at baseline for example. Under these assumptions we would need to observe 88 events (total) to have 90% power to detect a hazards ratio of 2.0 (for exposed versus unexposed). To detect a hazards ratio of 1.5 we would need to observe 256 events to have 90% power, 191 events for 80% power. Based on the projected number of events shown above we should thus have over 90% power for hypotheses involving the whole cohort for any endpoint. Analyses involving continuous variables, which will be the preferred approach in practice when possible, will have even greater power.

## 4.2 Description of Field Center Communities and Source Populations

### 4.2.1 Overview

The MESA cohort was drawn from six regions in the U.S.: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA. The source population for each Field Center varied in size and ethnic composition. The MESA cohort is comprised of men and women of diverse ethnic background who were 45 to 84 years old at the baseline exam and free of clinical cardiovascular disease. Each site recruited between 1,066 to 1,319 eligible participants, equally divided between men and women, and according to specified race/ethnicity proportions.

Prior and concurrent to recruitment, the purpose, rationale, and design of the study was publicized to residents of target areas. Successive efforts were directed at targeted households or individuals, and included mailings of letters and brochures, followed by personal contacts via telephone or in person. Phone calls were the primary method of recruitment at all Field Centers. Each Field Center developed its recruitment procedures according to the characteristics of its community, past experience, available resources, and site-specific logistics. This protocol describes the target populations, the sampling frames, and details of recruitment methods and procedures.

### 4.2.2 Description of Field Center Source Populations

**Wake Forest**: The source population was comprised of the resident population of Forsyth County, NC. The county had an estimated 270,000 inhabitants living in both urban and rural settings. The 1997 population of age-eligibles was 94,650.

**Columbia**: The source population was comprised of Local 1199 National Benefit Fund (NBF) members, retirees, and their spouses residing in 18 contiguous zip codes of Northern Manhattan and the Bronx. Additional participants in these areas were also recruited. Members of the union included health care workers (e.g. nurses, laboratory technicians, social workers etc.) and other individuals who work in places that provide health care (e.g. custodians, food handlers, and clerical workers of nursing homes or hospitals). Membership was compulsory for all employees. There were approximately 125,000 active and retired members and their adult dependents living in New York City, of whom approximately 10,000 lived in the target zip codes for MESA.

**Johns Hopkins**: The source population was comprised of residents of a series of census tracts that run along the rapid transit line from Johns Hopkins University to the Western suburbs of Baltimore County. This area had a racially diverse population, ranging from lower SES neighborhoods in East and West Baltimore City to the higher SES pockets of the inner city and Baltimore County. The approximate size of these census tracts was 164,513, of whom approximately 55,000 were aged 45 and older.

**Minnesota**: The source population was comprised of residents of four contiguous census tracts (361, 370, 371, 372) in the southern part of the city of St. Paul. The target area was located in Ramsey County and is locally known as the “West Side”. Its borders were the Mississippi River to the north, west, and east, and a street (Annapolis St.) in the south. All of the area dwellings and businesses shared a single postal zip code. According to the 1990 census data, there were about 6,000 age-eligible residents in that community

**Northwestern**: The source population reside in Community Areas 6, 8, 34, and 60 in the city of Chicago. The four selected Community Areas of Chicago were very close to the Northwestern University Medical Center and contain multiple ethnic groups. Based on the census data, about 56,000 age-eligibles were living in these areas in 1990.

**UCLA**: The source population was comprised of residents in Los Angeles County within a 15 mile radius from the UCLA Medical Center. In 1990, this area had a total population of 3,990,122 of whom approximately 1.2 million were >45 years old. Census tracts with more than 50% Hispanic and/or >25% Asian (Chinese) Americans were targeted.

The ethnic composition of the source communities for MESA is summarized in Table 5.

**Table 5**

**Estimated Race/Ethnic Composition of the Source Populations1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | African-American | Asian-American | Caucasian | Hispanic |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Wake Forest | 19% | 0 | 81% | 0 |
| Columbia | 35% | 0 | 15% | 45% |
| Johns Hopkins: City Tracts County Tracts | 56%27% | 00 | 41%68% | 00 |
| Minnesota | 2% | 4% | 75% | 16% |
| Northwestern | 8% | 8% | 76% | 7% |
| UCLA | 14% | 11% | 45% | 30% |

1 Percentages based on 1990 census except Wake Forest (1997 estimates) and Columbia (1995 survey).

## 4.3 Study Population and Sampling

### 4.3.1 Overview

Each of the six Field Centers recruited between 1,066 and 1,319 participants from two or more of the following ethnic groups: African Americans, Asian (Chinese) Americans, Caucasians, and Hispanics. Marginal distributions of ethnicity, gender, and age -- overall and at each Field Center -- are shown in Tables 6 and 7. Two factors were considered in determining Field Center-specific goals for ethnic composition: (1) the overall ethnic profile of the MESA cohort; and (2) the ethnic composition of the source population at each Field Center. In addition, it was deemed important to have overlapping ethnic groups among Field Centers in order to minimize confounding of ethnicity by site. The cohort had approximately equal number of men and women at each Field Center. The MESA age range was chosen to permit analyses of the relations between age and subclinical disease progression, and to include pre-menopausal women.

 **Table 6**

 **Ethnic Distribution of Study Participants,**

 **Overall and by Field Center**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Caucasian | African American | Hispanic | Asian American |
|   |   |   |   |   |
| Wake Forest | 53.4% | 46.3% | 0.0% |   |
| Minnesota | 56.8% |   | 43.2% |   |
| Northwestern | 47.9% | 25.9% |   | 26.2% |
| Columbia | 20.2% | 34.6% | 45.0% |   |
| Johns Hopkins | 49.1% | 50.9% |   |   |
| UCLA | 9.9% | 11.7% | 40.6% | 37.7% |
|   |   |   |   |   |
| TOTAL | 38.5% | 27.7% | 22.0% | 11.8% |

 **Table 7**

 **Gender and Age Distribution of Study Participants**

|  |  |  |
| --- | --- | --- |
| Gender: | Men | 47.2% |
|   | Women | 52.8% |
|   |   |   |
| Age: | 45-54  | 28.6% |
|   | 55-64  | 27.6% |
|   | 65-74  | 29.6% |
|   | 75-84 | 14.2% |

### 4.3.2 Sampling

The sampling frame and methods for sampling participants at each Field Center varied, depending on site-specific recruitment plans and logistics. While the cohort was community-based, the emphasis of MESA sampling was to obtain balanced recruitment across strata defined by gender, ethnicity, and age group rather than to represent the demographic distribution of the source communities. Selection from the sampling frames differed by site. In three Field Centers (Wake Forest, Columbia, Northwestern), random samples, stratified by age and gender, were selected from the sampling frames. In the others (Minnesota, Johns Hopkins, UCLA) the sampling frame did not contain demographic information and recruitment proceeded along geographic boundaries (Minnesota, Johns Hopkins) or by random digit dialing (UCLA) to target areas. Regardless of the nature of the sampling unit (households or individuals), multiple eligible participants who resided in a single household could be recruited into the cohort. Recruitment progress was monitored regularly by the Field Centers and Coordinating Center within strata defined by two genders, four age groups, and four ethnic groups (16-32 strata, depending on the Field Center). Field Centers attempted to maintain a balanced distribution across these strata throughout the recruitment period. Site specific details are described below.

**Wake Forest**: Two sampling frames were used: the North Carolina Division of Motor Vehicles (DMV) list for identifying participants aged 45 to 64 and the HCFA list for participants aged 65 to 84. The HCFA lists were estimated to be approximately 98 percent representative of the population aged 65 years and over. The DMV list was supplemented with the voter registration list from Forsyth County and with consumer lists available through such organizations as the Piedmont Publishing Company and I Rent America. These lists were combined, eliminating duplicate names from the resultant sampling frame. The combined frame from these multiple sources was more comprehensive than the DMV list alone. This sampling frame included information on gender, age, race, mailing addresses and telephone numbers. From this master list, 16 separate lists based on gender (2 levels), race (2 levels), and age (4 levels) were constructed. Each list was then randomly ordered and potential participants were invited to participate in the order they appeared on the randomized lists. Each of the 16 lists was used to recruit the required number of participants for each gender-race-age group.

**Columbia**: The sampling frame was a listing of all age-eligible, 1199 members, retirees, and their spouses living in the target zip codes in Northern Manhattan and the Bronx. Members with less than 2 years of employment (and their dependents) were excluded from the frame, since this group (about 2%) -- unlike those with 2+ years -- does not have long-term employment guarantees in the current union contract. An up-dated computer file of all age-eligible 1199 NBF beneficiaries residing in study zip codes was compiled every 6 months. The sampling frame contained age, gender, names, addresses and phone numbers of potential participants. (Ethnicity was not available in the database.) The sampling frame was stratified by gender and age.

**Johns Hopkins**: The sampling frame consisted of dwellingsfrom selected census tracts. A list of dwellings including address and telephone numbers (when available) within these census tracts was obtained from a commercial mailing serviceor from enumeration done by study staff. Given the available data on the sociodemographic composition of each census tract, the sample size from each tract was able to be selected according to the study’s recruitment goals. The final sampling strategy was developed after analyzing the results of a survey to be conducted as part of student course work prior to developing the sample. The survey obtained information on key variables from the population frame, such as socioeconomic status and factors related to the likelihood of successfully conducting the recruitment by telephone (for example, frequency of use of answering machines, which if high may make recruitment over the phone problematic, and suggest that in-person recruitment may be more efficient). The general plan was to select dwellings within the chosen census tracts using simple random sampling, and within dwellings to recruit all study eligibles. With the knowledge of the demographic characteristics of the census tracts, such as distribution by age and ethnic background, it was possible to adjust sampling fractions periodically so as to reach the desired demographic composition of the study sample.

**Minnesota**: The sampling frame was comprised of dwellings (single-family dwelling and apartment buildings) in the target area. The Ramsey County assessor’s office provided the list on a computer file, sorted by street and, within street, by house number. The county assessor’s data identified apartment buildings and businesses; the latter was deleted from the sampling frame. A listing of Hispanic members of a local church was used as another source for minority recruitment. The type of dwelling (apartment, single family, or business) and the name of the owner were also available. Phone numbers (or unlisted status) were identified by reverse phone directories. The list of dwellings in each target area was divided into “neighborhoods” of 100-150 houses each, which was targeted successively over a two-year period. Recruitment proceeded along contiguous blocks starting from the East and South borders of the community. To ensure a 1:1 ratio of the target ethnic groups (Caucasians and Hispanics) throughout the recruitment period, Caucasians were under-sampled in each neighborhood, but all consenting and eligible Hispanics were likely be recruited.

**Northwestern**: The sampling frame was determined from census data for the target area which were compiled and maintained by the city of Chicago Department of Planning and Development. The sampling frame was supplied by a commercial company (the Americalist Division of Hanes & Company, North Canton, Ohio) on a community by community basis. Information obtained included name (head of household and secondary name, e.g., spouse), complete mailing address, telephone number (or unlisted status), census tract number, dwelling type (single family, multiple unit), estimated family income, and age. This list also provided complete mailing addresses for those who had unlisted telephone numbers. Surnames of Chinese Americans were identified from the database. Within each race group, age group, and gender category, the names were divided randomly into batches of 100 names each. A specific number of batches were selected for contact each week, with preferential selection of strata for which recruitment lagged behind

**UCLA**: The sampling frame was comprised of telephone exchanges corresponding to census tracts in Los Angeles County within a 15 mile radius from the UCLA Diabetes Center. This area had a heavy representation of Hispanics and Asian Americans**,** particularly Chinese Americans. Separate but overlapping sampling frames was used, one for each of these two ethnic groups. Respondents from either frame (including African-Americans and Caucasians) were recruited, as needed. The frame for Hispanics included telephone-exchanges that matched census tracts where, at the time of the 1990 Census, Hispanics accounted for at least 50% of the total population (n=213). The frame for Asian Americans included telephone exchanges that matched census tracts where, at the time of the 1990 Census, Asian Americans accounted for at least 25% of the total population (n=54). The targeted Hispanic and Asian Americans census tracts overlapped and were representative of these two populations in Los Angeles County. The small number of African-American and Caucasians targeted for recruitment (about 110 each) were also recruited from these two sampling frames. Random digit dialing was used to recruit from the target area. Telephone numbers were generated with the help of Genesys Sampling Systems (Fort Washington, PA), a company specialized in developing random digit dialing samples. Based on the experience of UCLA Survey Research and preliminary data, it was necessary to contact approximately 5,000 households to enroll 1,100 participants in the study.

## 4.4 Eligibility and Exclusion Criteria for MESA

### 4.4.1 Eligibility Criteria

Eligible MESA participants were defined as persons living within the defined geographic boundaries for each Field Center who were between the ages of 45 and 84 at enumeration, who were African-American, Chinese-American, Caucasian, or Hispanic, and who did not meet any of the exclusion criteria (see below). Target ethnic groups for each field center were chosen to maximize efficiency to detect ethnic differences and to allow the separation of the effect of ethnicity from that of study site.

### 4.4.2 Exclusion Criteria

MESA’s primary hypotheses are concerned with the determinants and natural history of subclinical cardiovascular disease. Therefore, participants with known clinical disease were not recruited. Most other exclusion criteria related to the long-term nature of the study or to incompatibility with certain components of the MESA exam. Eligibility (or ineligibility) status was determined from self-reported information; no attempt was made to validate the participant’s response. MESA’s exclusion criteria are shown in Table 8.

 **Table 8**

 **Exclusion Criteria**

* Age younger than 45 or older than 84 years
* Physician-diagnosed heart attack
* Physician-diagnosed angina or taking nitroglycerin
* Physician-diagnosed stroke or TIA
* Physician-diagnosed heart failure
* Current atrial fibrillation
* Having undergone procedures related to cardiovascular disease (CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries)
* Active treatment for cancer
* Pregnancy
* Any serious medical condition which would prevent long-term participation
* Weight >300 pounds
* Cognitive inability as judged by the interviewer
* Living in a nursing home or on the waiting list for a nursing home
* Plans to leave the community within five years
* Language barrier (speaks other than English, Spanish, Cantonese or Mandarin)
* Chest CT scan in the past year

Potential participants who responded “Don’t know” to questions about medical conditions were not considered ineligible.

## 4.5 Recruitment

### 4.5.1 Overview

Each site recruited between 1,100 participants, equally divided between men and women, and in the race proportions shown in Table 6. Wake Forest, Johns Hopkins, Minnesota, and Northwestern all started by creating community awareness of the study and enlisting the support and endorsement of community-based organizations and leadership. All sites implemented techniques that have been used successfully in other studies to recruit minority populations. Columbia worked closely with the 1199 National Benefit Fund during recruitment, including using study staff hired through the union for recruitment, retention, and study publicity. UCLA recruited using random-digit dialing. All sites that recruited Hispanics employed staff fluent in Spanish, and sites recruiting Chinese-Americans employed staff fluent in Cantonese and Mandarin.

Prior to recruitment, the purpose, rationale, and design of the study were publicized to residents of target areas at each site. Successive efforts were directed at targeted individuals, and included mailings of letters and brochures, followed by personal contacts via telephone or in person. Sites modified these materials to meet unique aspects of the source population and recruitment strategy. Standard press releases were written, and templates were developed for participant letters, brochures, and scripts.

### 4.5.2 Screening

Since multiple eligible persons in a household could be recruited, the interviewer first attempted to enumerate all age-eligible persons in a household (typically two, but occasionally more) using a Household Enumeration Form. Name, gender, and relationship to the first respondent was obtained, followed by an attempt to interview all age-eligibles on one or multiple calls. To determine MESA eligibility, the interviewer administered a Screening Questionnaire that provided basic information about the study and was used to determine ability to communicate in languages to be accommodated in the study, age eligibility, history of heart disease, and other eligibility criteria, as well as determine willingness to participate. An associated script helped the interviewer introduce (or re-introduce) the study and stimulate interest. The questionnaire was usually administered over the phone and sometimes during a home visit. The interviewer was provided with rules to determine eligibility status and guidelines for under-sampling certain strata, when needed. Alternative scripts for ineligible participants, or for eligible participants who were not recruited in the interest of balanced recruitment, were provided with the Screening Questionnaire.

In this era of aggressive marketing and telemarketing, some contacted persons terminated the interview before its completion, sometimes as early as the first sentence, or before household enumeration. In other cases, the respondent terminated the interview after providing a certain amount of information but before eligibility status could be ascertained. The first items to be ascertained by the interviewer were the absence of language barrier and availability of age-eligible residents.

Once enumeration was completed (or at least one age-eligible is identified), each age-eligible person was classified into one of the mutually exclusive categories shown in Table 9.

 **Table 9**

 **Classification of Age-Eligible Persons Contacted for MESA**

Group 1. Medical Screening refuser, No characterization, Unknown eligibility status

Group 2. Medical Screening refuser, Demographic characterization, Unknown eligibility status,

Group 3. Medical Screening refuser, Demographic characterization, Partial eligibility status

Group 4. Completed screening, Ineligible

Group 5. Completed screening, Eligible, Refused

Group 6. Completed screening, Eligible, Not recruited (due to under-sampling)

Group 7. Completed screening, Eligible, Recruited

To provide some characterization of various types of refusers, an attempt was made to collect a limited amount of information on groups 2 and 3 above, using an abbreviated questionnaire.

### 4.5.3 Definitions of Participants, Non-respondents, Volunteers, and Participation Rate

Participant (i.e., cohort member): an eligible person who completed the baseline MESA clinic exam and underwent chest CT.

Baseline MESA clinic exam: interviews, physical exam (anthropometry, blood pressure etc.) and blood draw.

Non-respondent: a person known to be eligible, invited to participate, and declined or did not complete baseline clinic examination and chest CT.

Volunteer: a person who initiated contact with MESA -- whether eligible or not -- and asked to participate. In general, volunteers can be used to test exam procedures but would not be considered cohort members.

Participation rate: Number of participants divided by participants plus non-respondents. Eligibles who are not sampled will not be included.

### 4.5.4 Clinic Examination Scheduling

At the end of the screening, clinic appointments and CT/MR appointment(s) were scheduled for eligible and consenting respondents. A follow-up call was scheduled for eligibles who wanted additional time to consider their decision. Two weeks prior to the clinic visit, the potential participant was sent a packet containing an appointment reminder, directions, instructions for the visit, and a tracking form (to be filled out at home and brought to the clinic). Potential participants were phoned 48-72 hours prior to the appointment to remind them. Additional information about the CT and MR were provided in person during the clinic visit. No-shows were contacted shortly after the missed appointment in an attempt to reschedule.

### 4.5.5 Recruitment Material

Study-wide recruitment-related materials for the first exam are listed below:

● Media release about the study

● Introductory Letter

● Study Brochure

● Screening questionnaire and script

● Questions & Answers

● Letter to employer

● Appointment Reminders

● Recruitment Tracking Form

● Consent Forms (site-specific versions to meet site-specific IRB requirements)

Sites modified materials to meet unique aspects of the source population and recruitment strategy.

### 4.5.6 Recruitment Tracking and Progress

Given unique logistics of recruitment at each Field Center, some tracking was done locally. A study-wide tracking form was used to record recruitment status including outcome of contact efforts, scheduled appointments, and completion status for the various components of the baseline exam. Recruitment tracking information was recorded on a paper form (or a computerized form) and entered into a database at the field center, allowing for review of recruitment status of a given person as well as database queries for groups (e.g., “pending scheduled visit”). An updated database was sent periodically to the Coordinating Center for centralized tracking.

The Coordinating Center reported, on a monthly basis, Field Center-specific recruitment counts by gender, ethnicity, and age-group strata. Recommendations to over-sample or under-sample within certain strata were made every four months on the basis of cumulative counts.

# **Overview of Study Methods**

## 5.1 Funding Structure for the 6th Examination

The current MESA Contract for Exam 6 is structured differently than prior contracts. Unlike prior exams, the current core exam is very small with only a few key components. These components include demographics, anthropometry, blood pressure, smoking history, medical history (including medications), and phlebotomy. Grant proposals were solicited by NHLBI for MESA Exam 6 ancillary studies under the assumption that Exam 6 would become economically feasible when a sufficient quantity of ancillary studies received grant funding. The intent was for these ancillary studies to provide the necessary financial support for the Coordinating Center, the Field Centers and the Lab to integrate the activity into the Core Exam. The advantage of this approach is that it allows the science of exam 6 to be determined based on a full peer-review within the standard NIH grant system. The challenge has been creating a unified seamless exam from multiple ancillary studies that were not proposed in conjunction with one another, and have been reviewed and funded at different times.

