Multi-Ethnic Study of Atherosclerosis (MESA)

Protocol

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MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

PROTOCOL

1 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 6,500 men and women aged 45-84. Approximately 40 percent of the cohort will be white, 30 percent African-American, 20 percent Hispanic, and 10 percent Asian, predominantly of Chinese descent.

The cohort will be 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 will allow study of the progression of disease. Blood samples will be assayed for putative biochemical risk factors and stored for case-control studies. DNA will be extracted and lymphocytes immortalized for study of candidate genes and possibly, genome-wide scanning. Participants will be followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; mortality; and for cardiovascular disease interventions.

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, and Electrocardiography. Protocol development, staff training, and pilot testing are planned for the first 18 months. The first examination will take place over two years, followed by two 18-month examination periods, followed by a fourth two-year examination period. The content of the third and fourth examinations will be finalized after assessing the experience of the preceding two examinations. Participants will be contacted every 6-9 months throughout the study to assess clinical morbidity and mortality. The final 18 months will be dedicated to close out and data analysis and publication.

2 Objectives and Research Questions of MESA

In a population of men and women aged 45 to 84 from four ethnic groups, the Multi-Ethnic Study of Atherosclerosis is designed to meet the primary and secondary objectives below and to address the following research questions:

Table 1

OBJECTIVES OF THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS[1]

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

3. To assess ethnic, age, and gender differences in subclinical disease prevalence and risk of progression and clinical cardiovascular disease.

4. 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.

5. To develop population-based methods, suitable for application in future screening and intervention studies, for characterizing the risk of asymptomatic persons.

[1]Modified objectives from the Request for Proposals issued November 1997.

Table 2

KEY RESEARCH QUESTIONS OF THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS[2]

1. What are the risk factors for clinical coronary heart disease and stroke among persons with subclinical cardiovascular disease (CVD)?

    a. 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?

    b. Does the risk associated with these factors vary among different gender and ethnicity subgroups?

    c. Are there new CVD risk factors that are important predictors after accounting for the effects of traditional risk factors?

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

    a. Are there new risk factors that are important predictors after accounting for the effect of traditional risk factors?

    b. Does the risk associated with these factors vary among different gender and ethnicity subgroups?

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

[2]Research questions formulated by the Steering Committee during protocol development, on which power calculations are based.

3 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 a number of 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 will 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) optimizing the study of 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 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

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

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.

4 Study Design

4.1 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 will be females. Approximately 40 percent of the cohort will be 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 will be reduced by one third.

- A large proportion of the cohort is 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 Tables 4a and 4b.

Table 3

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[3]

	All	Men	Women	Whites	Blacks	Hispanics	Asians
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

[3]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.

4.1.2. Power Calculations

Power calculations were done separately for three key research areas. The first is the association of baseline risk factors with clinical CVD events, the second is the association of baseline risk factors with the progression of coronary calcium, and the third is the association of progression of coronary calcium with clinical CVD events.

All gender-specific calculations were adjusted for age. Other calculations were adjusted for age and gender. Type I error was set at 5%. Table 5 shows the power to detect associations of dichotomous risk factors of varying prevalence levels with cardiovascular events. Table 6 shows the power to detect associations of baseline dichotomized risk factors with a positive two-year coronary calcium score change. Event rates in minority populations were adjusted using expected event rate proportions in the MESA cohort. Table 7 shows the power to detect association of two-year calcium score progression (dichotomized into progression vs. no progression) with clinical CVD events. It was assumed that a second calcium score would be derived on half the MESA participants after an average of two years. This results in an average of four years of event follow-up for these participants, and, thus, two-thirds of the estimated number of events from the 6-year follow-up.

Table 4a

Prevalence (%) of coronary calcium in an asymptomatic population[4]

Age	Men	Women
0-29	11	6
30-39	21	11
40-49	44	23
50-59	72	35
60-69	85	67
70-79	94	89
80-89	100	100

[4]Reference: Janowitz, et al. Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. JACC 1993;72:247-254.