## 5.2 Timetable

**First contract period (January 15, 1999 – August 14, 2008):**



 Protocol development, training, pilot testing January 15, 1999 - July 14, 2000

 Examinations 1-4, surveillance (data analysis/

 publication from 2002) July 15, 2000 - July 14, 2007

 Surveillance, data analysis/publication July 15, 2007 - January 14, 2008

**Second contract period (August 15, 2008 – August 14, 2015):**



 Surveillance, protocol development, training,

 pilot testing, data analysis/publication August 15, 2008 – March 31, 2010

 Examination 5, surveillance, data

 analysis/publication April 1, 2010 – September 30, 2011

 Surveillance, data analysis/publication October 1, 2011 - August 14, 2015

**Third contract period (August 15, 2015 – August 14, 2020):**



 Surveillance, protocol development, training,

 pilot testing August 15, 2015 – August 31, 2016

 Examination 6, surveillance September 1, 2016 – March 31, 2018

 Surveillance, data analysis/publication March 31, 2018 - August 14, 2019

 Data analysis/publication August 15, 2019 - August 14, 2020

## 5.3 Overview of Examinations and Contacts with Participants

Table 10 below shows components performed in Exams 1-5

* **"X"** indicates procedure was done in a given exam
* Partial cohort is indicated by a percent or specific N
* "A" indicates that a procedure was done as part of an ancillary study and is further described in the Ancillary Studies section. These were typically subsets of the cohort.

 **Table 10**

C**omponents Performed in Exams 1-5**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Component** | **Exam 1** | **Exam 2** | **Exam 3** | **Exam 4** | **Exam 5** |
| ***Main examination*** |  |  |  |  |  |
| Reception, Consent | **X** | **X** | **X** | **X** | **X** |
| Urine Collection | **X** | **X** | **X** |  | **X** |
| Blood pressure | **X** | **X** | **X** | **X** | **X** |
| Anthropometry | **X** | **X** | **X** | **X** | **X** |
| Phlebotomy  | **X** | **X** | **X** | **X** | **X** |
| ECG | **X** |  |  |  | **X** |
| Ankle-Arm Blood Pressure | **X** |  | **X** |  | **X** |
| Medical history | **X** | **X** | **X** | **X** | **X** |
| Personal history, Demographics | **X** | **X** | **X** | **X** | **X** |
| Cognitive Function |  |  |  |  | **X** |
| Medications | **X** | **X** | **X** | **X** | **X** |
| Psychosocial | **X** | **X** | **X** | **X** | **X** |
| Neighborhood Characteristics | **X** |  |  |  |  |
| Family History Questionnaire |  | **X** |  |  |  |
| Physical activity | **X** | **X** | **X** |  | **X** |
| Tracking (address, contacts, etc.) | **X** | **X** | **X** | **X** | **X** |
| Sleep Questionnaire |  | **X** |  | **X** |  |
| Diet Assessment | **X** |  |  |  | **A** |
| Carotid Ultrasound  | **X** | **A** | **A** | **A** | **A** |
| Ultrasound Endothelial Function | **X** |  |  |  |  |
| Ultrasound Arterial Pulse Wave | **X** |  |  |  | **A** |
| CT Scan of the Heart | **X** | **50%** | **50%** | **25%** | **A** |
| MRI Scan of the Heart | **X** |  |  | **n=1200** | **X** |
| Carotid MRI  |  | **n=1000 (n=400 A)** |  |  |  |
| ***Ancillary Studies*** |  |  |  |  |  |
| Residential Hx; Neighborhood Qx |  | **X** |  |  |
| Aortic CT  |  | **30%**  | **15%**  |  |
| MESA Lung (60%) ; spirometry, CT |  |  | **X** | **X** | **X** |
| MESA Eye  |  | **X** |  |  | **X** |
| MESA Family (Genetics) |  | **X** |  |  |
| Carotid Ultrasound  |  | **50%** | **50%** | **20%**  | **A** |
| MESA Stress (2 sites) |  |  |  | **X** | **X** |
| MESA Air |  |  |  |  |  |
| Air Questionnaire |  |  |  | **X** | **X** |
| Home monitoring |  |  |  | **~900** |  |
| Personal monitoring |  |  |  | **~50** |  |
| MRI Tagging |  | **~1500** | **~1200** |  |
| MRI Coronary Wall |  |  |  | **~300** |  |
| MESA Sleep Study |  |  |  |  | **X** |

A general timeline for the third contract period is provided in Table 11.During the surveillance period, participants have been and will continue to be contacted by telephone at 12 month intervals.

**Table 11**

**Timeline for MESA Exam 6**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | **8/15/2015 to 8/14/2016** | **8/15/2016 to 8/14/2017** | **8/15/2017 to 8/14/2018** | **8/15/2018 to 8/14/2019** | **8/15/2019 to 8/14/2020** |
| Task Area 1  |  |   |   |   |   |   |   |   |  |   |   |   |  |   |   |   |  |   |   |   |
| Task Area 2.A |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Task Area 2.B |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Task Area 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Conduct FU contacts |  |   |   |   |   |   |   |   |  |   |   |   |  |   |   |   |   |   |   |   |
| Investigate clinical events |  |   |   |   |   |   |   |   |  |   |   |   |  |   |   |   |   |   |   |   |
| Support study collaboration |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Establish and maintain study databases |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Establish and maintain biological repository |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Coordinate and participate in study committees |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Arrange and manage OSMB meetings |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Design and implement QA/QC procedures |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Statistical analysis, publications & presentations |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Prepare and submit technical and financial reports |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Work cooperatively with all MESA groups and tasks. |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Exam protocol development |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Forms development/translation |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Training, certification |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Pilot testing |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Exam 6 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Exam closeout |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Study closeout activities |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

## 5.4 Description of Field Center Clinics for the 6th Examination

**Wake Forest**:

The primary clinic facility for examinations and interviews will be located at the General Clinical Research Center (GCRC), on the main Wake Forest University Baptist Medical Center campus. The GCRC has a reception area, 8-10 examination rooms, a processing / shipping laboratory, a dining area and food services for study participants. If required, CT and MRI will be done in the MRI Building. Participants will park in the GCRC parking lot or in the hospital parking deck. All areas of the medical center involved in the exam are within easy walking or wheelchair distance of each other.

**Columbia**: Exams will take place at the CTSA of Columbia University Medical Center. The CTSA has a reception area, 8-10 examination rooms, a processing / shipping laboratory, and food services for study participants. If required, CT and MRI will be done in separate areas on the main campus. CT will be done in NewYork-Presbyterian Hospital; MRI will be done in the Neurological Institute.

**Johns Hopkins**: The clinic exam, echocardiogram and spirometry will take place in the cardiology division on Blalock 5 and may also include the Clinical Research Unit (CRU), part of the CTSA at Johns Hopkins Hospital. The brain MRI and lung CT examinations will take place in the Radiology Department at the Johns Hopkins Hospital which is in the same vicinity as the cardiology division.  The MESA field center staff are located in Fells Point, Baltimore, which is around 1 mile from the Hospital.

**Minnesota**: The clinic exam will take place at the University of Minnesota Epidemiology Clinical Research Center in Minneapolis, which is about 10 miles from the MESA study community. The CT and MR exams will take place at the University of Minnesota Medical Center, within approximately 1 mile of the clinic.

**Northwestern**: Participants will have the clinic exam in the Northwestern Center.  Following completion of the physical examination, questionnaires and phlebotomy, a staff member will escort participants to Northwestern Memorial Hospital EBCT and MRI Center for their examination (if required), which may be scheduled with a separate appointment.

**UCLA**: The Examination will be conducted at the research clinic in Alhambra.  If required, CT and MRI will be done in the Radiology Department at the UCLA campus (25 miles from the clinic).  Participants will park at the clinic and be transported by research center van to the Radiology Department and then back to the clinic after completion of the procedures.

## 5.5 Exam 6 Ancillary Study Aims

The MESA contract supports only the core components of the sixth exam. The innovative scientific measures from Exam 6 are being supported by grant-funded Ancillary Studies secured by MESA investigators. A brief summary of the funded Exam 6 Ancillary Studies is provided below.

### 5.5.1 From Risk Factors to Early Heart Failure: The Multi-Ethnic Study of Atherosclerosis (PIs: Alain Bertoni, MD and Sanjiv Shah, MD)

Sites: All Field Centers

Obesity, diabetes, chronic kidney disease (CKD), and hypertension (HTN) are strong risk factors for heart failure (HF) and in the context of an aging population are driving an ongoing epidemic of HF. These risk factors may specifically predispose older adults to have HF with preserved ejection fraction (HFpEF), which is projected to be more common than HF with reduced ejection fraction in the near future. Many older adults are at risk for HF due to these risk factors, and subclinical abnormalities in cardiac structure and function are also common (respectively stage A and B HF). The pathophysiology of the transition from Stage B to clinical, Stage C HFpEF is not well understood, and there is little information on the prevalence of early stage C HF. Our primary goals are to determine the prevalence of early HF, better understand the pathophysiology of HF, particularly HFpEF, and to delineate the key risk factors associated with the transition from Stage B to Stage C HF among 3500 older adults attending the Year-15 examination of the Multi-Ethnic Study of Atherosclerosis (MESA). The exam will assess functional status (six-minute walk), physical activity (survey), echocardiography, arterial stiffness measures, symptoms, risk factors, biomarkers, and in a 300 person sub-sample at Wake Forest only, cardiopulmonary exercise testing. We will utilize prior MESA data including risk factors, subclinical atherosclerosis measures, NTproBNP, and cardiac MRI to perform longitudinal analyses determining the extent to which obesity, diabetes, CKD, and HTN affect cardiovascular structure/function, predict the prevalence of Stage B and early Stage C HF, and the extent to which these risk factors and cardiovascular parameters specifically promote HFpEF.

### 5.5.2 Atrial fibrillation burden, vascular disease of the brain and cardiac MRI in MESA (PI: Susan Heckbert, MD)

Sites: All Field Centers

Atrial fibrillation (AF) is an important arrhythmia that is associated with substantially elevated risks of arterial emboli, cognitive decline, dementia, and heart failure. Existing studies of AF, including the AF analyses to date in MESA, rely on clinical recognition of AF when a patient presents with symptoms, but studies in patients with implanted monitoring devices such as pacemakers or defibrillators indicate that a large proportion of AF episodes produce no symptoms at all (subclinical AF). Therefore, relying on patient symptoms to identify AF seriously underestimates AF burden, defined as the proportion of monitored time that the cardiac rhythm is AF. Convenient new external ECG patch monitors now permit extended ambulatory monitoring for up to 14 days at reasonable cost, and permit estimation of AF burden. However, there is little information about the distribution or predictors of AF burden, the association of AF burden with brain structure and function, the association of left atrial or ventricular function or structure with AF burden, or the association of AF burden with clinical cardiovascular (CV) events. We will conduct a study of AF and AF burden at Exam 6 in relation to cerebral and cardiac structure and function and CV events in MESA. We will recruit a total of 1500 MESA participants from all 6 Field Centers using a cohort design: 1) 300 participants with clinically-recognized AF during MESA follow-up; 2) 450 participants at high risk for AF based on Exam 5 NT-proBNP level and a published AF risk score, and 3) a random sample of about 750 participants. The 1500 participants will have two 14-day ECG monitoring episodes at Exam 6 and 1350 of them will have a brain MRI one to two years later. We will relate the presence of AF and AF burden to participant characteristics and biomarkers, to variables from the Exam 5 cardiac MRI, to the brain MRI done one to two years later, and to CV events during follow-up after Exam 6.

### 5.5.3 Pulmonary microvascular perfusion in the Multi-Ethnic Study of Atherosclerosis (PI: R. Graham Barr, MD DrPH)

Sites: All Field Centers

Chronic obstructive pulmonary disease (COPD) and emphysema are, jointly, the third leading cause of death in the United States. COPD prevalence and mortality are increasing, particularly among women and minorities. Cardiopulmonary function overlaps: approximately 1/3 of patients with COPD have HF, mostly HFpEF, and 1/3 of hospitalized patients with HFpEF have COPD, when tested systematically.

The MESA Lung Study found that percent emphysema on computed tomography (CT) was the major correlate of impaired LV filling in the general population with a preserved ejection fraction. We therefore examined in the MESA Lung Study II if reduced LV-end diastolic volume, greater percent emphysema, and airflow limitation were associated with an increase in the pulmonary arterial (and venous) vascular volume on CT, which we termed the total pulmonary vascular volume (TPVV). In fact, we observed large and significant reductions in the TPVV with reduced LV-end diastolic volume, greater percent emphysema, and airflow limitation, which may reflect larger reductions in venous than arterial volumes, a site of resistance proximal to the pulmonary vasculature, or reduced total blood volume. Furthermore, findings from the smaller MESA COPD Study show that pulmonary microvascular blood flow and volume are severely reduced in COPD. We therefore propose to use novel CT measures on 1000 contrast-enhanced lung CT scans and 1000 lung CT scans among returning MESA Lung participants in MESA Exam 6 to test the following hypotheses: 1) pulmonary microvascular blood volume (PMBV) on contrast-enhanced CT is reduced and total pulmonary artery volume (TPAV) is increased in panlobular emphysema, suggesting that the site of resistance in this disease is the pulmonary microvasculature; 2) lower PMBV is associated with dyspnea and reduced activity levels; 3) lobar and overall reductions in TPVV predict progression of percent emphysema over 6 years.

### 5.5.4 Chronic obstructive pulmonary disease in non-smokers (PI: Benjamin M Smith, MD MS)

Sites: All Field Centers

Chronic obstructive pulmonary disease (COPD) is a leading cause of death globally, and in the US, where one-quarter of COPD occurs in non-smokers. Non-smokers represent 50% of the US population over 50 years old, but have been excluded from major COPD studies.

In the MESA Lung Study, we recently demonstrated that variant airway anatomy was common and associated with higher COPD prevalence. Findings were consistent among smokers and non-smokers but underpowered in the latter group. Preliminary computational fluid dynamic (CFD) modeling suggests that variant airway anatomy may alter airway resistance and particulate matter transit to the distal airways. Additional pilot work suggests that these proximal airway variants may be markers of altered airway branching through the lung, suggesting a global increase in airway resistance with the variant applying to non-smokers. Airway anatomy has developmental origins and may provide a refined phenotype (compared to lung function) for genetic investigation. The proposed study will assess respiratory symptoms, and perform full-lung CT scans and spirometry among MESA non-smokers who have not performed these study components previously in order to test the following hypotheses: 1) Variant airway anatomy is independently associated with COPD and respiratory symptoms cross-sectionally among 2,635 non-smokers and with incident COPD and decline in lung function among 2,000 non-smokers followed for a median of 10 years; 2) COPD-associated common airway variants alter regional airflow in a CFD model using participant-specific geometry, and are associated with globally altered airway branch patterns; 3) Genome-wide association study will discover genetic variants underlying the common airway variants, with replication in an independent sample.

### 5.5.5 Obesity-related epigenetic changes and type-2 diabetes (PIs: Yongmei Liu, PhD and Jingzhong Ding, PhD)

Sites: Wake Forest University, University of Minnesota, and Columbia University

The goal of this proposal is to use an integrated transcriptomics and epigenomics to identify and validate molecular features linking obesity to type-2 diabetes. The ongoing obesity epidemic calls for an improved understanding of the molecular mechanisms linking obesity to type-2 diabetes, one of its major health consequences. Genome-wide analysis of epigenetics and gene expression, a unifying pathway linking genetic and environmental factors to disease, offers a unique opportunity to understand cellular processes in an unbiased fashion. To date, epigenomic and transcriptomic studies have been hampered by use of mixed cell types and small sample sizes. In a MESA ancillary study, we purified circulating monocytes from 2,800 Caucasian, African American, and Hispanic men and women aged 55-94 years in 2010-2012. Our preliminary analysis has yielded promising signals in a transcriptomic analysis of monocytes. For example, the top obesity-associated co-expression network underlying cellular cholesterol accumulation was the strongest correlate of type-2 diabetes. We hypothesize that obesity-related changes in monocytes, including cholesterol accumulation, may contribute to the development of type-2 diabetes. In the proposed study, we will simultaneous characterize the genome-wide DNA methylation (a major layer of epigenetic modifications) and transcriptional profiles and investigate whether obesity-associated methylation and transcriptional modifications predict incident type-2 diabetes over a 7-year interval in MESA participants.

### 5.5.6 Cell-specific genomic features of Alzheimer's disease progression (PIs: Jingzhong Ding, PhD and Yongmei Liu, PhD)

Sites: Wake Forest University and Johns Hopkins University

Age is the primary risk factor for Alzheimer’s disease (AD). Using transcriptomic profiles in purified monocytes from 1,263 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), we reported a transcriptional network of co-expressed oxidative phosphorylation (OXPHOS) genes that decline with age. Our following transcriptomic analysis demonstrated that this OXPHOS network of 21 genes (FDRs<0.05) were positively associated with cognitive function. These human data, combined with our non-human primate data correlating mitochondrial function of monocytes and frontal cortex tissue and recent data in transgenic mice showing a causal role of mitochondrial dysfunction in AD, suggest that monocyte transcriptional profiles may reflect brain bioenergetic dysfunctions linking age to AD. The goal of the proposed study is to determine the impact of cell specific gene networks, especially aging-related networks such as OXPHOS, on the development of AD through an integrated analysis of genomic, epigenomic and transcriptomic data in a longitudinal community-based study. The specific aims are: 1) To determine whether aging-related changes in transcriptomic/epigenomic profiles predict cognitive decline over a 6-year follow-up; 2) To determine whether aging-related changes in transcriptomic/epigenomic profiles predict development of AD over a three-year follow-up; and 3) To determine whether differences in mitochondrial activity and content, which would be predicted from the OXPHOS alterations, relate to development of AD.

### 5.5.7 HDL-mediated cholesterol efflux and carotid FDG PET in MESA. (PI: Stephen Shea, MD)

Site: Columbia University

Observational data support the role of HDL cholesterol as a protective factor in atherosclerosis, but recent trials targeted at raising HDL cholesterol have failed to have expected clinical effects. The relevance of HDL cholesterol to atherosclerosis has potential importance both for risk prediction and drug targeting. Using newly developed assays of HDL-mediated cholesterol efflux developed in Dr. Alan Tall’s laboratory, we propose to examine the association of HDL-mediated cholesterol efflux from macrophages with measures of carotid plaque metabolic activity and plaque burden using combined FDG-PET MRI scanning. In vivo cholesterol efflux occurs from cells to HDL. This process could be defective either because of a problem with the HDL or with the cells. The second aim will use the subject’s HDL to see if it has defective ability to mediate cholesterol efflux, while the exploratory aim will use subjects’ monocytes to see if there is a cellular defect in cholesterol efflux. The specific aims are as follows:

1. To test the hypothesis that HDL-mediated cholesterol efflux using subjects’ HDL from MESA Exam 1 samples assayed in cultured macrophages is inversely associated with (a) incidence of CVD, and (b) progression of carotid plaque, after adjustment for standard CVD risk factors.
2. To test the hypothesis that HDL-mediated cholesterol efflux using subjects’ HDL assayed in cultured macrophages is inversely associated with FDG uptake in carotid plaque and with carotid plaque burden, using blood samples and PET-MRI data to be collected at MESA Exam 6. In addition, we will explore the hypothesis that HDL-mediated cholesterol efflux using subjects’ monocytes and control HDL is inversely associated with FDG uptake in carotid plaque and with carotid plaque burden, in a subsample with established plaque and normal efflux based on the subject’s HDL and cultured macrophages.

### 5.5.8 Cardiometabolic Determinants of Alzheimer's Disease: The MESA Memory Study (PIs: Timothy Hughes, PhD, and Suzanne Craft, PhD)

Site: Wake Forest University

While there is currently no means to prevent dementia, vascular and metabolic disorders are proposed to be potent modifiable risk factors for the development of AD and other related dementias. We propose to leverage MESA’s unique and extensive cardiovascular, metabolic, genomic and transcriptomic data to identify novel risk cardiometabolic risk factors that may provide key pathophysiologic targets for therapeutic intervention. In order to do so, we will offer the following components to the Wake Forest Exam 6 participants (N=540): a detailed assessment of cognitive function and brain health using MRI, optional PET imaging, and optional cerebrospinal fluid samples for AD biomarkers (40% subset, n=216). We will also reassess cognitive function and MRI three years later in 2019-20 to examine cognitive trajectory and brain atrophy. Finally, we will offer an optional brain donation to permit further study of the metabolic and vascular disease effects on AD-related pathology. While this proposal will increase participant burden at one MESA site, it will provide rich novel data that can be related to other outcomes in ongoing studies in MESA and provide a framework to support future multi-site investigations of brain aging and dementia risk in MESA. The specific aims of the study are to:

1. Identify the antecedent biomarkers of metabolic and vascular dysregulation in middle and older age that predict global and domain-specific cognitive impairment (executive function, episodic memory), reduced whole brain and hippocampal volume, microvascular injury, hypoperfusion and abnormal connectivity patterns (using structural and functional MRI), and abnormal AD biomarkers (amyloid PET imaging, cerebrospinal fluid amyloid and tau).
2. Determine if biomarkers of metabolic and vascular health prospectively predict cognitive trajectory (decline and resilience) and incident MCI and AD over 3 years of follow-up.
3. Conduct multidimensional systems-based analysis of genetic, epigenetic, and phenotypic data to determine the extent to which metabolic and vascular pathways predict dementia risk (e.g., cognitive impairment, AD brain imaging profiles, AD biomarkers in CSF).
4. Examine racial differences in metabolic and vascular dysregulation and associated epigenetic and transcriptional signatures, as they relate to cognitive function, brain MRI parameters, and AD biomarkers.

### 5.5.9 The Urinary KNOWledge (UKNOW) Study (PI: Holly Kramer, MD, MPH)

Sites: All Field Centers

The aims of the Urinary KNOWledge (UKNOW) study are to:

1. Quantify the prevalence, severity and bother of UI and other urinary symptoms (e.g. urinary frequency, urgency and nocturia) in MESA using validated questionnaires and determine whether prevalence and bother of UI and other lower urinary tract symptoms differs by sex and by race/ethnicity. We hypothesize that prevalence of both urgency UI and stress UI are higher among women than men regardless of race/ethnicity.
2. Determine the association between levels of total 25-hydroxyvitamin D (25[OH]D) and UI and other urinary symptoms in MESA by sex and by race/ethnicity. We hypothesize that total 25[OH]D levels are inversely associated with presence of urinary symptoms including UI and UI severity and bother after adjusting for covariates in both women and men.

The long-term goal is to design innovative clinical trials seeking effective and personalized approaches for the prevention and reduction of UI and other bothersome urinary symptoms. Identifying preventive strategies for urinary symptoms in women fits well with the Office of Research on Women’s Health strategic goal number 3 to “actualize personalized prevention, diagnostics, and therapeutics for women.”

### 5.5.10 Tissue Sodium, Inflammation, and Blood Pressure in MESA (PIs: Thomas Wang, MD and Deepak Gupta, MD)

Sites: NWU Field Centers

Hypertension (HTN) is a major risk factor for cardiovascular, cerebrovascular, and renal disease, and its prevalence is increasing, particularly among the elderly. While the pathophysiology of HTN is multi-factorial, two major contributors appear to be salt-sensitivity and activation of the immune system. The prevailing paradigm regarding salt-sensitive HTN is based upon increased plasma volume induced by intravascular sodium retention. Until recently, there was little consideration of the possibility that extravascular sodium stores may play a role. Through use of a novel non-invasive 23Na-magnetic resonance imaging (MRI) technique, we have demonstrated the presence of significant sodium accumulation in the skin and muscle. Experimental evidence indicates that these tissue sodium stores can trigger the immune system, particularly the T cells (Th17) that produce interleukin-17 (IL17). Activation of these T cells and the cytokines they produce, such as IL17, induces hypertension in animal models. Therefore, we postulate that tissue sodium-induced inflammation may contribute to the development and progression of HTN, particularly salt-sensitive HTN. In preliminary studies, we have shown that skin sodium content is associated with blood pressure, particularly in older individuals and men. We also found that circulating IL17 levels are higher in hypertensive compared with normotensive individuals. More definitive data from larger, community cohorts are needed. The Multi-Ethnic Study of Atherosclerosis is the ideal cohort in which to translate our preliminary findings, by testing the hypothesis that tissue sodium levels are positively associated with blood pressure and inflammation. We propose an ancillary study with the following specific aims: 1) To examine the association of tissue sodium with blood pressure in MESA participants. We will non-invasively quantify skin sodium concentration using 23Na-MRI and measure blood pressure in all eligible MESA participants at the Chicago, IL field center during exam 6 (2016-2018) and 2) To examine the association of tissue sodium with circulating cellular markers of inflammation. We will quantify the number and types of circulating immune cells, such as Th17 cells, among MESA participants who undergo MRI measurement of tissue sodium concentration.

### 5.5.12 Epigenetics of Atherosclerosis (PI: Yongmei Liu, MD, PhD)

Sites: Johns Hopkins University, Wake Forest University, University of Minnesota, and Columbia University

This study will validate predictive effects of atherosclerosis-associated genomic features identified at Exam 5 on initiation and progression of carotid atherosclerosis in a prospective study with 6-years of follow-up. It will characterize the associations of genomic features with carotid plaque vulnerability. And will identify potential temporal and causal relationships between known genetic and non-genetic CVD risk factors, genomic features, and plaque burden.

### 5.5.13 Impact of Air Pollution Exposure on Heart and Brain Aging in MESA (PI: Joel Kaufman, MD, MPH)

Site: Johns Hopkins University

This study collaborates with Dr. Heckbert’s study of atrial fibrillation to examine the effect of air pollution on early heart failure and changes in brain structure and cognition. This study will use results from the novel ECG monitoring, interrogation of implanted cardiac devices, tests from clinical exams, including speckle-tracking echocardiography, exercise testing, biomarker levels, and magnetic resonance imaging. We will deploy monitors with novel sensor technology to continuously measure air pollutants, and combine these with state-of-the-art statistical prediction methods incorporating geographic covariates, home characteristics, and chemical transport modeling. These innovative approaches enable estimation of long- and short-term exposures to PM2.5, oxides of nitrogen (NOX), nitrogen dioxide (NO2), ozone (O3), and carbon monoxide (CO) outside all participants’ homes.

## 5.6 Exam 6 Components

Informed consent and permission to release medical information will be obtained in writing in the clinic (Appendix B).

### 5.6.1 Table of Exam 6 Components by Core or Ancillary Study

The MESA contract supports only the core components of the sixth exam. The innovative scientific measures from Exam 6 are being supported by grant-funded Ancillary Studies secured by MESA investigators. A brief summary of the funded Exam 6 Core and Ancillary Studies Components is provided below in Table 12.

**Table 12: Exam 6 Components**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **PI** | **Title** | **Centers** | **Participants** | **Components** | **Time** | **Blood/Urine** | **Radiation** |
|
| Barr, Graham | Pulmonary microvascular perfusion in Multi-Ethnic Study of Atherosclerosis (MESA Lung III) | All FCsCCLabRC | 2000 MESA Lung participants | ConsentPhlebotomySpirometryQuestionnairePulse oximetryFull lung CT scan (50% with contrast) | 65 min | 250 uL blood for creatinine, Urine for cotinine | 4mSv |
| Smith, Ben | Chronic Obstructive Pulmonary Disease in Non-Smokers (MESA Lung Non-Smokers) | All FCsCCLabRC | 650 non-smoking participants | ConsentSpirometryQuestionnairePulse oximetryFull lung CT scan  | 65 min | Urine for cotinine | 4mSv |
| Bertoni, Alain/Shah, Sanjiv | From Risk Factors to Early Heart Failure: The Multi-Ethnic Study of Atherosclerosis (MESA Heart Failure) | All FCsCCLabRC | **All** participants for main components**Wake Forest** exercise testing \* | **All:** Consent, phlebotomy, functional status (six-minute walk), physical activity (survey), echocardiography, symptoms, risk factors, biomarkers , arterial stiffness**Wake only:** cardiopulmonary exercise testing in 300 participants\*  | Estimated 90 minutes for the entire sample beyond the core exam and an additional 2 hours for subsample with additional Cardiopulmonary Exercise Testing. | 20ml blood10ml urineTsai lab: glucose and creatinine.Tracy lab: urine microalbumin, NTproBNP, CorinGalectin-3, ST2, and FGF23 |   |
| Liu, Mei/Ding, Jingzhong | Obesity-related epigenetic changes and type-2 diabetes  | WF, MinnColCCLab | all participants from the 4 sites | ConsentPhlebotomy | 15 min for consent and blood draw | 32ml for transcriptomic and methylomic profiles of monocytes. |   |
| Liu, Mei/Ding, Jingzhong | Epigenetics of cognitive function  | WF, HopkinsCCLab | 1,000 MESA participants from the Wake Forest and Hopkins sites | ConsentPhlebotomyCognitive function testing (CASI, Digit Span, Digit Symbol)Alzheimer’s Disease Assessment (Uniformed Data Set) at Exam 6 and three years later | 15 min for consent and blood draw1hr 20 min cognitive function and AD assessment | 32ml for transcriptomic and methylomic profiles of monocytes. |  |
| Liu, Mei/Ding, Jingzhong | A longitudinal epigenetic study of atherosclerosis | WF, MinnColHopkinsCCLab | 1,892 with isolated monocytes and ultrasound scans available from Exam 5 | ConsentPhlebotomyCarotid Ultrasound | 15 min for consent and blood draw30 min carotid ultrasound | 32ml for transcriptomic and methylomic profiles of monocytes. |  |
| Heckbert, Susan | Atrial fibrillation burden, vascular disease of the brain and cardiac MRI in MESA (MESA AF) | All FCsCCLabRC | 1) 300 participants with AF 2) 450 participants at high risk for AF 3) a random sample of about 750 participants, for a total of 1500 participants to participate in the ECG monitoring.1350 for repeat physical function qqf and brain MRI 1-2 years later | ConsentPhlebotomyCognitive function testing (CASI, Digit Span, Digit Symbol), Physical function questionnaireApplication of an ECG patch monitor | 50 min at Exam 62 14-day ECG monitors60 min for FU MRI plus 10 minutes for physical functioning qqf  | 5ml blood for NTproBNP, galectin, and ST2 in 1500 ppts |   |
| Kaufman, Joel | Impact of Air Pollution Exposure on Heart and Brain Aging in MESA | JHU only | 20-40 non-smokers | ConsentHome air pollution monitoring | A total of 2 hours: 30 minutes at home for set-up and take down of equipment in 2 seasons [separate from Exam 6] | N/A | N/A |
| Hughes, Tim/Craft, Suzanne | Cardiometabolic Determinants of Alzheimer's Disease: the MESA Memory Study  | Wake only | Estimated 80% of Wake participants will be eligible (N=540)\*Estimated 40% (n=216) enrolled into optional biomarker intensive subgroup to receive lumbar puncture and amyloid PET imaging.\*Brain donation program optional  | ConsentPhlebotomyVisit 1: Cognitive function testing (CASI, Digit Span, Digit Symbol, UDS v. 3 and PACC )Visit 2: Brain MRI, Brain Amyloid PET Imaging\*Visit 3: lumbar puncture\* TBD: brain donation\* | 1 hour 5 min for first visit, 1 hour for brain MRI, 1.5 hours for each PET and lumbar puncture | 15 mL blood draw for future assay of established and evolving AD biomarkers | 3.47 mSv including head CT\* |
| Shea, Steve | HDL-mediated cholesterol efflux and carotid FDG PET in MESA (MESA PET) | ColCCLab | 350 ppts (~150-200 from MESA) | ConsentPhlebotomyPET MRI | 3-4 hours including transportation and preparation | 14ml blood in all for lipids panel plus additional 14ml in 40 ppts for monocytes assay at Col. (All assays run at Col.) | 4.7 mSv |
| Kramer, Holly | The Urinary KNOWledge (UKNOW) Study | All FCsCC | All participants | Consent/Check-inICIQ - Female and Male LUTS questionnaires | 30 minutes | none |  |
| Wang, Thomas and Gupta Deepak | Tissue Sodium, Inflammation, and Blood Pressure in MESA | NWUCCLab | All participants at Northwestern | ConsentMRI of lower extremitiesPhlebotomy | 45 minutes for MRI5 minutes for phlebotomy | 10 ml whole blood for flow cytometry;5 ml Serum for sodium and circulating cytokines; all to Tracy Lab |  |
| Kestenbaum, Bryan andDe Boer, Ian | Vitamin D pharmacogenomics | Wake, Col, Hopkins, NWU, Lab, CC | 1600 participants | Exam 6Consent/Check-inScreeningSeated Blood PressureAnthropometryPhlebotomyMedicationsVitamin D/Placebo randomizationExam 6aAdverse EventsPill CountSeated Blood PressureAnthropometryPhlebotomyMedications |  | Exam 61mL serum2.5mL PAX gene tubeRandom urine sampleExam 6a4mL serum, 2.5mL PAX-RNA |  |
| Core Exam |   | All FCCCLab | All participants | Consent/Check-inSeated Blood PressureAnthropometryPhlebotomyMedical HistoryPersonal History/DemographicsMedications Inventory | 90 min | 40 ml, 2.5mL PAX-gene |   |

\*optional components Exam 6 Study Component Details

### 5.6.2 Description of Exam 6 Components by Core or Ancillary Study

An outline of the planned examination and rationale is provided in the following sections.

The Field Centers will schedule participants on a minimum of 5 days a week, with an average of 1.7 participants examined per day; however, some clinics will have heavy clinics on Saturdays, with an average of 4 participants. Not all participants will be able to complete the examination in a single visit. Although clinic schedules will be tailored to the needs of participants and the arrangements of the clinics, certain constraints will be imposed to standardize data collection:

* Blood pressure, anthropometry, oximetry, and urine collection will be measured in fasting state, before phlebotomy.
* All participants will be scheduled fasting, with initial blood samples to be drawn before 10:00 AM.

The examination will start in September 2016 (unless otherwise noted) and will be completed in 18 months. All participants will undergo the following, also shown in Table 13:

* **Blood Pressure:** Resting blood pressure will be measured in the right arm after five minutes in the seated position. An automated oscillometric method (Dinamap) and appropriate cuff size will be used. Three readings will be taken; the second and third readings will be averaged to obtain the blood pressure levels used in analyses.
* **Anthropometry:** Height and weight will be measured to the nearest 0.1 cm and 0.5 kg respectively. Body mass index (kg/m2) will be used a measure of overall obesity. Girths (waist at the umbilicus and hips at the maximal circumference of buttocks) will be measured to the nearest 0.1 cm using a steel measuring tape (standard 4 oz. tension).
* **Pulse Oximetry:** Resting oxygen saturation will be measured in the seated position. A pulse oximeter with a finger probe will be used. Nail-polish will be removed, if necessary. Oximetry will be measured off supplement oxygen, if used. For participants who use supplement oxygen, supplement oxygen will be restarted immediately if they are short of breath or their oxygen saturation drops below 82%.
* **Laboratory Measurements**: These may include a lipid profile, glucose, creatinine, insulin, and HgA1C. White cells may also be cryo-preserved for future generation of cell-lines and isolation of DNA needed for genetic studies.
* **Questionnaires**: Standard questionnaires will be used to collect information about demographics, socioeconomic and psychosocial status, physical function medical and family history, medication use, dietary and alcohol intakes, and smoking.

Participants who are enrolled in the MESA Heart Failure Ancillary Study will undergo the following, also shown in Table 13:

* **Six Minute Walk Test:** The Six Minute Walk Test consists of walk for 6 minutes on a level surface to see how far the participant can go. If the participant uses supplemental oxygen, it will be used during the test.
* **Echocardiography:** All study participants will undergo comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging (TDI) using a commercially available ultrasound system with harmonic imaging to study the structure and function of the heart. Blood pressure will be recorded at the time of echocardiography.
* **Arterial Stiffness Measures:** Assessment of arterial pulse waves and pulse wave velocity will be performed using a brachial and leg cuff-based approach (with simultaneous, automated recording of the cuff blood pressure) using a Fukuda VaSera and/or SphygmoCor XCEL device. Arterial stiffness measures will occur at the same time as echocardiography.
* **Physical Activity Questionnaire:** The MESA Typical Week Physical Activity Survey is designed to identify the time and frequency spent in various physical activities during a typical week in the past month. The rationale for the selected time frame of a typical week in the past month is the intention to capture typical activity patterns in one’s daily life.
* **Heart Failure Symptoms/Risk Factors Questionnaire:** A heart failure symptoms questionnaire will be completed by all participants to determine the presence of symptoms and risk factors such as dyspnea and edema.
* **Blood and Urine Collection:** Obtain specimen for measurement of NTproBNP and microalbumin.
* **Cardiopulmonary Exercise Testing (CPET; Wake Forest participants only):** CPET will be performed at the Wake Forest exercise lab. Electrically-braked bicycle ergometry with metabolic measurement systems will be utilized. During the CPET, a 12-lead ECG will be continuously monitored and will be printed at the end of each 2-minute stage. Blood pressure will be taken during the last minute of each stage and entered into the computer. Oxygen uptake and respiratory exchange ratio (RER) will be monitored continuously throughout exercise.

Participants who are enrolled in the MESA Atrial Fibrillation Ancillary Study will undergo the following, also shown in Table 13:

* **Cognitive Function Tests:** The Cognitive Abilities Screening Instrument (CASI), Digit Span Test, and Digit Symbol Substitution Test will be administered to all participants to better understand the relationship of subclinical vascular markers with cognitive function.
* **ECG patch monitor application to the upper left chest – 2 monitoring episodes of up to 14 days each, for a total of up to 28 days of monitoring:** The ECG patch monitor detects the presence of atrial fibrillation and other arrhythmias and quantifies the atrial fibrillation burden (the proportion of the monitored time that the heart rhythm is atrial fibrillation). Each patch monitor records heart rhythm continuously for up to 14 days. At the end of the first 14-day monitoring session, the participant mails the patch to the manufacturer for rhythm interpretation. A second patch monitor will be mailed to the participant, who will apply it to the chest, and return it by mail at the end of the second 14-day monitoring period.
* **Brain MRI:** 1350 participants will undergo brain MRI on designated 3T MR scanners 18 months after the Exam 6 clinic exam. The protocol includes 1.0 mm, isotropic 3D FLAIR, proton density and T1 weighted images, a 2D axial resting arterial spin labeling (ASL) blood flow sequence, susceptibility-weighted imaging, and a resting/breath-hold blood oxygenation level-dependent (BOLD) sequence to evaluate vascular reactivity. The image analysis methodology classifies all brain tissue into either normal or ischemic gray or white matter and assigns the tissue type to all voxels, each of which is assigned to one of 92 anatomic regions of interest of the cerebrum. Ischemic tissue is further classified into necrotic (traditional infarct) vs. non-necrotic (leukoaraiosis) tissue. In addition, cerebral blood flow is calculated from the ASL sequence for each voxel as well as vascular reactivity by resting and breath-hold BOLD imaging. Variables of interest include ventricular volume, cerebral blood flow, ischemic lesion volume, infarction, and white matter disease (leukoaraiosis).

Participants who are enrolled in the MESA Lung Ancillary Study will undergo the following, also shown in Table 13:

* **Spirometry:** Spirometry consists of participants inhaling and exhaling as hard and as fast as they can through the mouth. Participants will also be asked to breathe in and out slowly through the mouth. These actions will be repeated at least three times to ensure valid readings. A SensorMedics model 1022 rolling-barrel spirometer will be used for all readings, and the procedure will follow American Thoracic Society guidelines. A new mouthpiece will be used for each volunteer. Participants with airflow limitation (prebronchodilator FEV1/FVC ratio<0.70 or <LLN) will receive two inhalations of 90 mcg albuterol via MDI and spacer, and will then repeat the spirometry test (“post-bronchodilator spirometry”).

Lung function measured by spirometry is a specific, quantifiable marker of obstructive lung disease. It strongly predicts both pulmonary and cardiac events, including incident heart failure. Post-bronchodilator spirometry is necessary to define chronic obstructive pulmonary disease (COPD), the third leading cause of death. Repeat measures over time, as we are doing in MESA Lung, define of progression of lung disease.