Table 4b

Prevalence (%) of coronary calcium in a self-referred population[5]

	Men		Women	
Age	Score >0	Score >150	Score >0	Score >150
45-54	68	15	35	2
55-64	83	36	60	13
65-74	93	54	83	33
75-84	95	79	85	30

Table 5

Power (%) to detect relative risks for associations of dichotomous risk factors and clinical cardiovascular disease outcomes, by risk factor prevalence

Prevalence of risk factor	RR	All 6500	Men 3250	Women 3250	Whites 2470	Blacks 1820	Hispanics 1495	Asians 715
5%	1.5	--	--	--	--	--	--	--
	1.8	72	A	--	--	--	--	--
	2.0	86	63	--	--	A	--	--
	3.0	+	+	83	92	82	67	--
10%	1.5	63	A	--	--	--	--	--
	1.8	93	77	--	58	--	--	--
	2.0	+	87	70	74	61	--	--
	3.0	+	+	+	+	+	90	A
20%	1.5	83	60	--	--	A	--	--
	1.8	+	91	67	78	65	A	--
	2.0	+	+	81	91	81	65	--
	3.0	+	+	+	+	+	+	57
30%	1.5	91	71	A	54	--	--	--
	1.8	+	+	76	85	74	57	--
	2.0	+	+	92	94	87	72	A
	3.0	+	+	+	+	+	+	62

-- : Much less than 50% power A : approaching 50% power +:More than 95% power

[5]Reference: Alan Guerci, unpublished.

Table 6

Power (%) to detect associations of baseline dichotomous risk factors with positive two-year calcium score progression

% with positive calcium score change	All	Men	Women	Whites	Blacks	Hispanics	Asians	
		25	44	6	25	31	20	15
Prevalence of risk factor	RR							
5%	1.5	58	--	--	--	--	--	--
	1.8	88	70	--	53	--	--	--
	2.0	+	83	--	68	52	--	--
	3.0	+	+	79	+	88	85	--
10%	1.5	84	65	--	--	--	--	--
	1.8	+	92	--	79	63	54	--
	2.0	+	+	58	91	77	69	--
	3.0	+	+	+	+	+	+	65
20%	1.5	+	86	--	69	53	--	--
	1.8	+	+	--	95	85	76	--
	2.0	+	+	79	+	93	88	--
	3.0	+	+	+	+	+	+	84
30%	1.5	+	93	--	79	63	53	--
	1.8	+	+	--	+	91	85	--
	2.0	+	+	86	+	+	94	52
	3.0	+	+	+	+	+	+	90

--: Much less than 50% power A : approaching 50% power +:More than 95% power

Note: Progression is defined as any positive change in calcium score, for half of the cohort (expected to have repeat calcium measurements).

Table 7

Power (%) to detect associations of two-year calcium score progression with cardiovascular events

Prevalence of progression	RR	All	Men	Women	Whites	Blacks	Hispanics	Asians
5%	1.5	--	--	--	--	--	--	--
	1.8	--	--	--	--	--	--	--
	2.0	--	--	--	--	--	--	--
	3.0	88	65	--	52	A	--	--
10%	1.5	--	--	--	--	--	--	--
	1.8	51	--	--	--	--	--	--
	2.0	67	A	--	--	--	--	--
	3.0	+	87	61	76	61	A	--
20%	1.5	--	--	--	--	--	--	--
	1.8	72	A	--	--	--	--	--
	2.0	86	64	--	--	--	A	--
	3.0	+	+	80	90	78	62	A
30%	1.5	--	A	--	--	--	--	--
	1.8	80	58	--	--	--	--	--
	2.0	+	73	--	57	A	--	--
	3.0	+	71	85	92	83	67	--

--: Much less than 50% power A : approaching 50% power +: More than 95% power

4.2 Description of Field Center Communities and Source Populations

4.2.1 Overview

The MESA cohort will be 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 and the village of Maywood, IL; and Los Angeles County, CA. The source population for each Field Center varies in size and ethnic composition. The MESA cohort will be comprised of men and women of diverse ethnic background who are 45 to 84 years old at the baseline exam and free of clinical cardiovascular disease. Each site will recruit 1,100 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 will be publicized to residents of target areas. Successive efforts will be directed at targeted households or individuals, and will include mailings of letters and brochures, followed by personal contacts via telephone or in person. Phone calls will be the primary method of recruitment at all Field Centers.

Each Field Center has 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 is comprised of the resident population of Forsyth County, NC. The county has 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 is 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. Members of this union include 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 is compulsory for all employees. There are approximately 125,000 active and retired members and their adult dependents living in New York City, of whom approximately 10,000 live in the target zip codes for MESA.