* **Pulmonary Blood Volume on Contrast-Enhanced CT Scan:**  Pulmonary blood volume be will be measured on contrast enhanced full-lung CT scan. Experienced and trained technologists will scan the lungs of each consenting subject in order to obtain an accurate and reproducible assessment of pulmonary emphysema. The technologist will transmit the scans to the CT Reading Center. Serum creatinine will be checked prior to the administration of contrast in order to confirm normal renal function (eGFR>60).
* **Airway Anatomy on CT Scan:** Airway anatomy will be measured on non-contrast full-lung CT scan. Experienced and trained technologists will scan the lungs of each consenting subject in order to obtain an accurate and reproducible assessment of airway anatomy. The technologist will transmit the scans to the CT Reading Center.

Pulmonary emphysema on CT scan is a specific, quantifiable marker for the presence of anatomical pulmonary emphysema. Its presence on CT scan is the contemporary measure of emphysema. Quantitative measures of emphysema on CT scan predict pulmonary and possibly cardiac events, and are strongly correlated with left ventricular filling in a pattern that resembles subclinical heart failure with preserved ejection fraction. Repeat measures over time provide a measure of progression of emphysema.

* **Respiratory Questionnaire and Safety Forms** Participants will be asked to complete a respiratory questionnaire in addition to items to ensure safety of spirometry and, if selected, administration of albuterol and iodinated contrast.

Participants who are enrolled in the MESA Lung Non-Smokers Ancillary Study will undergo the following, also shown in Table 13:

* **Spirometry:**  Pre-bronchodilator spirometry will be performed as described above, as will post-bronchodilator spirometry for participants with airflow limitation.
* **Pulmonary Emphysema on CT Scan:** Pulmonary emphysema will be measured on non-contrast full-lung CT scan. Experienced and trained technologists will scan the lungs of each consenting subject in order to obtain an accurate and reproducible assessment of pulmonary emphysema. The technologist will transmit the scans to the CT Reading Center.
* **Respiratory Questionnaire and Safety Forms** Participants will be asked to complete a respiratory questionnaire in addition to items to ensure safety of spirometry and, if selected, administration of albuterol.

Participants who are enrolled in the MESA PET ancillary study will undergo the following, also shown in Table 13 (scheduled to start in November 2016):

* **PET MRI of Carotid Arteries:** FDG PET imaging provides a non-invasive measure of inflammatory activity in plaque in the carotid vessel wall. Several studies have found strong correlations of carotid FDG uptake with macrophage infiltration and inflammatory gene expression. Thus, FDG PET will provide a unique measure of metabolic activity in macrophages in carotid plaque that we propose to relate to the HDL assays, over and above the information available from MRI regarding plaque burden, which represents a phenotypic manifestation of atherosclerosis accrued over a long period of time.
* **Additional blood collection:** 14ml blood will be collected in all participants for lipids panel, plus an additional 14ml in 40 participants for monocytes assay.

Participants who are enrolled in the **MESA Epigenetics of Type 2 Diabetes Ancillary Study** will undergo the following, also shown in Table 13:

* **Additional blood collection:** 32mL blood will be collected to assess fasting glucose and insulin measures and to assess monocyte and T lymphocyte phenotypes.

Participants who are enrolled in the **MESA Epigenetics of Cognitive Function Ancillary Study** will undergo the following, also shown in Table 13:

**Additional blood collection:** 32mL blood will be collected to assess fasting glucose and insulin measures and to assess monocyte and T lymphocyte phenotypes. Note: participants selected for both Epigenetics Studies will complete a single 32mL blood draw.

**Cognitive Function Testing:** Cognitive testing (CASI, Digit Span, Digit Symbol, UDS v. 3 and PACC) will be performed at Exam 6 and repeated 3 years later to facilitate the cross-sectional adjudication of cognition (AD, vascular dementia, mild cognitive impairment and normal) and decline in cognitive performance over time. Wake Forest participants also enrolled in the Atrial Fibrillation Study will undergo the CASI, Digit Span and Digit Symbol portion of the tests at Exam 6, then repeat these tests along with the UDS v. 3 and PACC tests 15-18 months after the initial Exam 6 visit, at the time of the Atrial Fibrillation MRI. These participants will also receive the full battery (CASI, Digit Span, Digit Symbol, UDS v. 3 and PACC ) 3 years later. All Wake Forest participants will receive an interim cognitive test (1.5 years) administered by telephone in between the two detailed cognitive assessments to assess interim changes in thinking and memory. For Johns Hopkins participants whose cognitive tests indicate possible mild cognitive impairment or dementia, we will obtain his/her written or verbal consent to a proxy interview. An interviewer at Wake Forest School of Medicine will obtain a verbal consent from a person designated by the participant who is familiar with his/her current abilities, and then administer Functional Assessment Questionnaire (FAQ) by telephone.

Participants who are enrolled in the **MESA Memory Ancillary Study** will undergo the following, also shown in Table 13:

* **Additional Blood Collection:** an additional 15 mL will be collected in ancillary study participants for future assay of established and evolving AD biomarkers.
* **Cognitive Function Testing:** Cognitive testing (CASI, Digit Span, Digit Symbol, UDS v. 3 and PACC ) will be performed at Exam 6 and repeated 3 years later to facilitate the cross-sectional adjudication of cognition (AD, vascular dementia, mild cognitive impairment and normal) and decline in cognitive performance over time. Wake Forest participants also enrolled in the Atrial Fibrillation Study will undergo the CASI, Digit Span and Digit Symbol portion of the tests at Exam 6, then repeat these tests along with the UDS v. 3 and PACC tests 15-18 months after the initial Exam 6 visit, at the time of the Atrial Fibrillation MRI. These participants will also receive the full battery (CASI, Digit Span, Digit Symbol, UDS v. 3 and PACC) 3 years later. All Wake Forest participants will receive an interim cognitive test (1.5 years) administered by telephone in between the two detailed cognitive assessments to assess interim changes in thinking and memory.
* **Brain MRI:** MRI data will be acquired in accordance with multisite protocols including ADNI2, and the NINDS Common Data Elements recommendations. All images will be acquired on a 3T Siemens Skyra MRI scanner with a high resolution 20-channel head/neck coil. Sequences include: T1 (for morphology), T2 FLAIR (to quantify white matter hyperintensities), DTI (to assess microstructural integrity of the white matter), BOLD/fMRI (for resting state brain connectivity) and pseudo-continuous arterial spin labeling (pcASL, for quantification of cerebral blood flow). Plus the addition of specialized MRI sequences to assess neurite integrity using neurite orientation dispersion and density imaging (NODDI) and cerebral microbleeds and microinfarcts in vivo using susceptibility-weighted Images (SWI). The brain MRI protocol will be the same as in the Atrial Fibrillation Study, with a couple of extra sequences. For Wake Forest participants also enrolled in the Atrial Fibrillation Study, the initial brain MRI will be completed 15-18 months after the Exam 6 visit, concurrently with the Atrial Fibrillation MRI.
* **Amyloid PET Imaging:** The subset of study participants who agree to participate in the optional Brain Biomarker Sub study (40%, n=216) will receive amyloid imaging. Amyloid PET brain imaging procedure is similar to those used in Alzheimer’s Disease Neuroimaging Initiative (ADNI) and several large multicenter clinical trials and observational studies. Participants will be injected with an intravenous bolus of up to 5-15mCi (370 MBq) (+/- 10%) of Pittsburgh compound B (PiB, over 5-10 seconds), followed by an uptake period of 40 minutes (+/- 10%) as it crosses the blood brain barrier and binds to fibrillar amyloid in the brain. Once the participant is positioned in the PET research scanner (GE 16-slice PET/CT Discovery ST Scanner), brain emission images will be acquired continuously for 30 minutes to quantify amyloid uptake analyzed in over 700 MRI-defined regions. The extent of Aβ deposition in the brain will be quantified by PiB uptake visualized by PET using standardized uptake volume ratio (SUVR) of 6 primary cortical areas (i.e., anterior cingulate, prefrontal cortex, lateral temporal cortex, posterior parietal cortex, precuneus cortex and anteroventral striatum) relative to the uptake in the cerebellum. The total radiation exposure of the PET scan is 0.347 rems, which includes exposure associated with the head CT completed prior to the PET. Participants will be monitored from the time of tracer injection until after the imaging session is complete for signs of rare adverse events. Participants will also be contacted 24-72 hours after the procedure by telephone to inquire about adverse events.
* **Lumbar CSF draw:** In a subset of ancillary study participants who agree to participate in the optional Brain Biomarker Sub study (40%, n=216), a lumbar CSF draw will be performed to collect cerebrospinal fluid (CSF) for assay of AD biomarkers using the standardized and well-established ADNI protocol established in 2004. Within two weeks of the first Exam 6 visit, participants will undergo LP at our Kulynych Center Clinic at WFSoM (proximal to the MESA examination site). After an overnight fast, 25cc of CSF will be collected into polypropylene tubes using a small gauge (22-24g) atraumatic Sprotte needle, immediately frozen and then stored for future assay of levels of β-amyloid, phosphorylated tau protein, isoprostanes and other neuroinflammatory markers, and markers of metabolic dysregulation (Mayo Clinic panel).
* **Optional brain donation:** Participants will be invited to participate in an optional brain donation program (separate from the Brain Biomarker Sub study) that will collaborate with the National Alzheimer’s Coordinating Center (NACC) database. Donated brains will be added to our existing brain bank for future analyses of existing and evolving neuropathological markers that may provide additional important information regarding the role of early cardiometabolic risk that leads to AD pathological features. These donated brains will receive standard AD neuropathological evaluation to quantify burden of amyloid plaque, neurofibrillary tangles and other protein aggregates that lead to dementia as well as evidence of infarction and atherosclerotic plaque burden in the Circle of Willis.

Participants who are enrolled in the **UKNOW Ancillary Study** will undergo the following, also shown in Table 13:

**Urinary incontinence questionnaires:** Urinary symptoms will be assessed using the International Consultation on Incontinence Modular Questionnaire (ICIQ) is a tool to identify female and male lower urinary tract symptoms.

Participants who are enrolled in the **Tissue Sodium Ancillary Study** will undergo the following, also shown in Table 13:

**MRI of the Lower Extremities:** Imaging is performed on a 3.0T MRI scanner equipped with a knee coil to allow imaging of the lower extremities. Sodium and water content is imaged from serial sequences with calibration against “standard” tubes. This is a well-tolerated procedure that takes approximately 30 minutes of scanner time to acquire images.

Participants who are enrolled in the **Vitamin D Ancillary Study** will undergo the following, also shown in Table 13 (scheduled to start in January 2017):

**Additional Blood Collection:** an additional 6.5 mL will be collected in ancillary study participants to test vitamin D levels after the 16 week intervention.

**Vitamin D/Placebo Randomization:** Participants will receive either 2000 IU vitamin D3 or placebo daily for 16 weeks. Because it is considered a dietary supplement rather than a drug, vitamin D3 is not regulated by the FDA.

Participants who are enrolled in the **MESA Epigenomics of Atherosclerosis Study** will undergo the following, also shown in Table 13 (scheduled to begin in January 2017):

 **Carotid Ultrasound:** Carotid ultrasound images will be obtained bilaterally with an M9 portable ultrasound system (Mindray DS USA, Inc., NJ).

Participants who are enrolled in the **Impact of Air Pollution Exposure on Heart and Brain Aging in MESA** will undergo the following:

**Home Air Pollution Monitoring:** A total of 2 hours: 30 minutes at home for set-up and take down of equipment in 2 seasons (separate from Exam 6).

### 5.6.3 Order of Exam 6 Components

Table 13

Day 1 Components

|  |  |  |
| --- | --- | --- |
|  | **Purpose** | **Main or Ancillary** |
| Reception and Consent | Greet the participant. Review eligibility.Explain the schedule. Determine adherence to the fasting requirement.Obtain informed consent. | Main |
| Change Clothes | Standardize and facilitate anthropometric and other measurements. | Main |
| Blood Pressures | Obtain measure of sitting blood pressure of the brachial artery, at rest. | Main |
| Pulse Oximetry | Measure resting oxygen saturation. | Main |
| Anthropometry | Measure weight, height, waist and hip circumferences. | Main |
| Phlebotomy | Obtain blood samples for lipids, chemistry, hemostasis, and other laboratory tests and for storage.  | Main/Ancillary  |
| Urine Collection | Obtain specimen for measurement of microalbuminuria. | Ancillary (HF, N=All) |
| Snack | Provide the participant with a snack. | Main |
| Echocardiography | Assess the structure and function of the heart. | Ancillary (HF, N=All) |
| Arterial Stiffness Measures | Measurement of arterial pulse waves and pulse wave velocity | Ancillary (HF, N=All) |
| Carotid ultrasound | Bilateral carotid plaque imaging with high frequency ultrasound and offline analysis of plaque presence, number, size, and other characteristics related to plaque vulnerability | Ancillary (Epigenetics of atherosclerosis, CU, UM, JHU, and WFU) |
| Medications | Obtain information on types and dosages of all prescribed and over the counter medications. | Main |
| Medical History | Obtain relevant medical history.  | Main |
| Personal History/Demographics | Obtain standard measures of education, income, wealth, occupation, smoking, and alcohol intake. | Main |
| Physical Function | Obtain measures of physical functioning. | Main |
| Urinary Symptoms | Obtain information on urinary tract symptoms. | Ancillary (UKNOW, N=All) |
| Physical Activity | Obtain information on usual low, medium, and high-level activities during past month. | Ancillary (HF, N=All) |
| Heart Failure Symptoms/Risk Factors | Obtain information on heart failure symptoms and risk factors. | Ancillary (HF, N=All) |
| Cognitive Function Test | Obtain measures of cognition function (CASI, Digit Symbol Coding, Digit Span Test). Will be repeated at 15-18 months after Exam 6 visit for participants in the Memory Study, at the time of their first brain MRI. | Ancillary (AF, N=1500) and Memory, N=540) |
|  | **Purpose** | **Main or Ancillary** |
| Additional Cognitive Function Testing | UDS v. 3 and PACC: expanded cognitive testing to permit adjudication of mild cognitive impairment (MCI) and dementia (includes standard outcomes collected by all Alzheimer’s Disease Centers to distinguish cognitive impairment from normal aging). Will be conducted 15-18 months after initial Exam 6 visit for participants also in the Atrial Fibrillation Study. | Ancillary(Memory, N=540) and Epigenetics of Cognitive Function (N=1000) |
| Respiratory Questionnaire | Respiratory symptoms and diagnosis | Ancillary (Lung and Lung Non-Smokers, N=2650) |
| Spirometry | Measure lung function (including post-bronchodilator spirometry in a subset)  | Ancillary (Lung and Lung Non-Smokers, N=2650) |
| Contrast-Enhanced Lung CT | Obtain lung CT scan to measure the pulmonary blood volume. Creatinine will be checked prior to this test. | Ancillary (Lung, N=1000) |
| Non-contrast Lung CT | Obtain lung CT scan to study the structure of the lungs. | Ancillary (Lung, and Lung Non-Smokers, N=1650) |
| ECG Patch Application | Application of ECG patch monitor. | Ancillary (AF, N=1500) |
| 6 Minute Walk Test | Measure walking distance as a measure of functional status. | Ancillary (HF, N=All) |
| Vitamin D Randomization | Dispense Vitamin D supplements or placebo. | Ancillary (Vit D, N=1600) |
| Exit Interview | Explain next steps and answer questions and solicit comments about the exam.Discuss referrals.Obtain tracking information.Schedule second visit if needed.Thank participant. | Main |

Second Visit Components

|  |  |  |
| --- | --- | --- |
|  | **Purpose** | **Main or Ancillary** |
| PET MRI  | Provides a non-invasive measure of inflammatory activity in plaque in the carotid vessel wall | Ancillary (MESA PET, N=350) |
| Cardiopulmonary Exercise Testing | Provides an assessment of activity limitation and dyspnea | Ancillary (MESA HF, N=300) |
| Brain MRI | In Atrial Fibrillation study, obtain MRI of the brain 18 months after Exam 6 to evaluate atrial fibrillation burden in relation to brain structure and function. Provides gray and white matter volumes, perfusion, and microvascular injury. In Memory study, brain MRI occurs within 2 weeks of first Exam 6 visit and is repeated 3 years later. First MRI will be conducted 15-18 months after Exam 6 visit for participants also in the Atrial Fibrillation Study, and will be repeated 3 years later. | Ancillary(MESA Memory, N=540; MESA AF, N=1350) |
| Brain Amyloid PET Imaging | An optional test that quantifies β-amyloid deposition in the brain. Occurs within 2 weeks of first Exam 6 visit Will be conducted 18 months after the Exam 6 visit for participants also in the Atrial Fibrillation Study. | Ancillary(MESA Memory subset, N=216) |
| MRI of the lower extremities | Imaging is performed on a 3.0T MRI scanner equipped with a knee coil to allow imaging of the lower extremities. Sodium and water content is imaged from serial sequences with calibration against “standard” tubes.  | Ancillary (Tissue Sodium, N=753) |
| Vit D Ancillary Study Exam 6a | Seated Blood PressureAnthropometryPhlebotomyMedicationsPill CountAdverse Events | Ancillary (Vit D, N=1600) |

Third Visit Components

|  |  |  |
| --- | --- | --- |
|  | Purpose | Main or Ancillary |
| Lumbar CSF draw | An optional test that collects cerebrospinal fluid (CSF) for assay of AD biomarkers. Occurs within 2 weeks of first Exam 6 visit Will be conducted 18 months after Exam 6 visit for participants also in the Atrial Fibrillation Study. | Ancillary(MESA Memory subset, N=216) |

Note: Ancillary study components above are set; additional components may be added for other ancillary studies.

## 5.7 Cohort Surveillance and Follow-up

Annual follow-up phone calls will be used to maintain contact, to correct addresses of participants, and to ascertain medical events between the examinations. Follow-up contacts will be made within a month of the target.

During the follow-up telephone interview, affirmative answers to preliminary queries about new medical conditions will be followed up to complete an additional, more detailed questionnaire specific to the type of event which they reported. The additional questionnaire will gather information on hospitalizations, treatments and lifestyle changes recently instituted.

## 5.8 Clinical Review and Classification of CVD Events

In order to classify cardiovascular events during follow‑up in MESA, information will be collected from a variety of sources, including public files (death certificates), medical records from hospitalizations, autopsy reports, and interviews from participants, and in some instances, interviews or questionnaires from their physicians, relatives, or friends. Criteria for classification of events and algorithms are detailed in the Manual of Operations.

During the MESA exam or follow‑up contacts, a participant may report a hospitalization for a health endpoint of interest to the study (CHD, peripheral vascular disease, congestive heart failure, cerebrovascular disease). In these cases the hospital record will be retrieved and abstracted for inclusion in the MESA database. (The participant will have signed a medical release form allowing study access to records.)

While the great majority of data will be collected from existing documents such as the medical records, information will also be gathered from in‑person interviews. The data collection tasks which involve contact with the participants, their physicians or relatives are summarized below.

* Participants who die from cardiovascular disease: Physicians and their relatives or friends will be interviewed.
* Participants who suffer an incident or recurrent non‑fatal CVD event: The majority of these participants will have been hospitalized for their events. For those few participants who suffer MI, stroke or worsening congestive heart failure without being hospitalized, the participant's physician will be asked to complete a brief questionnaire.
* Participants who screen positive for possible CVD events on surveillance contacts: Participants who screen positive for newly diagnosed angina, claudication, or congestive heart failure in the medical history will have the appropriate supplemental questionnaire administered (angina, CHF or claudication). (See Section 5.6).

Information from these sources of hospitalizations and deaths will be reviewed by the designated local and central reviewers and a determination of the occurrence of coronary heart disease, peripheral vascular disease and cerebral vascular disease will be made according to defined criteria (see Manual of Operations). Cause of death will also be determined.

Standard information abstracted from available sources will be produced for reviewers on a secure Web site. Reviewers will discuss and resolve any discrepancies in final diagnoses. If the reviewers are unable to agree, the Morbidity and Mortality Committee will meet. (This is expected to occur in a minimum of situations.)

## 5.9 Notification of and Referral for Study Findings

One of the benefits of the study to the participants will be the provision of an extensive battery of medical tests at no cost to them. This information will be made available to the participant and his/her physician if desired. An initial report will summarize results available at the completion of the clinic visit, such as height, weight, and blood pressure. This report will be given to the participant at the end of the clinic examination or mailed to the participant 1-2 weeks after the examination. A second report will be mailed within one month after the clinic visit and will include routine laboratory results (e.g., plasma glucose, lipids, and serum creatinine). A third report will be mailed 1-2 months after the completion of the examination and will include results of additional tests or procedures. Participants and their physicians (or health care providers) will be immediately notified if potentially serious medical problems are identified during any of the examinations. A referral system will be established based on the urgency of the need for medical attention. Criteria for emergent and urgent notification are provided in the Manual of Operations section entitled, "Notification and Referrals."

# **Data Management**

## 6.1 Field Center Data Management

### 6.1.1 Field Center Procedures

The following principles and procedures will be followed at the Field Center for data collection:

* Most clinic data will be entered directly via computer screens and will not include other personal identifiers. Only the tracking form will have the participant’s name and address.
* Study records will be stored in locked cabinets in a locked room.
* Only the study personnel will have access to the data and the codes.
* All computerized information will be protected by access codes known only to the principal investigator and certain designated staff members.
* No data will be published with participant names or other identifying information.
* All staff members will be trained to keep participants' information confidential, and will be informed of the penalty for breach of confidentiality.

### 6.1.2 Data Entry and Transmission

Each Field Center will be responsible for entering the clinic data it collects. Data entry will be accomplished by entering results or responses via computer screens that connect to the Coordinating Center database. This task will be performed by the technician or interviewer who is collecting the data. The data entry software will be programmed for table lookups, range checks, skip pattern rules, consistency checking and ID selection from a list of valid ID numbers. Data will reside centrally on the password-protected CC database, and Field Center personnel will be able to perform updates as needed.

Field Center personnel will electronically transfer data to the Coordinating Center at least once a week. This transfer will include limited exam data, events data, tracking data, and follow-up data.

## 6.2 Confidentiality and Security

The consent form signed by the participant will provide written assurance that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act of 1974 and by the Health Insurance Portability and Accountability Act (HIPAA). Each center which has data with personal identifiers will provide file security so that confidential data are not released. Specifically, participants will be informed that: (1) the only people who will know that they are research participants are members of the research team and, if appropriate, their physicians or health care providers; (2) no individual identifying information about them will be disclosed to others, except as part of ascertainment of events information, as permitted by the consent form, or 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.

## 6.3 Coordinating Center Data Management

### 6.3.1 Development of the Database Management System.

The Coordinating Center has established an “Intranet” for use by all sites involved in MESA. (Intranet is the term used for the implementation of Internet technologies within an organization, rather than for external connection to the global Internet.) Using the Intranet, all sites will have access to selected Coordinating Center databases for uploading of data and queries to the database. As members of our Intranet, each Field Center and Central Reading Centers and Laboratory will have access to downloadable data files as well as electronic versions of manuals, forms, staff directories and collaborative manuscripts. Having only one central copy of these documents and files will make it easier to assure that all centers have access to current information. Safeguards will be put in place so that only specific files can be accessed over the Intra- or Internet, and then only by authorized users.

The Coordinating Center developed a series of databases to store and manage data which forms a comprehensive system linked by unique participant ID numbers. There will be one raw database to which data files from Field Centers and Reading Centers and Laboratory will be uploaded. After local cleaning and verification of the data, they will be loaded into the appropriate master database accessible only by Coordinating Center personnel. This master set of databases at the Coordinating Center will not be accessible to anyone on the Intra- or Internet; they will physically reside on a different computer.

A tracking database will be developed for the sole purpose of monitoring data completeness for each individual at each visit. This database will be programmed so that the different sets of data expected from different sub-sets of the cohort at various points in time can be tracked separately. The database will include both Field Center data and Reading Center data. Reading Center data will be tracked to assure that the data have been: (1) collected at the Field Center; (2) sent to the Reading Center; (3) received at the Reading Center; (4) processed at the Reading Center and sent to the Coordinating Center; and (5) received at the Coordinating Center.

Data on cardiovascular events will reside in a separate database as well. Because of sensitivity issues surrounding medical record data, this database will not be accessible over the Web. However, Field Centers will be able to check on the status of data for a particular event on the Web.

Since the Field Center, Reading Center and Central Laboratory staffs will be allowed to edit and correct data in the raw database, there will also be a database that tracks all changes to data fields. This change database will record the date, time, who made the change, name of variable, form it came from, and the reason change was necessary as well as the original value. Included in this database will be documentation of changes to computed variables.

The Coordinating Center has also developed and maintains a database to track publications and presentations. The database allows quick and easy access to information about publications and presentations for authors, the Publications and Presentations Committee, the Steering Committee, the Monitoring Board and the NHLBI Project Office. Elements of the database include: title, authors, manuscript proposal date, date for completion, submission date to journal, status of manuscript with the journal, publication date, and abstract. Information from this database is accessible for viewing on the web to all investigators.

All data sets that are ready for dissemination to study investigators or staff will be moved to the computer that is acting as the Coordinating Center web server as compressed files ready to be transferred. Medical record security is a current topic of concern, and the Microsoft SQLServer databases will be fully protected with user/password security and “firewall” software that acts as a screening tool, providing an electronic barrier to unauthorized use of a computer system by hackers or other unauthorized users. To maintain privacy, no names, addresses, Social Security numbers or other personal identifiers will reside on an Intra- or Internet accessible database.

### 6.3.2 Development of Web Sites

The Coordinating Center has developed and maintains three web sites, an external site for the general public, a web site for MESA participants, and an internal site for study investigators and personnel.

External Web Site This external web site informs its target audiences about the project, generates project support, and reduces mailing and printing costs. Specifically, the external web site includes: (1) Project description and rationale; (2) Contact information for project centers and staff; (3) Text of project newsletters; (4) Study component schedules of administration; (5) Study forms and manuals; (6) List of publications with copies of abstracts; and (7) Search capability.

Participant Web Site This web site is specifically targeted to MESA participants. The purpose is to disseminate up-to-date information about the study, report new findings, and post appropriate links and documents that participants would find interesting.

Internal Web SiteThis web site provides a way for project staff to facilitate communication, share information, reduce mailing and printing costs, and increase efficiency. Staff are able to both view and contribute documents or files to this web site. Bulletin boards will be used as the primary method of communication for each study committee. In addition, the web site will be used to allow multiple authors of a manuscript to view the current draft of the manuscript and then make revisions online. The internal web site will also include: (1) Data files for download, at varying levels of access; (2) Data documentation; (3) Access to P&P database; (4) All study Manuals; (5) Study component schedules of administration; (6) E-mail directory of project staff; (7) Calendar of project deadlines; (8) Steering Committee and other reports; (9) Project meeting schedules; (10) Links to other web sites of potential interest; and (11) Search capability.

Passwords are used to maintain the security of this site. One password will be required to access the site, and a second password, which will change frequently, will be required in order to download data.

### 6.3.3 General Coordinating Center Management

The following principles and procedures will be followed by the Coordinating Center:

* Only MESA Coordinating Center staff will have access to the Coordinating Center's personal computers, thus simplifying security arrangements.
* The Coordinating Center will store MESA data on servers employing fault tolerant RAID volumes. “RAID” stands for Redundant Array of Inexpensive Disks, which means that all data stored on the server is written across multiple disks. This helps to protect against data loss due to mechanical disk failure. The Coordinating Center will also maintain incremental system backups on a nightly basis using secure offsite network backup provided by UW Technology. This includes a copy of the data stored outside the seismic area at a secure facility in Eastern Washington. Additionally, backups may be retrieved from this system using the version stored locally on campus servers in less than 10-15 minutes. The last backup of each year is also kept as a permanent archive throughout the study period. System backups are routinely checked to make sure that they are readable and complete. Raw data in a computer readable form (from data transmissions or data entry at the Coordinating Center) will be archived separately.
* Sensitive data, such as participant names and social security numbers, will be kept in a separate data base table with additional security passwords required for access.

## 6.4 Reading Center and Laboratory Data Management

The Reading Centers will receive data from the clinics transmitted electronically. After receiving the data, Reading Center personnel will retrieve the studies and either send the medium back to the Field Center or store them on site. A list of studies received will be sent to the Coordinating Center for purposes of tracking. Processed data from the Reading Center will be transmitted to the Coordinating Center each week.

The Central Laboratory will receive blood and urine specimens and an inventory list from the clinics on a weekly basis. A list of samples received will be sent to the Coordinating Center to add to the Tracking Database. Analysis results will be transmitted to the Coordinating Center every week.

Reading Centers and Laboratories will perform routine backups of all data regularly.

# **Participating Centers Organization, Roles and Responsibilities**

## 7.1 Organizational Structure

A diagram of the organization structure of the study is in Appendix C.

## 7.2 Participating Organizations

The centers involved in the study and their principal investigators are listed in Table 14. Awards for the original MESA contract were made on January 15, 1999 and additional centers were added through the various exams and ancillary studies. All Exam 6 investigators are listed in Appendix D.

 **Table 14**

**List of Centers and Principal Investigators in MESA**

Center Site Principal Investigator

Coordinating Center University of Washington Richard Kronmal, PhD

 Robyn McClelland, PhD

Field Center Columbia University Steven Shea, MD

Field Center Johns Hopkins University Wendy Post, MD, MS

Field Center Northwestern University Kiang Liu, PhD

Field Center University of Minnesota Aaron Folsom, MD, MPH

Field Center University of California at Karol Watson, MD, PhD

 Los Angeles

Field Center Wake Forest University Gregory Burke, MD, MS

Central Laboratory University of Vermont Russell Tracy, PhD

Echocardiography Northwestern University Sanjiv Shah, MD

Imaging Reading Center

Magnetic Resonance Johns Hopkins University David Bluemke, MD, PhD

Imaging Reading Center\* Joao Lima, MD, PhD

ECG Reading Center\* Wake Forest University Elsayed Soliman, MD, MSc

Cardiac CT University of California Matthew Budoff, MD, PhD

Reading Center\* at Los Angeles (UCLA)

Ultrasound Reading Tufts Medical Center Joseph Polak, MD

Center\* Daniel O’Leary, MD

Ultrasound Reading University of Wisconsin James Stein, MD

Center\*

Lung CT University of Iowa Eric Hoffman, PhD

Reading Center†

Spirometry Reading Center† Columbia University R Graham Barr, MD DrPH

 John Hankinson, PhD

\*Centers not directly involved in MESA Exam 6.

†Supported by the MESA Lung and MESA COPD ancillary studies.

The Project Office is in the Prevention and Population Sciences Program, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute.

The roles and responsibilities of each center are as follows:

### 7.2.1 Coordinating Center

* + Establish a study timeline to guide overall study activities, including planning and oversight of Steering Committee and subcommittee activities.
	+ Provide leadership and coordination for establishing and maintaining study communications, including the use of conference calls, meetings, and a central, accessible web site.
	+ Provide administrative leadership and scientific coordination for the development of the final study protocol, manuals of operations, and forms, including sample selection, recruitment, certification of field staff, examination, interview, medical record abstraction and follow-up procedures.
	+ Develop, implement and maintain a data base management system capable of: storage of existing participant data; data entry and weekly transmittal at each of the Field Centers, Reading Centers and Laboratories; generation of reports for use by Field Centers, Project Office and Steering Committee; and summaries of exam to be sent to participants and their physicians.
	+ Coordinate training and certify Field Center staff in examination procedures and interviews, in accordance with protocol.
	+ Purchase, distribute, and coordinate utilization of appropriate common mechanical and electronic equipment among all centers, including computer hardware and software and electrocardiogram machines.
	+ Develop and maintain manuals of operations describing in detail study activities at each participating center.
	+ Develop, implement and maintain system for quality control of data to verify completeness, compare distribution of values from different Field Centers and different examiners, identify outlying values for separate review, review adherence to schedules for reexaminations and other data collection and analyze laboratory performance on external standards and blind duplicates.
	+ Provide leadership for the editing, analysis, and publication of study data in collaboration with the Steering Committee and the NHLBI Project Office.
	+ Provide support for conduct of Monitoring Board meetings.
	+ Select subcontractors and manage subcontracts for Field Centers, designated laboratory measurements, and specimen repository.
	+ Produce data sets of MESA data for use by investigators and for distribution to the public, according to NHLBI guidelines.

### 7.2.2 Field Centers

* Provide individuals with expertise in cardiovascular epidemiology, clinical cardiovascular disease, noninvasive imaging, laboratory measurements, statistics, longitudinal studies management, and related fields who will participate in the development of the protocol, the manual of operations and the specific forms used for recording interviews, abstracting records, and examination results.
* Examine, and maintain follow-up of currently enrolled participants.
* Provide adequately trained and certified technicians and imaging centers to carry out data collection procedures, and implement quality control procedures as determined by the Coordinating Center.
* Inform participants and their physicians of any important medical findings discovered on examination.
* Enter all data derived from the recruitment interview, clinic examinations, and surveillance phone calls into computer storage and transmit to the Coordinating Center.
* Collect, process, and transmit data to appropriate reading centers, and of blood samples to laboratories.
* Collaborate with the Steering Committee, Project Office and Coordinating Center in analyses of data and publication of results.
* Participate in investigations pertaining to aberrations in quality control and in making procedural corrections, as necessary.

### 7.2.3 Central Laboratory

* Recommend specific blood and urine analyses to be performed on all participants and other analyses on selected cases and controls.
* Develop, with assistance and input from the Blood Laboratory Subcommittee and the Steering Committee, protocols for Field Center collection and processing of blood samples, and analysis of samples at the Central Blood Analysis Laboratory.
* Recommend feedback to participants and their physicians regarding measurements.
* Perform or coordinate the performance of analyses.
* Enter all data derived from the blood analyses into computer storage and provide measurements to the Coordinating Center in a computer readable format.
* Design and implement quality control measures for blood collection and processing at the Field Centers, and for analysis of samples at the Central Laboratory.
* Train, certify, and oversee quality control monitoring of Field Center laboratory technicians in details of blood collection and processing protocols, and of laboratory technicians in the analysis of samples.
* Participate in analysis and publication of study results.

### 7.2.4 Project Office

* Participate in the Steering Committee and its subcommittees in development of the study protocol.
* Ensure that the study meets its scientific objectives while remaining on schedule and within budget, and work with the Steering Committee to resolve any technical problems that arise.
* Monitor the progress of the study by maintaining close contact with investigators, reviewing study documents, inspecting and accepting contract deliverables, and performing periodic site visits.
* Interpret the contract Statements of Work and any other technical performance requirements for the Steering Committee.
* Assist Contracting Officer in authorizing reimbursement of costs and in negotiating any changes in the contract Statements of Work, periods of performance, or delivery schedules.
* Participate in analysis and publication of study results.

### 7.2.5 Contracting Office

* Participate in the Steering Committee and its subcommittees to assure that study resources are used within funding allotments and in accordance with contractual requirements.
* Provide Project Officer an interpretation of contractual requirements.
* Monitor the study expenditures and deliverables. Recommend appropriate action to Project Officer and upon Project Officer’s approval provide authorization for any required action.
* Assist Project Officer in negotiating any funding and/or contractual changes. Upon Project Officer’s approval provide authorization for funding and/or contractual changes.

## 7.3 Committee Structure and Charges

The Steering Committee is comprised of the principal investigators from the Coordinating Center; six Field Centers; and MRI Reading Center; Central Laboratory; and the Project Officer. Subcommittees include Design, Laboratory, MRI, CT, Morbidity and Mortality, Operations, Participant Relations, Publications, Ancillary Studies, and Quality Control. Subcommittees make recommendations to the Steering Committee, which finalizes decisions. The charges to the specific committees are provided in the following sections.

### 7.3.1 Steering Committee

* Develop and approve all aspects of the study protocol.
* Identify modifications of the study protocol or operational policy as necessary, and recommend changes to NHLBI.
* Resolve operational problems.
* Review reports of the Coordinating Center regarding study progress.
* Advise and assist the Field Centers, Coordinating Center, Reading Centers, Central Laboratory and Project Office in the performance of the study.
* Review ancillary studies for compatibility with MESA goals, and recommend priorities to the MESA Monitoring Board and NHLBI.

### 7.3.2 Design Committee

* Evaluate and prioritize proposed examination components and make recommendations to the Steering Committee regarding inclusion.
* Consider timing of the components, repetition of the component, participant burden, and cost, along with scientific value.

### 7.3.3 Participant Relations Committee

* Oversee the timely provision of individual clinical examination results to participants.
* Develop, coordinate and disseminate participant information material, including ongoing updating and enhancement of a participant web site.
* Advise and coordinate with the Operations Committee on strategies to maximize participant satisfaction with the study and retention.
* Develop a regular newsletter to keep participants informed about the study and foster good will.

### 7.3.4 Operations Committee

* Evaluate recommended examination components in terms of participant burden; operationalize approved examination components.
* Make recommendations to the Steering Committee regarding methods to minimize participant burden and optimize comfort, interest, and satisfaction.
* Assure that participant concerns are addressed and ensure maximum participation.
* Develop methods to train examination staff; plan and execute training for examination procedures; develop procedures for exam technicians to obtain and maintain certification to perform study procedures; plan and monitor the pilot study.
* Develop the Manual of Operations for clinic operations.
* Develop system of "alert" values and procedures for providing feedback to and referrals for participants and their health care providers.

### 7.3.5 Quality Control Committee

* In conjunction with the Operations Committee, develop methods to assess accuracy and reliability of examination methods and control variability, including collection of quality control data.
* Evaluate quality control data, report to the Steering Committee on a regular basis, alert the Steering Committee when reliability or variability are unacceptable, and recommend and oversee further investigation and corrective action, as appropriate.

### 7.3.6 Laboratory Committee

* Recommend blood-based laboratory measurements, based on the study goals. Develop a protocol for Field Center phlebotomists.
* In conjunction with the Quality Control Committee, recommend a plan for quality assurance, and develop and recommend methods to assess comparability among centers and to investigate reasons for lack of comparability or unacceptable variability among Field Centers or within a Field Center.
* Recommend further investigation and corrective action, as appropriate.

### 7.3.7 Morbidity and Mortality Committee

* Oversee implementation of protocol for identifying and evaluating cardiovascular events, including (1) clinical event manifestations of coronary heart disease, cerebrovascular disease, and congestive heart failure and (2) clinical diagnostic testing and interventions.
* Classify cardiovascular events.

### 7.3.8 Ancillary Studies Committee

* For studies intended to be funded from other than contract funds, review, recommend modifications to the science and logistical conduct, and recommend approval or disapproval to the Steering Committee.

### 7.3.9 Publications and Presentations Committee

* Oversee and enforce policies for proposing and conducting data analyses; establishing authorship and reinforcing responsibilities of authorship; monitoring progress of data analyses; and use of data in abstracts, presentations, and publications.
* Assist in the maintenance of the publications data base of the Coordinating Center.
* Recommend to the Steering Committee directions for publications and presentations.
* Review, recommend modifications for, and consider for approval all abstracts, presentations, manuscripts, and other data analyses emanating from the study.

# **Quality Assurance and Quality Control**

## 8.1 Overview of Quality Assurance and Quality Control

Activities undertaken to ensure the highest possible data quality for MESA can be divided into two areas: Quality Assurance and Quality Control. Quality assurance activities entail all steps taken prior to data collection to assure accuracy and to minimize errors. Quality control activities are the steps taken after data are collected to examine quality, particularly to measure reproducibility and identify errors.

MESA quality assurance will emphasize training of staff and maintenance of equipment. Quality control procedures will emphasize the technical procedures included in the exam, and will be designed to permit rapid identification of problems early enough in the study to have an effect. Due to the finite resources, both in terms of participant time and burden and Field Center and Central Agencies staff and time, quality control must be concentrated on key study components. The Operations Committee is charged with quality assurance related to training. Equipment maintenance is overseen by appropriate technical committees, such as the MRI Committee, while compliance with maintenance is monitored by the Quality Control Committee. The Quality Control Committee is charged with developing the details of the QC protocol; for monitoring its implementation during the data collection phase; and for quickly identifying and resolving any problems that are identified.

### 8.1.1 Quality Assurance

Quality Assurance activities are those performed before the data are collected, to minimize the number of data errors that occur. Primary steps in assuring good quality of study data are adequate training and periodic observation of study personnel. A highly motivated, conscientious staff may be the best guarantee of data quality. Other key considerations include adequate monitoring of technician performance by supervisory staff at the Field Centers and support units. Such monitoring can identify and correct problems weeks or months before they would become apparent from Quality Control activities such as statistical analyses performed by the Coordinating Center.