Johns Hopkins: The source population is 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 has 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 is 164,513, of whom approximately 55,000 are aged 45 and older.

Minnesota: The source population is 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 is located in Ramsey County and is locally known as the "West Side". Its borders are the Mississippi River to the north, west, and east, and a street (Annapolis St.) in the south. All of the area dwellings and businesses share 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 resides in Community Areas 6, 8, 34, and 60 in the city of Chicago and the village of Maywood, Illinois, located in the Western suburbs of Chicago. The four selected Community Areas of Chicago are 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. The village of Maywood is located near Loyola Medical Center approximately 10 miles from Northwestern University Medical Center and has a population of 27,000 residents, of whom 5,800 are age-eligible African Americans.

UCLA: The source population is 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 will be targeted.

The ethnic composition of the source communities for MESA is summarized in Table 8.

Table 8

Estimated Ethnic Composition of the Source Populations[1]

	African-American	Asian-American	Caucasian	Hispanic
Wake Forest	19%	0	81%	0
Columbia	35%	0	15%	45%
Johns Hopkins:				
City Tracts	56%	0	41%	0
County Tracts	27%	0	68%	0
Minnesota	2%	4%	75%	16%
Northwestern				
Area 1[2]	8%	8%	76%	7%
Area 2	72%	0	18%	0
UCLA	14%	11%	45%	30%

[1] Percentages based on 1990 census except Wake Forest (1997 estimates) and Columbia (1995 survey).
[2]Area 1 = Four Community Areas of Chicago; Area 2 = village of Maywood, IL

4.3 Study Population and Sampling

4.3.1 Overview

Each of the six Field Centers will recruit approximately 1,100 participants from two or more of the following ethnic groups: African Americans, Asian (Chinese) Americans, Caucasians, and Hispanics. Expected marginal distributions of ethnicity, gender, and age -- overall and at each Field Center -- are shown in Tables 9 and 10. Two factors have been 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 is expected to have 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 9

Desired Ethnic Distribution of Study Participants, Overall and by Field Center

	Caucasian	African American	Hispanic	Asian American
Wake Forest	50%	50%		
Minnesota	50%		50%	
Northwestern	50%	25%		25%
Columbia	20%	35%	45%	
Johns Hopkins	50%	50%		
UCLA	10%	10%	40%	40%
TOTAL	38%	28%	23%	11%

Table 10

Desired Gender and Age Distribution of Study Participants, Overall and by Field Center

Gender:	Men	50%
	Women	50%
Age:	45-54	28%
	55-64	28%
	65-74	28%
	75-84	16%

The ideal counts for each Field Center in strata defined by ethnicity, gender, and age group are shown in Table 11.

Table 11

Ideal Recruitment Goals (Counts) by Field Center, Ethnicity, Gender, and Age-Group

		Caucasian		African American		Hispanic		Asian American	
		M	F	M	F	M	F	M	F
Wake Forest	45-54	77	77	77	77	-	-	-	-
	55-64	77	77	77	77	-	-	-	-
	65-74	77	77	77	77	-	-	-	-
	75-84	44	44	44	44	-	-	-	-
Minnesota	45-54	77	77	-	-	77	77	-	-
	55-64	77	77	-	-	77	77	-	-
	65-74	77	77	-	-	77	77	-	-
	75-84	44	44	-	-	44	44	-	-
Northwestern	45-54	77	77	38	38	-	-	38	38
	55-64	77	77	38	38	-	-	38	38
	65-74	77	77	38	38	-	-	38	38
	75-84	44	44	23	23	-	-	23	23
Columbia	45-54	31	31	54	54	69	69	-	-
	55-64	31	31	54	54	69	69	-	-
	65-74	31	31	54	54	69	69	-	-
	75-84	17	17	30	30	41	41	-	-
Johns Hopkins	45-54	77	77	77	77	-	-	-	-
	55-64	77	77	77	77	-	-	-	-
	65-74	77	77	77	77	-	-	-	-
	75-84	44	44	44	44	-	-	-	-
UCLA	45-54	15	15	15	5	62	62	62	62
	55-64	15	15	15	15	62	62	62	62
	65-74	15	15	15	15	62	62	62	62
	75-84	10	10	10	10	34	34	34	34
Total	45-54	354	354	261	261	208	208	100	100
	55-64	354	354	261	261	208	208	100	100
	65-74	354	354	261	261	208	208	100	100
	75-84	203	203	151	151	119	119	57	57