Quality Assurance activities in MESA will include: (1) a well-documented, standard protocol to be performed at all sites in an identical manner; (2) centralized training of technicians so that all technicians are trained to perform MESA measurements in the same way; (3) requirements regarding demonstrated proficiency in performing MESA procedures before initial certification of technicians is granted, and requirements for a minimum number of procedures required to maintain certification; (4) routine observation of technicians to verify adherence to protocol; and (5) routine calibration of equipment such as scales and blood pressure devices.

### 8.1.2 Quality Control

Quality Control activities are those performed after data are collected, to identify any errors which have occurred. Quality control in a large study such as MESA has two major purposes: (1) to identify problems in data collection and measurement in time to institute appropriate corrections; and (2) to quantify the quality of data collected over the course of the study so as to provide information necessary to interpret study results. To accomplish the first goal, adequate data must be accumulated to enable valid analyses to be performed within a brief period after initiation of data collection. To accomplish the second goal, sufficient data must be compiled throughout the study to detect any drift or deterioration in data quality over time. Because of finite resources, both in staff and in acceptable burden on participants, each component of a quality control program must be selected on the basis of assessing the need, feasibility, and overall importance to the main goals of MESA.

Data from the specialized Reading Centers and the support laboratories are among the most important collected by MESA. High quality data must be obtained from these units in order to fulfill the primary goals of the study. For these reasons, the Quality Control Committee will place special emphasis on quality control of these units.

For the other examination components, the Coordinating Center can provide considerable quality control information by relatively simple analyses of data acquired from all participants. Monitoring of the distribution of individual values and of mean or median values by technician, center, time, subject subgroup, etc. may identify many problems. Because of the large numbers available, this will be a particularly useful way of detecting many problems. Some of this information, such as noting problems with blood processing at a certain Field Center, may be reviewed by a central unit.

The following sections summarize the quality control procedures to be conducted by the individual Central Laboratories and Reading Centers.

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## 8.2 Central Laboratory

All blood and urine samples collected for MESA will be shipped to the Central Laboratory every other week. Special shipping schedules will be set up for each Field Center to avoid loss of samples due to arrival on weekends or holidays. Quality control procedures will include:

* Sample monitoring
* Assay monitoring
* Participation in extrinsic quality assurance programs
* Measurement of blind duplicates from Field Centers
* Monitoring of Field Center logs
* Site visits to Field Centers
* Monitoring of local hematology quality control

For all of the central Reading Centers, certain scans will be cycled through the reading process at pre-defined intervals in order to assess whether any drift is occurring in the interpretation of the images.

# **Study Policies**

## 9.1 Publications and Presentations

The policies governing proposals for data analysis, presenting MESA data, and publication are provided in Appendix E.

## 9.2Ancillary Studies

The MESA investigators and NHLBI encourage ancillary studies, (sub studies that are supported by other than contract funds) to enhance the scientific contributions of the study. Policies and conditions for proposing ancillary studies, collaborating, and monitoring ancillary study activities are provided in Appendix F.

# **MESA Monitoring Board**

The MESA Monitoring Board has been appointed by the Director, NHLBI, to advise the Institute on the design and conduct of the study and on the analysis and interpretation of results. Meetings of the Board will be held approximately annually. Members of the Board are listed in Appendix G.

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# **Appendix B: INFORMED CONSENT TEMPLATE**

**Multi-Ethnic Study of Atherosclerosis (MESA) Exam 6**

**Informed Consent Template**

**Study Description**

You are invited to participate in the sixth examination of the Multi-Ethnic Study of Atherosclerosis (MESA), a research study sponsored by the National Heart, Lung, and Blood Institute and conducted by *[PI name]* from *[Department and Institution]*. The National Heart, Lung, and Blood Institute will obtain information from this study under data collection authority Title 42 U.S.C. 285 b. The *[Institute Name]* Institute is also supporting certain study components.

MESA is an ongoing study that includes over 6,800 participants from six centers across the country. You enrolled in MESA during July 2000 – August 2002, along with [*number*] other residents of [*location*].

Your participation in this study is entirely voluntary. You should read the information below and ask questions about anything you do not understand before deciding whether or not to participate in the sixth examination.

**Purpose of the Study**

The main purpose of MESA is to study heart disease and diseases of the blood vessels beginning in the early stages. People who may have early heart disease, known as “sub-clinical” heart disease, may not know it because they feel well. MESA is studying why some people develop clinical conditions such as heart attack, heart failure, and stroke. In order to learn this information, the people in the study are being followed for many years. Over time, MESA has studied other conditions, such as lung disease and visual impairment, and may include other conditions in the future.

**Procedures**

If you decide to take part in the examination, it will require *[X-X]* hours of your time, which may be split into two visits. The examination will include the following procedures, many of which you have done before:

1. Measurements of your blood pressure, height, weight, waist and hip size, and pulse oximetry. Pulse oximetry uses a sensor placed on your finger to painlessly measure the amount of oxygen in your blood. If you usually use supplemental oxygen, you will remove it for about 10 minutes for this test. These procedures will take about 25 minutes.
2. Interviews about previous illnesses, hospitalizations, physical activity and function, symptoms and risk factors, urinary incontinence, smoking, and use of alcohol and medications. It will take about one hour to complete the questionnaires.
3. Collection of a fasting blood sample (up to X tablespoons) to measure blood sugar, blood fats (including cholesterol), and other substances that may be related to the risk of disease. Samples will also be frozen and stored indefinitely for future analysis. The blood draw will take about 15 minutes, including preparation.
4. Collection of a urine sample (approximately one cup) to be frozen and stored for future analyses. The urine sample collection will take about 5 minutes.
5. A walk test to determine how far you can walk in six minutes. If you use oxygen when you walk, you will use it for this test.
6. Echocardiography, which is an ultrasound imaging test that uses sound waves to show how well your heart muscle and valves are working. A transducer (a device that looks like a microphone) is placed on your chest and is used to bounce sound waves off of your heart. These waves are harmless. A computer changes the sound waves into images that are seen on a video screen. The echocardiogram will take about 25 minutes.
7. Arterial stiffness measurement, which is a brief, painless test that uses blood pressure cuffs on your arms and legs to detect and record pulse waves in your arteries. The arterial pulse in your neck may also be checked. This measurement will take about 5 minutes.

In addition, you are asked to undergo the procedures next to the checked boxes:

* Spirometry: This is a lung function test that involves taking in a deep breath, then breathing out into a tube, as hard and as fast as you can, three or more times. A new, clean mouthpiece is used for each participant. Based on your spirometry test results, you may be asked to repeat the test after inhaling a bronchodilator (albuterol), which opens up the air passages. About one in five participants will be asked to use albuterol. You will be asked some questions about breathing symptoms and disease and to make sure that spirometry, with or without albuterol, is safe for you. Spirometry will take about 20 minutes.
* Computed Tomography (CT) of the Lungs at *[location]*: The CT scan is a special type of x-ray examination that will be done to examine your lungs. You will be asked to lie on a table with just the upper part of your body inside the CT scanner. You will need to remain still and, at times, hold your breath for about 10-20 seconds during the test. The CT scan will take about 30 minutes.
* CT of the Lungs with Contrast Dye: If you have normal kidney function, have not had an allergic-type reaction to contrast dye in the past, and agree you will be given an intravenous (IV) contrast dye during the CT scan described above. The purpose of the contrast dye is to see the blood vessels in the lungs. The procedure is the same as described in the prior paragraph for the CT scan except that an intravenous line will be placed in your arm, through which the contrast dye will be injected. Several small patches will also be placed on your chest to see your heart rhythm during the test. The contrast dye will add about 5 minutes to the CT scan.
* Heart rhythm recorders:

A patch that records your heartbeats will be applied to your upper left chest. This heart rhythm recorder, called a Zio Patch, is like a large band-aid that sticks to the skin. It will stay in place for up to 14 days and will record your heartbeat for the whole time. The purpose is to find any abnormal heart rhythms: too fast, too slow, or irregular. You will write down the time you go to bed and wake up each day, and any symptoms you feel. At the end of 14 days, you will peel the patch off, place it in a prepaid mailing box that we will give you, and return it for reading of the information stored on the patch. After that, we will mail you a second Zio Patch for you to apply again to the upper left chest and wear for up to another 14 days. You will again write down sleep and wake times and symptoms. At the end of the second 14 days, you will again return the patch by mail in a prepaid mailing box. These 2 patches will provide a total of up to 4 weeks of heartbeat recording. The patch does not transmit the heartbeat information to anyone, but simply stores it for later reading. For men, a small area of the chest may need to be shaved so that the patch will stick. It is okay to exercise and to shower while the patch is on, but showers should be brief. You should not submerge the patch in water. If you plan to travel by airplane or to have an MRI scan in the next 14 days, you can still participate, but we will need to reschedule the placement of the patch for a date after those are completed.

* Brain MRI:

A brain magnetic resonance imaging (MRI) scan will be done about 18 months from now. The brain MRI scan produces detailed images of your brain. At that time, we will ask you a few questions to make sure you are eligible for the MRI scan and get your consent. For this test, you will need to lie still on a table and will be moved into a large scanner that takes pictures of your head using magnetic fields. There is no injection and no contrast dye involved in this test. The MRI takes about 40 minutes.

* Cognitive Function Test: You will be asked questions to assess your memory. An audio recording may be made of these interviews. The test will take about 35 minutes.
* Cardiopulmonary Exercise Test: This test measures your heart’s and lungs’ responses to exercise. During this test you will pedal a stationary bicycle while being monitored by a health care provider and a respiratory therapist. You will breathe through a mouthpiece while wearing a clip on your nose to keep air from leaking out of your nose during the exercise. Your blood pressure, heart rate, and oxygen level will be monitored throughout the test. You may end the test at any time. This test will take about one hour, including preparation and recovery time.
* Carotid Ultrasound: Approximately one third of the MESA participants will have this test. Ultrasound will be used to look for cholesterol build up in the carotid arteries, which are the large arteries in the neck. For this test you will be asked to lie down on an exam table. Gel will be applied to the skin while a small hand held probe is used to examine the carotid arteries on both sides of the neck. You will have several blood pressure measurements at this time. You also will have ECG stickers placed on your chest to record electrical signals from your heart. The test will take approximately 30 minutes.
* Vitamin D Clinical Trial. This is a short-term trial that will investigate whether genes and hormones may explain why people have different responses to vitamin D treatment. You will be asked to take a study medication, a softgel capsule, once daily for 16-weeks. The capsule may contain 2000 IU of vitamin D or no vitamin D at all (placebo). Three out of four people will receive vitamin D. Neither you nor the study staff will know which treatment you received until the end of the study. You will be asked to return to your MESA study site 16 weeks later for a brief exam (about 30 minutes) in which we will collect an additional blood and urine sample, recheck your blood pressure, and ask you to complete a short questionnaire. We will then send you the results of your vitamin D and calcium tests before and after the study and tell you which treatment you received. MESA participants are eligible if they are not already taking high doses of vitamin D.

**Potential Risks and Discomforts**

* Clinic Exam: The procedures used in this study are considered to be low risk.
* Blood Draw: Risks of drawing a blood sample are discomfort at the site of needle insertion, bruising (black and blue discoloration) or inflammation at the site, and rarely, faintness. Bruising, if it occurs, is usually painless and disappears within a few days.
* Six Minute Walk Test.  Risks of this test include shortness of breath and chest tightness, and rarely, faintness or heart problems.  We will guard against these by asking you questions before the test to determine whether it is safe for you to have this test.  You will also be monitored closely by study staff during the test.
* Echocardiogram: There are no known risks associated with using sound waves to image your heart. Some individuals may experience some mild pressure, discomfort, and/or irritation from the transducer on the chest.
* Arterial stiffness measurement: This procedure has no known risks. The test is not invasive and involves the same amount of pressure used to measure blood pressure taken with a cuff. Checking the neck artery pulse involves slight pressure similar to feeling your pulse.
* Spirometry: This lung test can sometimes cause coughing or dizziness. Very rarely, the dizziness may be severe, but improves with resting or lying down. Occasionally after receiving the albuterol inhaler, a temporary sensation of "heart racing" and shakiness may develop. This will go away after a few minutes.
* CT of the lung: The CT scan uses x-rays to make pictures.  The amount of radiation you will be exposed to during the CT scanning is less than 6.5 mSev**,** which is 12% of the yearly on-the-job exposure allowed for radiation workers. Another way of understanding this is to compare the exposure from the CT to the radiation exposure you receive on average from natural sources.  The radiation exposure from the CT scanning is approximately the amount of natural background radiation that the average person in the United States receives in two years.  The radiation in this study is not expected to measurably increase your risk of cancer: the potential lifetime cancer risk associated with the above estimated radiation is less than 6 per 10,000. The scan will be reviewed for findings that may have a major impact on your health, such as lung cancer. These findings may cause worry, additional medical testing, and, potentially, cost.
* Intravenous Contrast Dye: The insertion of the intravenous catheter may cause pain, bruising, bleeding or infection at the site. Often people will feel a brief sensation of warmth and mild discomfort during the injection of the contrast dye. Other possible risks that occur rarely (in about 3 in 100 people) include irregular heart rhythms, chest pain, low blood pressure, dizziness, temporary vision changes, headache, nausea and vomiting, itching, hives, or flushing.

Severe reactions to contrast dye are very rare (fewer than 1 in 1000 people). Severe reactions can include difficulty breathing and anaphylactic shock (very low blood pressure), which can result in death. To minimize these risks, you will not be allowed to receive the contrast dye if you have a known allergy to it. In the event that you have an allergic reaction, medical treatment will be available.

There is also a very small risk of kidney damage, which almost always goes away and tends to happen in people whose kidneys are not working properly. Your kidney function will be measured before the CT scan with a blood test and you will not be allowed to receive the contrast dye if your kidney function is abnormal. To reduce the risk of kidney damage, you will be asked to drink one quart of water before and also after the CT scan. If you take metformin (Glucophage) for diabetes, you should not take this medication on the day of the CT scan with contrast dye and for 2 days after it.

* Heart rhythm recorder: In some people, the adhesive on the patch (Zio Patch) may cause skin irritation. If this happens, you should call the MESA clinic at [Insert clinic phone number].
* Brain MRI: We will ask you a few questions to find out if you are eligible for the MRI scan. For those who are eligible, there are no known risks to having a brain MRI. You will be given earplugs or earphones to wear during the test because the machine can produce loud noises, which may be uncomfortable. With earplugs, the risk to hearing is very small. Some people may feel anxious in the scanner if they are uncomfortable in tight places (known as claustrophobia). You will be able to speak directly to the MRI technologist at all times, and the scan will be stopped at any time upon your request. The MRI will take place about 18 months from now, and you will be asked to sign a consent form at the time of the MRI.

If you have a history of metal in your head or eyes, you will need an x-ray exam of your skull in order to confirm that the MRI exam is safe for you.

Since the MRI machine uses a strong magnet that will attract other metals, you may not take part in this procedure if you have a pacemaker, an implanted defibrillator, or certain other implanted electronic or metallic devices, shrapnel, or other metal.

* Carotid Ultrasound: There are no known risks associated with using sound waves to image your neck arteries. The neck position might be uncomfortable for some participants, but adjustments can be made to minimize discomfort. The ECG stickers can irritate some people’s skin.
* Vitamin D Clinical Trial: Vitamin D is a commonly used supplement that does not require a prescription. The dose of vitamin D used in this study is a usual dose that is very unlikely to cause adverse events. Rarely, people may be allergic to vitamin D or the gelatin capsule. In rare instance, people have reported stomach discomfort, indigestion, nausea, or diarrhea while taking vitamin D. In very rare instances, vitamin D may raise the serum calcium level and increase the risk of kidney stones. These small risks are further minimized by the short duration of this trial (16-weeks). Participants who have a history of kidney stones or are already taking high doses of vitamin D will not be eligible for this study.
* Participation in research carries a theoretical risk for some people of being given information that they might prefer not to have heard (for example, some test results) or that may be difficult for them or their health care provider to interpret. This may lead to other tests, which MESA will not pay for.

**Follow-up Information**

We will continue to contact you by phone every 12 months and ask you about your health since our last contact. If you are unable to answer questions yourself, or if we cannot locate you, we may contact one of the people you have named who could answer questions for you, including questions about your health status. We will ask you to confirm or update these people’s names and contact information at the time of your clinic exam. If you are hospitalized or admitted to a convalescent or nursing home, we will ask that institution for your records. We will review the records to determine the reason for your admission and your diagnosis. We may request records from your health care provider for certain office or clinic visits to determine if you have been diagnosed with one of the diseases that MESA is studying. We may also request Medicare records for information about your health and use of health care services.

**DNA Testing**

Genetics, or the study of genes and gene products, has progressed rapidly since MESA began. If you gave your permission at an earlier exam, MESA collected DNA, the material that contains the genes, from your blood samples and stored it at that time. MESA will not be collecting more blood for DNA at this visit. Your stored DNA is being used to try to learn who is at increased (or decreased) risk of heart disease, stroke, and other diseases. MESA is looking at specific genes and also at other parts of participants’ DNA. MESA is also looking at a substance called RNA, which is closely related to DNA and may help to understand how genes work.

Some people have been worried that genetic information could be used to discriminate against them. A law was passed in 2008 by the Federal Government (called “GINA” or Genetic Information Nondiscrimination Act) that prevents some, but not all, forms of discrimination based on genetic information. GINA protects against genetic discrimination for health insurance and employment, but does not protect against discrimination for life, disability, or long-term care insurance.

**Confidentiality**

* We will store all information, tests, images, and specimens that we collect about you. We assign a coded ID number to your information, but we do also store your personal identifiers so we can contact you in the future. These personal identifiers are kept in locked files separate from the information we collect about you for research. Only the *[Institution]* Principal Investigator and his/her staff, representatives of the National Institutes of Health, the *[University Name]* Institutional Review Board, representatives of the U.S. Department of Health and Human Services Office for Human Research Protections, and the MESA Coordinating Center at the University of Washington will have the authority to review your study records and identifying information. These individuals are required to maintain confidentiality regarding your identity. Other researchers can only access the coded ID number.
* Any information we obtain will only be used for statistical, scientific purposes. In any report we publish or present, we will not include any information that will make it possible to identify you. Information may be released to other researchers for scientific purposes, but only after removing your name and all other personal identifiers.
* To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you. Unless you give permission, MESA can only disclose information about you in very special cases (for example, if you or someone else is in serious risk of harm).

**Sharing of Data and Samples**

In order for science to progress, it is necessary for researchers to exchange scientific resources and information while at the same time ensuring that your confidentiality is strictly maintained. As described below, we will be sharing your data and samples with researchers who are not part of MESA, in a way that cannot be used to directly identify you and under strict guidelines.

Use of data and samples:

* Portions of samples of your blood and urine, in addition to study information and genetic data, will be stored indefinitely for use by researchers.

* The National Institutes of Health will allow non-MESA researchers who qualify to analyze your data and samples, after your identity has been removed. Researchers can qualify by proposing a research study that is approved by the National Institutes of Health and by agreeing to protect your privacy. If your samples are no longer useful for research purposes at some time in the future or if you instruct us to do so, they will be destroyed.
* Samples and data sent to other laboratories and researchers will be labeled only with a code number. No standard information that identifies you, such as your name, date of birth, social security number, address, etc., will be available to other researchers.

Commercial use of data and samples:

* Researchers from private companies, such as those that develop diagnostic lab tests or treatments for diseases, may request access to your study information or samples. However, these researchers will not have access to personal information that identifies you, such as your name, date of birth, social security number, address, etc.
* Your samples will not be sold to any person, institution, or company and will not be used for human cloning (creating body organs, tissues, fluids, or human beings from your genetic material).
* MESA data may lead to inventions or patents in which private companies or the universities conducting MESA may participate and may benefit.
* Neither you nor your family would benefit financially from discoveries made using the information and/or specimens that you provide.

Use of data in genetic research:

* Very detailed information about your previously collected DNA will be stored centrally at the National Institutes of Health, where it will be shared with other investigators for research. This information, along with all of your other clinical data, will be used by researchers to look for genes that affect the risk of developing diseases and may lead to better methods for prevention and treatment of disease. The stored information is de-identified, which means that identifying information such as your name, date of birth, social security number, address, etc., is removed. Access to this stored information will be controlled by the National Institutes of Health. The National Institutes of Health is committed to protecting the confidentiality of all the information it receives, but will also comply with relevant laws which might include Freedom of Information Act (FOIA) requests for de-identified information. This is explained on the following website: <http://www.nih.gov/icd/od/foia/efoia.htm>

MESA takes extensive efforts to protect your identity and privacy. Yet, because of the large amount of information collected about you, we cannot absolutely guarantee that information about you or your blood relatives will never become known. This is partly because of the possibility of matching your DNA sample with other DNA collections (such as those kept by law enforcement agencies). However, researchers are strictly prohibited from attempting to identify you.

**What are the alternatives to participating?**

Your alternative is either to not participate in MESA or to continue to participate in MESA but not take part in this MESA examination (Exam 6).

**Benefits and Study Results Reporting**

You will receive no direct benefits by taking part in MESA. The information learned from this study will increase scientific knowledge about the causes of early heart disease and diseases of the blood vessels, as well as other conditions.

You will receive results from some tests at no cost. (These tests, like the entire study, are paid for by the National Institutes of Health). Information from the tests will be given to you and your health care provider, if you want. However, please keep in mind that these tests are being performed for research purposes and not to diagnose any specific medical conditions. Also, MESA is not intended to provide medical care or interfere with your relationship with your own health care provider. If you do not have your own health care provider, you can be referred to one if you would like.

**Study Compensation/Costs**

The tests MESA performs, like the entire study, are paid for by the National Institutes of Health. You will be reimbursed for your out of pocket expenses related to coming to the clinic.

Should your results require further evaluation or treatment, you will be referred to your health care provider (or, if you don't have one, we will help you with the referral). However, MESA does not cover the cost of follow-up care that might be related to the study tests. Such care (if needed) must be covered by you or your insurance company. MESA will not pay for additional medical tests.

You will be reimbursed a total of $\_\_\_ for time and transportation expenses for the exam.

If you are selected to complete additional exam procedures, you will be compensated for your time:

|  |  |  |
| --- | --- | --- |
|  | Lung CT and spirometry test  | $XX |
|  | Lung CT with intravenous contrast (dye) | $XX |
|  | Heart Rhythm Recording, two times  | $25 for each monitor, total of $50 |
|  | Brain MRI | $50 |
|  | Cardiopulmonary Exercise Test | $XX |
|  | Carotid Ultrasound | $XX |

**Research Related Injury**

In the unlikely event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research-related injury, let the study staff know right away. Their contact information is found at the end of this form.

**Giving & Withdrawing Consent**

* You may withdraw your permission for anyone to use your health information (data and samples) at any time. To do this, send a written notice to the investigator in charge of the study at the following address:

*[Insert PI name and clinic address]*

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* If you decide to leave the study, you may request that your records, test results, blood samples, and DNA be removed from the study to the extent possible.

**Statement of Exam 6 Consent:**

I have read the above information. I have asked questions and received answers. I agree to participate in this examination and to allow researchers to store and analyze my data and blood and urine samples, in a way that will not identify me, for the research described above. I understand that these responses will replace those on my previous informed consent if answered differently. I will receive a copy of this consent form.

Furthermore, I agree to the following:

**Consent for Sharing of Information with Health Care Provider:**

I agree that MESA may share findings important to my health from MESA Exam 6 tests and examinations with my health care provider.

* Yes, share my results
* No, do not share my results

**Consent to Allow Sample Storage**

I agree to permit MESA to store my DNA, blood, and urine samples indefinitely for research purposes.

* Yes, store my samples
* No, do not store my samples

**Consent to Communication with MESA Contacts**

I agree to permit MESA to send a letter or brochure to the contact person(s) that I have named to inform them about MESA and to help them understand their role as a MESA contact. The letter will tell my MESA Contacts that I am enrolled in MESA and that I gave MESA permission to mail them information about the study.

* Yes, send a letter or brochure to my MESA Contacts
* No, do not send a letter or brochure to my MESA Contacts

With my signature I also am giving permission for my hospital and/or health clinic to release any of my health records that MESA needs and requests. This permission has no expiration date.

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Signature of Participant Date

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Signature of Person Conducting Consent Process Date

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Signature of Investigator Date

**Contacts and Questions:**

*[Insert as needed at each Field Center]*

*\*\*\*SOME SITES WILL HAVE STANDARD TEXT FOR A SIGNATURE FOR EACH ANCILLARY HERE.* **Optional Consent Form Language as Required/Desired at Specific Sites. Ignore if not applicable or out of date.**

1) For sites requiring reporting of imaging study incidental findings to participants:

Incidental Finding

The CT scan you are having as part of this research study is not the same as a clinical exam. It is designed to answer specific research questions. The exam will be reviewed by a qualified person and read to an appropriate standard. Research studies are not a replacement for clinical studies and are often less comprehensive.

There is a possibility that while reviewing your CT scan we may see a finding that we did not expect to see in this study. If this finding might be significant to your immediate health we will report this to you. This is what is called an “incidental finding.”

We will let you know (INSERT or your legal representative if appropriate for the study) if we see such an incidental finding.  Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, we will make every effort to contact you in a timely manner.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary health care provider, or we will refer you to an appropriate health care provider for further evaluation.

* An incidental finding may cause you to feel anxious.
* Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance.
* The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by MESA.  These costs would be your responsibility.

2) For sites whose IRBs require consent for commercial use of data and samples, and medical records release:

Consent to permit data and samples to be used for commercial or for-profit use

* Yes, I agree that my data and samples may be used for commercial or for-profit use
* No, I do not agree that my data and samples may be used for commercial or for-profit use.

Consent for Medical Records Release:

I authorize the Multi-Ethnic Study of Atherosclerosis (MESA) to obtain medical records from my physician or from any hospitals or convalescent/nursing homes where I might be admitted, death certificates and coroners’ reports from the appropriate city or state agencies, and information from state and other cancer surveillance systems. This authorization applies to the full medical record for hospital admissions.

* Yes, MESA may obtain my medical records
* No, MESA may not obtain my medical records

Consent for Anonymous Data and Sample Sharing

* Data and samples may be used for research other than that related to the heart and blood vessels
* Data and samples may be used for research by investigators who are not working for the National Heart, Lung, and Blood Institute or on studies not funded by the National Heart, Lung, and Blood Institute.

Data and samples may be used for commercial purposes

* Yes, I agree
* No, I do not agree

# **Appendix C: STUDY ORGANIZATION**



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# **Appendix D: MESA SCIENTIFIC PERSONNEL**

University of Washington Coordinating Center

Lyndia Brumback, Ph.D.

Joseph Chris Delaney, Ph.D.

Annette L. Fitzpatrick, Ph.D.

Susan R. Heckbert, M.D., Ph.D.

Craig Johnson, M.S.

Richard A. Kronmal, Ph.D.

Robyn McClelland, PhD

William T. Longstreth, M.D.

Bruce M. Psaty, M.D.

Ken Rice, Ph.D.

Columbia University Field Center

R. Graham Barr, M.D. Dr. Ph.

Elizabeth Oelsner, M.D.

Walter Palmas, M.D. M.S.

Steven J. C. Shea, M.D. M.S.

Benjamin M. Smith, M.D., M.S.

Wake Forest University Field Center

Alain G. Bertoni, M.D.

Gregory L. Burke, M.D.

Haiying Chen, Ph.D.

Suzanne Craft, PhD

Jingzhong Ding, PhD

David M. Herrington, M.D.

Timothy Hughes, PhD

Yongmei Liu, PhD

Carlos Rodriguez, M.D., M.P.H.

Joseph Yeboah, M.D., M.S.

University of Minnesota Field Center

Alvaro Alonso, M.D., Ph.D.

Aaron R. Folsom, M.D.

David R. Jacobs, Jr. Ph.D.

Pamela Lutsey, Ph.D.

James Pankow, Ph.D.

Lyn Steffen

Lin-Yee Chen, M.D.

Susan Everson-Rose, Ph.D., M.P.H.

Suma Konety, M.D.

Johns Hopkins Field Center

Roger S. Blumenthal, M.D.

Rebecca Gottesman, M.D. Ph.D.

Joao A. C. Lima, M.D., F.A.C.C.

Erin Michos, M.D. M.H.S.

Pamela Ouyang, M.D.

Wendy S. Post, M.D.

Michael Blaha, M.D.

Moyses Szklo, M.D., M.P.H., Dr.Ph

University of California at Los Angeles Field Center

Christine Darwin, M.D.

Preethi Srikanthan, M.D. M.S.

Tamara Horwich M.D., M.S.

Karol E. Watson, M.D., Ph.D.

Northwestern University Field Center

Norrina Allen, PhD.

Mercedes Carnethon, PhD.

Benjamin Freed, M.D.

Philip Greenland, M.D.

Kiang Liu, Ph.D.

Donald Lloyd-Jones, M.D.

Sanjiv Shah, M.D.

John Wilkins, M.D.

Lihui Zhao, PhD.

University of Vermont Laboratory

Mary Cushman, M.D.

Nancy Jenny, Ph.D.

Russell P. Tracy, Ph.D.

National Heart, Lung, and Blood Institute

Jean Olson, M.D., M.P.H.

George Papanicolaou, Ph.D.

Lorraine Silsbee, M.H.S.

# **Appendix E: MESA PUBLICATIONS AND PRESENTATIONS POLICY**

The success of the MESA Study will be judged largely on the number and quality of its scientific publications and presentations. The purpose of the policies established herein is to encourage and facilitate important analyses while providing guidelines that ensure appropriate use of the MESA data, timely completion of projects, and adherence to the principles of authorship.

### I. Administrative Structure

The MESA Steering Committee will appoint a Publications and Presentations (P&P) Committee and select a chairperson. In 2007 a separate Genetics P&P Committee was established to review MESA papers with genetics data.

The P&P Committee will report to the MESA Steering Committee on all matters relating to the publications or presentations of MESA material.

The Genetics P&P Committee will report to the MESA Steering Committee on all matters relating to the publications or presentations of MESA genetics material.

All communications to the P&P Committee (for Main and Ancillary study papers) should be sent to the P&P Program Coordinator, Karen Hansen, hansenk3@u.washington.edu

All communications to the Genetics P&P Committee (for Genetics papers) should be sent to the Genetics P&P Coordinator, genpp@uw.edu

### II. Objectives

* To stimulate scientific presentations and papers from MESA investigators;
* To ensure and expedite orderly and timely reports to the scientific community of all pertinent information resulting from MESA;
* To ensure that abstracts, presentations, and publications based on MESA material are accurate and objective, and do not compromise the scientific integrity of this collective study;
* To ensure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in the study-wide MESA papers;
* To establish procedures that allow the MESA Steering Committee and NHLBI to exercise review responsibility in a timely fashion for MESA publications and presentations;
* To encourage manuscripts based on the information collected at all MESA study sites;
* To prevent overlap of published material and duplication of analyses.

### III. Procedures

A. Papers

1. Potential Overlap

It is the first author’s responsibility to avoid overlap with manuscripts already in progress or published. Review previously approved proposals and MESA published manuscripts for potential overlap with your proposal. Manuscript proposals will be available on the MESA Web site to help investigators determine available topics in advance. Search MESA proposals and manuscripts. The titles and abstracts are available online. Indicate directly on the online form which (if any) proposals/manuscripts could potentially overlap with your proposal. Describe how your proposal is different from those with potential overlap (if any) in the space provided in the online form.

2. Submission of a Proposal for a Paper

This will consist of a formal proposal to the P&P Committee submitted via the online proposal submission form available on the Publications page of the internal MESA Web site. See: MESA Manuscript Proposal Submission Form. The proposal must include the following “Summary Information”:

Proposal Title

P&P Committee members adopted a P&P policy that requires authors to include the study name (: The Multi-Ethnic Study of Atherosclerosis) at the end of their paper title. The only exceptions to this policy are when the Journal restricts the number of words allowed in the title or the paper combines data from multiple studies.

Abbreviated Title (up to 50 letters and spaces)

Authors (including sponsor if first author is not a MESA researcher) \*

Abstract/Brief Description (events, longitudinal, cross-sectional, methods)

Type of Manuscript (Main, Ancillary Study, Title & PI for Ancillary)

Data Analysis location (Coordinating Center or local: Will data analysis be conducted locally or via a Coordinating Center statistician/epidemiologist collaborator?)

Genetic Information (used? to address MESA aims?)

PI approval \*\*

Keywords

Additional Comments

The scientific “Proposal Details” should be summarized in a separate Word document and uploaded on the online proposal template. Proposal Details should include the following:

1. Introduction: Rationale and background, brief.

2. Research Hypothesis: Clearly state scientific questions to be addressed.

3. Data: List variables to be used, sample inclusions/exclusions.

4. Analysis plan and methods: Give detailed description of proposed statistical analyses. **Please include the total sample size for this study and any subsets of interest.**

5. References

Important: New proposals should be no more than 2-4 pages in length, excluding the references. Proposals exceeding 4 pages will not be accepted. (Proposal examples can be found on the Publications page under Example Proposals.)

\* Main study proposals with more than 3 authors at one site requires justification from the first author. Ancillary study proposals with more than 4 authors at one site requires justification from the first author. First authors are asked to explain how each coauthor will contribute to the paper. (Examples include data collection, analysis or help writing the paper.) **Both Main and Ancillary study proposals can only have an additional author from the same site (maximum 4 authors for Main study proposals and 5 for Ancillary study proposals). These maximums include the analyst.**

For each paper proposal, MESA P&P requires a Senior MESA author who will act as the responsible, sponsoring author (ideally from the same site). P&P expects that the Senior MESA author will be an experienced MESA investigator and familiar with P&P policies and procedures. The Senior MESA author is responsible for advising the first author concerning these procedures and MESA P&P deadlines for submission of abstracts, proposals and manuscripts. (This role is only for the MESA review process. Once a pen draft receives MESA approval, any member of the writing team can assume the corresponding author role for submission to a journal.)

**Important reminders:**

* **Make sure that your Word proposal attachment is correct before sending the submission.**
* **Check the online information for accuracy as you complete each online page.**
* **Once “finish” is selected to submit your proposal, the submitting author can’t revise the submission.**

**When corrections are needed after an online submission is sent:**

* **Please don’t resubmit the same proposal online if the first online submission has a mistake! Instead e-mail the P&P Coordinator right away with any changes and attach a corrected Word document if needed.**

The P&P Coordinator will review the proposal to verify that the P&P policies have been followed.

*\*\** **All proposals from investigators are to be submitted with the knowledge of their PI.**

All coauthors must have seen and approved the manuscript proposal prior to submission.

In general, P&P encourages proposals for analysis that can be done within a reasonable amount of time from submission.

**Paper proposals will not be considered by the P&P committee unless it is feasible to begin data analysis within 12 months of proposal approval, based on the availability of sufficient endpoint data.  This does not include unavailability of data due to technical problems (e.g., re-readings of scans or correction of quality control problems), delays in data cleaning, or delays in data release.**

Upon approval by the P&P Committee, the proposal will be assigned a manuscript number in the MESA database and will be visible online in the Table of Status and Authorship Information (on the internal P&P Web page). The approved proposal will then be submitted to the MESA Steering Committee for their approval, which may include additional writing group nominations by Steering Committee members.

The P&P Committee, in consultation with the Coordinating Center, will determine priorities for data analyses of manuscripts and abstracts to be performed by the Coordinating Center. A local paper (one in which the data analyses are not performed by the Coordinating Center) may start as soon as it is approved.

3. Types of Studies and Location of Analyses

There are two study types: Main and Ancillary, which are defined below. Analyses may be done either centrally (at the Coordinating center) or locally (at a field or reading center).

**Main Study Manuscripts**

A Main study manuscript analyzes data collected as part of the contracted MESA data set and may be analyzed centrally or locally. A Main study manuscript may be proposed with local analysis by an investigator or group of investigators at a particular MESA site or reading center. Data for these papers are analyzed by the proposing investigator rather than by a statistician at the Coordinating Center.

All Main study paper proposals are circulated to the Steering Committee where additional coauthors may be nominated, regardless of whether analysis is done centrally or locally.

Both centrally and locally analyzed papers are monitored for progress and will undergo a verification of analyses prior to submission to a journal.

**Ancillary Study Manuscripts**

An Ancillary study derives funding from other than MESA contract funds. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies), or those performed at no cost (generally because of the special interest of a researcher).

Definition of an ancillary study:
1) A project that collects new data in MESA, whether directly from participants or from previously collected samples, images, or other sources (e.g., medical records).

2) A project that analyzes existing MESA data as part of a new external funding application, for which additional MESA Coordinating Center (CC) services will be requested beyond downloading of data already available on the MESA website (e.g., analysis by a CC Statistician or preparation of a unique dataset). Note: as of November, 2010, analysis-only grants involving no such additional CC services require the submission of a Manuscript Proposal form, but not an Ancillary Study Proposal Form. Submit the Manuscript Proposal form online and see MESA Publications submission details at: <http://www.mesa-nhlbi.org/Publications.aspx>. To check the availability of online data, please contact your MESA Sponsor.

**Important P&P Committee policy updates as of late February 2011:**

* **When a paper proposal is based on an ancillary study (regardless of when the “protected” period has finished), the main author should be strongly encouraged to invite the PI of the ancillary study to join the writing group.**
* **Papers based on ancillary studies should always be classified as “ancillary”, even after data transferred to the main database.**
* **In all papers based on ancillary studies, the funding agency should be acknowledged.**

Analyses are usually done by the proposal group, but may be done at the Coordinating Center if funds have been allocated for an analyst. Ancillary study papers are not tracked centrally for progress, and will only undergo a verification of analyses prior to submission to a journal if analysis is done at the Coordinating Center and funds have been allocated to do so.

Ancillary Study proposals are circulated to the Steering Committee for approval and coauthor nominations are restricted to those with special expertise in the area of the proposal.

4. Formation of Writing Groups

In order to ensure that all investigators have the opportunity to participate and be recognized in the main study papers, writing groups usually include investigators from several centers. Writing Group members for both Main and Ancillary study papers may be nominated by the first author and by the Steering Committee, although nomination is no guarantee of coauthorship.

Usually the manuscript proposer will be designated as the Writing Group Chairperson and first author of the paper. He/she will receive written notification of all Writing Group members and his/her responsibilities as chair (see below). In general, an investigator should have only two approved and active, unpublished manuscripts which haven’t yet progressed to the pen draft stage in which he\she is the Writing Group Chairperson. The P&P Committee will be more lenient with limiting the number of active proposals for Ancillary study papers. This issue will be discussed on a case-by-case basis as new proposals are received.

For papers using the MESA Coordinating Center for analyses, a second manuscript will be eligible to start after the penultimate draft of the first manuscript is approved.

5. Writing Group Responsibilities

The Writing Group Chairperson is responsible for all phases of manuscript preparation, from conception through publication. These responsibilities include:

* Preparation of outlines, the identification of data analyses needed, and submission of interim status reports to the P&P Committee;
* Assignment of tasks to Writing Group members with clear deadlines for completion of these tasks and determination that the tasks are completed on schedule;
* Preparation and circulation of drafts for approval by each member of the Writing Group before submission of a Penultimate Draft to the P&P Committee and before submission to a journal;
* Determination of the order of authorship on the manuscript. A major criterion will be the effort and contribution made by each member of the Writing Group in the preparation of the manuscript;
* Choice of a journal to which the manuscript will be submitted;
* Correspondence with coauthors, communication with the Coordinating Center and the P&P Committee, responses to the Steering Committee and NHLBI reviews, and to journal editors.

The Writing Group Chairperson should contact each member of the Writing Group to discuss the outline of the paper, data analysis plan, and the responsibilities and assignments for each member. Members of the Writing Group are responsible for performance of tasks assigned by the Chairperson within the allotted time period. Each member is expected to actively participate in the preparation of the manuscript.

All coauthors should let the Writing Group Chairperson know of a change in contact information. Failure to respond within a reasonable amount of time to a Chairperson’s request for coauthor feedback, could result in removal from the Writing Group.

If a Writing Group member does not accomplish the tasks assigned to him/her and has not contributed to the manuscript, he/she may be removed from the Writing Group. The chairperson must send an email to the P&P Program Coordinator requesting the removal of non-contributing members.

If the initial results lead to a split of the original paper into more than one manuscript, a new proposal should be submitted to the P&P Committee. The new proposal should be submitted via the online proposal submission form available on the Publications page of the internal MESA Web site. See: MESA Manuscript Proposal Submission Form.

6. Schedule for Manuscript Preparation

The expected schedule for the development of a manuscript is described below. Deviation from this schedule must be approved by the P&P Committee. Failure to adhere to this schedule will prompt a review of circumstances. If it is determined that a manuscript is delinquent, this could be the basis for replacing member(s) of the Writing Group responsible for the delay, or for disbanding the Writing Group.

**Draft**. After notification by the P&P Committee of manuscript approval and the availability of an analyst for central papers, the Writing Group will have four (4) months to prepare a first draft. A first draft will consist, at a minimum, of an Introduction, Methods and Results Sections. This draft should be sent to the members of the Writing Group. It is recommended that a response deadline of 4 (four) weeks be given to Writing Group members to prevent unnecessary delays.

**Penultimate Draft**. The penultimate draft becomes due three (3) to six (6) months after the first draft is distributed to the Writing Group. A penultimate draft should be sufficiently developed for subsequent submission to a journal. After review and approval of the penultimate draft by Writing Group members, the penultimate draft should be sent to the P&P Program Coordinator as an email attachment.

Include the following required information with each new pen draft:

1. MESA manuscript number (examples: MC 001, AC 025)
2. **In January 2015 the committee set a limit of only 2 separate documents (excluding the lay summary) for pen draft submissions.**
3. Confirmation that all coauthors have seen and **approved** the manuscript prior to submission
4. Specify one target journal that the author is thinking of submitting the manuscript to
5. Lay summary (see below for details)

As of October 2007 authors are also required to attach a separate lay summary (Word) document when submitting a new pen draft. The lay summary should meet the following criteria:

* In 2-4 sentences (100-200 words), please describe the relevance of this research to clinical practice and/or public health. Use plain language that can be understood by a general, lay audience.
* If an author believes that a manuscript is too technical for a lay summary, a brief explanation should be included in the submission e-mail.

P&P Committee members adopted a P&P policy that requires authors to include the study name (: The Multi-Ethnic Study of Atherosclerosis) at the end of their paper title. The only exceptions to this policy are when the Journal restricts the number of words allowed in the title or the paper combines data from multiple studies.

**Review/Deadlines***.* The P&P Program Coordinator will make every effort to include manuscript submissions in the next available P&P Committee teleconference. To allow sufficient time for processing and review, please submit all manuscripts by noon Pacific Time on Monday of the week before the next P&P teleconference. Refer to P&P Meetings and Paper Submission Deadlines located at the very top of the Publications page (on the internal Web site) for teleconference dates and deadlines.

The P&P Committee will review each manuscript followed by a discussion during a P&P Committee conference call. Afterward, the author will be sent a summary of any pertinent reviewers’ comments.

If a manuscript is not approved by the P&P Committee, the draft will be returned to the Writing Group Chairperson with comments regarding the necessary revisions before resubmission.

If it is approved, it will be forwarded to the MESA Steering Committee for review within three (3) weeks. The Steering Committee members will vote to approve, approve with modifications or disapprove.

Effective June 24, 2008, the NHLBI will no longer review manuscripts that don’t include NHLBI staff as authors. Reviews will continue for manuscripts that include NHLBI staff in the author list. For papers that include NHLBI coauthors, manuscripts will be sent by the P&P Coordinator to NHLBI the same day they are sent for Steering Committee review. Papers that are not deemed High Impact will undergo expedited review -- within 5 business days. Papers that are deemed High Impact will undergo a detailed review -- within 10 business days.

The Coordinating Center will initiate verification (independent replication of the analysis data set and results) of the manuscript results after approval by the P&P Committee. Completion of verification is expected within thirty (30) days and the P&P Committee and Writing Group Chairperson will be notified.

**Journal**. Within thirty (30) days of receiving Steering Committee and P&P Committee comments and verification confirmation, the revised manuscript will be circulated by the writing group chair to the Writing Group for final sign-off.

The manuscript will immediately be submitted to a journal. A copy of the journal cover letter and final draft of the manuscript must be sent to the P&P Committee in addition to all coauthors.

The Writing Group Chairperson must keep the P&P Committee and the coauthors informed as to the manuscript’s progress through journal review. Upon publication of the manuscript, the Writing Group Chairperson must provide either a reprint or copies of the final publication to the P&P Committee*.* If there are substantive changes made in the manuscript during journal review (major findings or conclusions, alterations of the sample, exclusion/inclusion of major covariates), the revised manuscript should be submitted to the P&P Committee for re-review.

In order to stay informed of findings from large studies and to prepare for press queries, the NHLBI Project Office would like a courtesy copy of manuscripts at the time of journal acceptance or before, particularly for "high-profile" papers. These generally include the following:

* Main results papers or key secondary results papers from clinical trials
* Papers with direct clinical implications, particularly if they impact NHLBI policies
* Papers on potentially sensitive topics
* Papers published in prestige high impact journals, such as Nature, Nature Genetics, Science, NEJM, JAMA, and Lancet.

**Letters to the Editor.** If an author chooses to write a letter to the editor instead of a pen draft, please contact the P&P Coordinator to get instructions. This is rare and will be handled on a case-by-case basis.

When the author already has an approved manuscript (pen draft), the following policy for additional letters to the editor and/or response letters is as follows:

As a general rule, P&P will not review letters to the editor, including response letters. New data should not be presented or published unless it is part of an approved paper that went through the standard MESA review/approval process. Also, all coauthors (on the approved manuscript) need to review/approve a letter to the editor.

7. Guidelines for Investigators Using CC for Data Analysis

Guidelines for investigators to use in dealing with the Coordinating Center are:

* Plan systematically for the analysis of your data.
* Communicate with the assigned Coordinating Center representative on the Writing Group for all requests and questions on analyses.
* Be sure that data requests are made in a timely fashion; interactive analyses will be allowed within the time window before and after the first draft.
* If the Coordinating Center falls behind on the analyses, the Chairperson of the Writing Group should inform the P&P Committee; if there is a problem, deadlines can be changed.

**B. Abstracts**

1. Preparation and Submission of Abstracts for Submission to Conferences

New abstracts mustbe based **exclusively** on an approved MESA proposal or submitted or published manuscript.

**An abstract based on an approved paper should be submitted (online) to the P&P Committee for review no less than 2 weeks before the conference (abstract) submission deadline.** It is strongly advised that authors submit abstracts well before this deadline, in order to allow sufficient time for revisions. **There is no guarantee that abstracts submitted after the P&P deadline will be approved prior to the conference deadline**. (For more deadline information and details regarding MESA abstracts refer to the “How to Submit an Abstract” document on the Publications page of the internal MESA Web site.)

**New abstracts must be submitted online using the MESA Web site.** Please use the online MESA Abstracts and Presentation Submission Form to submit a new abstract to the P&P Committee. This form is available on the Publications page of the internal MESA Web site. Non-MESA researchers must obtain the password to the internal site from a MESA sponsor prior to submitting an abstract.

The P&P Coordinator will notify the first author (via email) when P&P Committee approval is received.

Effective May 2012: NHLBI will review abstracts that have NHLBI staff as part of the author list.

If an abstract is not accepted upon its original submission, please let the P&P Coordinator know via email before you resubmit it to another conference.

If the abstract is accepted, a copy of presentation materials (including tables and graphs) and text are to be submitted to the P&P Program Coordinator as an email attachment.

**C. Data Requests**

Special data requests to the MESA Coordinating Center by an investigator for the purpose of development of a grant proposal, hypothesis generation and power calculations should be submitted to the Executive Committee for review and approval.

Data analysis requests for theses or dissertations should go through the P&P Committee provided there is a corresponding manuscript proposal.

**D. Access to the Internal MESA Web Site**

Non-MESA researchers or new MESA authors must obtain the password to the internal site from a MESA sponsor prior to submitting a manuscript. MESA sponsors have the responsibility for introducing the Web site to those they sponsor.

#

# **Appendix F: MESA ANCILLARY STUDIES POLICIES AND PROCEDURES**

Revised: November 30, 2013

**THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS (MESA)**

**MESA Ancillary Study Policy**

**Definition of an ancillary study:** A MESA ancillary study is one that uses MESA resources and derives funding from other than MESA contract funds. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies), or those performed at no cost (generally because of the special interest of a researcher). A study that involves the collection of new data, either directly from participants or from previously collected samples, images, or other sources (e.g., medical records), is an ancillary study, regardless of the method of funding. A study that provides external funding for the Coordinating Center, one or more Field Centers, or a Reading Center, is an ancillary study.

**When an ancillary study proposal is not needed:** If an investigator is seeking funding to support analysis of existing MESA data, and the project does not involve new data collection, new readings of imaging data, new lab/genotyping assays, or the preparation of a complex data set by the Coordinating Center, then an Ancillary Study application is not needed, but one or more Manuscript Proposals must be submitted and approved before grant submission. The investigator may submit the Manuscript Proposal approval to the funding agency as evidence of MESA study approval.

**Philosophy:** MESA investigators are encouraged to consider ancillary studies and to involve other investigators, within and outside of MESA, in this process.

**Necessary approvals:** The MESA Ancillary Studies Committee, Steering Committee, and NHLBI must approve ancillary study proposals prior to submission for funding and prior to implementation at the MESA sites. Studies proposing biospecimen use must also be reviewed by the Laboratory and/or Genetics Subcommittees. Studies involving participant contact/burden must undergo final review by the Monitoring Board.

**Review criteria:** At each level of review, highest priority will be given to studies that:

1. Do not interfere with the main MESA objectives
2. Have the highest scientific merit
3. Produce the smallest burden on MESA participants and the least demand on MESA resources, such as blood samples
4. Require the unique characteristics of the MESA cohort

In addition, priority for studies requesting biological samples will be highest if they:

1. Do not make use of samples from those participants with the fewest samples;
2. Use thawed samples whenever possible;
3. Involve assays that may be done on more than one sample type to allow selection of the most abundant type available (e.g. serum or EDTA plasma);
4. Use the smallest sample volume possible; evidence of attempts to minimize volumes will be examined by the Blood Laboratory Subcommittee.
5. Can be integrated with other studies to conserve sample or limit freeze-thaw cycles.

**Responsibilities of Ancillary Study Investigators**

1. Costs. The investigator applying for an ancillary study must supply all additional funds required to conduct the study. The Steering Committee will be concerned with both the obvious and the hidden costs to MESA entailed by an ancillary study (such as costs to the Coordinating Center for coordinating the additional data collection, costs to Field Centers for notification of alert values, costs to laboratory for retrieving samples, etc).

It is important to note that the MESA Coordinating Center (CC) at the University of Washington nearly always incurs expenses on behalf of ancillary studies by providing support in data collection, data management, quality control, data analysis, study coordination and communications, events ascertainment, and other functions. These services can be of critical value to an ancillary study. PIs who plan to propose an ancillary study with the intention of seeking grant funding should first consult with the MESA CC Project Director to determine what level of involvement will be required of the CC and the associated costs. In general, this will result in a subcontract proposal from the CC to be included in the PI’s grant application.

1. Confidentiality and identification of MESA participants. Confidentiality of individually identifiable data about MESA participants must be assured. As a general rule, no personal identification of participants will be provided to ancillary studies staff. There are no assurances that participants will be able to be identified and contacted in the future for the purposes of an ancillary study, particularly after MESA ends.
2. Clinical implications of findings. The proposing investigator must clearly delineate any findings of clinical significance that may result from the study, including genetic findings, and propose how these will be handled, including reporting to participants and their physicians and providing recommendations for follow up. This includes incidental findings, such as pathology identified from an imaging study that is not the focus of the study.
3. Genetic studies. Genetics studies may include only participants who provided appropriate informed consent. Investigators should consult the Coordinating Center to determine the number of participant samples eligible for analysis based on responses from the appropriate informed consent. Medical and other (ethical, legal and social) implications of the findings and reporting of results must be addressed in the proposal.
4. Ancillary studies to existing MESA ancillary studies. A new ancillary study that involves participants, staff, or biological samples of an existing MESA ancillary study but not those of the main MESA study is considered an ancillary study only to the parent (existing) ancillary study. (An example would be a proposal that involves air pollution monitoring only in new recruits in the MESA Air Study, but does not involve main MESA study participants.) Such proposals are to be submitted to the parent ancillary study for review and approval, and will also be circulated to the main MESA Ancillary Study and Steering Committees for informational purposes. If a new ancillary study involves participants, staff, or biological samples of an existing MESA ancillary study as well as those of the main MESA study, review and approval process by both the parent ancillary study and main MESA study will be required. Please contact the PI of the parent ancillary study for information regarding the appropriate administrative contact.
5. Inclusion of Sponsoring MESA investigator(s). A MESA-affiliated investigator must be included as a co-investigator on an ancillary study. This individual is responsible for presenting the study to the Ancillary Studies Committee, monitoring the study to assure continuing compatibility with MESA and serving as a liaison to the MESA Steering Committee. In addition, each manuscript and abstract is generally expected to include a MESA investigator.
6. Early communication with MESA Centers. The proposing investigator and/or his/her liaison should consult with PIs of pertinent Field Centers, Reading Centers, Laboratories, and/or the Coordinating Center, depending on the anticipated involvement of Field Center staff and oversight, blood or urine analysis, and data management and analysis. Such discussions should focus on feasibility and provision of necessary resources and do not constitute formal approval of the study.
7. Timeline. All proposed ancillary studies must be submitted to the MESA Coordinating Center for subsequent circulation and review. Studies must be submitted **6 weeks** prior to a funding application; **8 weeks** if biospecimens are requested. Studies submitted after these deadlines may not receive timely approval. In addition, studies that involve a subcontract to the Coordinating Center must have their final budget negotiated and approved for internal University of Washington review no later than **5 weeks** prior to a funding application.

1. Final application or proposal. A copy of the final proposal as submitted for funding should be submitted to the Coordinating Center and to the NHLBI Project Officer.
2. Industry participation. Proposals for industry sponsorship or collaboration will be evaluated in accordance with the procedures described above. In addition, it will be the responsibility of the PI to obtain agreement through an appropriate contractual mechanism that all data relevant to the MESA ancillary study will be shared with the Coordinating Center. As an initial step in study planning, the PI should contact the MESA Project Officer to determine if an agreement between NHLBI and industry should be developed and implemented or to approve the agreement between industry and the investigator’s institution. Industry-sponsored ancillary studies shall include only participants who provided appropriate informed consent and must comply with current NHLBI guidelines, which are available from the Coordinating Center or Project Office upon request.
3. Status reports. The ancillary study PI should keep the MESA Coordinating Center apprised of major developments in the life of the application or proposal, including success of funding, start date, changes in protocol, and any resulting publications or presentations. The MESA Coordinating Center will query PIs twice per year, or as needed, for a status update of their ancillary studies, the results of which will be included in the Steering Committee and Monitoring Board reports.
4. Revising or resubmitting proposals. Ancillary Studies that are not approved or not funded become inactive. If the PI wishes to resubmit the proposal for funding, s/he must communicate this to the Coordinating Center.

Substantial changes to the science or scope of an approved ancillary study require review by the MESA Ancillary Studies and Steering Committees and, if relevant, Lab or Genetics Subcommittee. The PI must submit to the MESA Ancillary Studies coordinator:

1. A revised study proposal with changes tracked, highlighted, or bolded;
2. A brief modification request memo summarizing the changes and stating the rationale for the changes. The memo may be addressed to the MESA Ancillary Studies Committee.

            Substantial changes include:

* requests for additional biospecimens
* significant additional data
* requests to add new outcomes or change the main analytical exposure
* any additional participant burden

Formal modification requests are NOT needed for the following:

* notification of a reduction in needed biospecimens
* requests to add co-investigators
* requests to slightly modify the analytic approach

However, all such minor changes must still be communicated to the Ancillary Studies Coordinator via a memo addressed to the MESA Ancillary Studies Committee.

1. Review of publications and presentations. Manuscript proposals based on ancillary study data require approval of the MESA P&P committee. All the publications, presentations and abstracts from an ancillary study must be reviewed and approved by the MESA Publications Committee and the Steering Committee prior to submission or presentation, in accordance with the general rules for publications and presentations.

**Incorporation of ancillary study data into MESA database**

The data collected by the ancillary study are first to be provided to the MESA Coordinating Center for integration into the main database, after which the ancillary investigators will receive the integrated file containing necessary data from the main study. The ancillary study PI will be given the exclusive opportunity to analyze, present and publish data collected under the auspices of the ancillary study. After a reasonable time (in general, 12 months after data collection and cleaning are complete) the ancillary study data will be made available for additional uses by other MESA investigators in collaboration with the ancillary investigators. It is the responsibility of the ancillary study PI to state in writing to the Steering Committee any special circumstances that would militate against these guidelines for data sharing.

**MESA Ancillary Study Review Procedures**

1. Investigators wishing to propose studies that pose participant, clinic, or Blood Lab burden are encouraged to discuss their studies with the NHLBI Project Office for MESA before submitting a proposal to the Ancillary Studies Committee.
2. Principal Investigator submits ancillary study proposal using the template provided on the MESA website via an email to the MESA Coordinating Center (CC) Assistant.
3. MESA CC Assistant reviews proposal for administrative compliance (assures that all questions have been answered) and to determine involvement of MESA labs and/or reading centers. If the proposal is not complete, it will be returned by email to the investigator for revision and resubmission.
4. MESA CC Assistant forwards the proposal by email to the MESA Ancillary Studies Committee (ASC), the MESA Steering Committee (SC), and to relevant subcommittees (e.g., Laboratory, Genetics, CT committees). The chair of the ASC will decide whether to convene a conference call, generally one week prior to the monthly SC call, or handle the review by email. Chairs of all relevant subcommittees communicate their reviews to all members of the ASC and SC by email (or in conference call). The ASC review and recommendation for approval are communicated to all SC members, including the ASC comments and the comments of relevant subcommittees.
5. Proposals will be discussed by the SC, generally during their regular monthly conference calls. The chair of the ASC is invited to be present for that portion of the SC conference call. In some cases, as determined by the chair of the SC, email reviews will be conducted. The SC may also invite the PI (and/or the PI’s MESA sponsor) to present the proposal and answer questions and absent him/herself during discussion and voting.
6. If the proposal requires revisions, the comments of the ASC (and LC, GC or SC, if applicable) are sent to the PI by the CC Assistant (with a copy to ASC and SC chairs and NHLBI Project Officer). The PI must address these comments in a separate letter that accompanies the revised proposal and send these to the CC Assistant who forwards them to the appropriate committee(s).
7. Proposals that are approved by the SC but involve no participant burden (though they may use scans or repository samples), and minimal clinical implications are sent by the CC Assistant to the NHLBI Project Officer who sends the formal letter of approval to the PI. (Copies of these communications are sent to the ASC and SC chairs and CC Project Director.)
8. Proposals that are approved by the SC and involve participant burden are sent by the CC Assistant to the NHLBI Executive Secretary and the NHLBI Project Officer, together with all review materials plus updated study and burden tables. (Copies are sent to the ASC and SC chairs, and CC Project Director) The CC Assistant also notifies the PI of the progress in the review process.
9. The Executive Secretary of the MESA Monitoring Board forwards the final proposal, any relevant review materials, and the modified Burden Table to the Monitoring Board for review (allow three weeks).
10. The results of the Monitoring Board review are communicated by formal letter to the PI by the Executive Secretary. The results are also communicated by email to the chairs of the Steering Committee and Ancillary Studies Committee, and the PI and Administrator of the Coordinating Center.
11. In addition to the NHLBI letter of approval, and if the PI of the ancillary study requests it, the SC Chair will write a letter of support that may be included in the PI’s grant application.

# **Appendix G: MESA MONITORING BOARD ROSTER**

Helen P. Hazuda, Ph.D. (Chair)

University of Texas Health Sciences Center

Ingrid B. Borecki, Ph.D.

Regeneron Genetics Center

James H. Chesebro, M.D.

University of Massachusetts Memorial Medical Center

Elisa T. Lee, Ph.D.

University of Oklahoma Health Sciences Center

Kristin L. Newby, MD, MHS

Duke University

Carlos A. Vaz Fragoso

Yale University

Lewis Wexler, M.D.

Stanford University School of Medicine

Phyliss Sholinsky, MSPH (Executive Secretary)

PPSP/DCVS

National Heart, Lung, and Blood Institute

1. Modified objectives from the Request for Proposals issued November 1997. [↑](#footnote-ref-2)
2. Note: events based on the Atherosclerosis Risk in Communities (ARIC) Study, years 1987-1994, generated August 1997, and the Cardiovascular Health Study, years 1989-1997, generated September 1999. [↑](#footnote-ref-3)