4.3.2 Sampling

The sampling frame and methods for sampling participants at each Field Center will vary, depending on site-specific recruitment plans and logistics. While the cohort will be community-based, the emphasis of MESA sampling will be 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 will differ by site. In three Field Centers (Wake Forest, Columbia, Northwestern), random samples, stratified by age and gender, will be selected from the sampling frames. In the others (Minnesota, Johns Hopkins, UCLA) the sampling frame will not contain demographic information and recruitment will proceed 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 reside in a single household can be recruited into the cohort. Recruitment progress will be 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 will attempt to maintain a balanced distribution across these strata throughout the recruitment period . Site specific details are described below.

Wake Forest: Two sampling frames will be 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 are estimated to be approximately 98 percent representative of the population aged 65 years and over. The DMV list will be 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 will be combined, eliminating duplicate names from the resultant sampling frame. The combined frame from these multiple sources will be more comprehensive than the DMV list alone. This sampling frame will include 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) will be constructed. Each list will then be randomly ordered and potential participants will be invited to participate in the order they appear on the randomized lists. Each of the 16 lists will be used to recruit the required number of participants for each gender-race-age group.

Columbia: The sampling frame will be 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) will be 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 will be compiled every 6 months. The sampling frame contains age, gender, names, addresses and phone numbers of potential participants. (Ethnicity is not available in the database.) The sampling frame will be stratified by gender and age.

Johns Hopkins: The sampling frame will consist of dwellings from selected census tracts. A list of dwellings including address and telephone numbers (when available) within these census tracts will be obtained from a commercial mailing service. The sampling frame will consist of dwellings from

selected census tracts. Census tract specific listings of dwellings will be obtained from either a commercial mailing service or from enumeration done by study staff. Given the available data on the sociodemographic composition of each census tract, the sample size from each tract will be able to be selected according to the study's recruitment goals. The final sampling strategy will be developed after analyzing the results of a survey to be conducted as part of student course work prior to developing the sample. The survey will obtain 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 is 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 will be possible to adjust sampling fractions periodically so as to reach the desired demographic composition of the study sample.

Minnesota: The sampling frame will be comprised of dwellings (single-family dwelling and apartment buildings) in the target area. The Ramsey County assessor's office will provide the list on a computer file, sorted by street and, within street, by house number. The county assessor's data identify apartment buildings and businesses; the latter will be deleted from the sampling frame. If needed, listings of Hispanic members of a local church will be used as another source for minority recruitment. The type of dwelling (apartment, single family, business) and the name of the owner will also be available. Phone numbers (or unlisted status) will be identified by reverse phone directories. The list of dwellings in each target area will be divided into "neighborhoods" of 100-150 houses each, which will be targeted successively over a two-year period. Recruitment will proceed 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 will be under-sampled in each neighborhood, but all consenting and eligible Hispanics will likely be recruited.

Northwestern: The sampling frame will be determined from census data for the target area which are compiled and maintained by the city of Chicago Department of Planning and Development. The sampling frame will be supplied by a commercial company (the Americalist Division of Hanes & Company, North Canton, Ohio) on a community by community basis. Information obtained includes 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 provides complete mailing addresses for those who have unlisted telephone numbers. Surnames of Chinese Americans will be identified from the database. Within each race group, age group, and gender category, the names will be divided randomly into batches of 100 names each. A specific number of batches will be selected for contact each week, with preferential selection of strata for which recruitment is lagging behind

UCLA: The sampling frame will be comprised of telephone exchanges corresponding to census tracts in Los Angeles County within a 15 mile radius from the UCLA Diabetes Center. This area has a heavy representation of Hispanics and Asian Americans**,** particularly Chinese Americans. Separate but overlapping sampling frames will be used, one for each of these two ethnic groups.

Respondents from either frame (including African-Americans and Caucasians) will be recruited, as needed. The frame for Hispanics will include telephone-exchanges that match 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 will include telephone exchanges that match 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 overlap and are representative of these two populations in Los Angeles County. The small number of African-American and Caucasians targeted for recruitment (about 110 each) will also be recruited from these two sampling frames. Random digit dialing will be used to recruit from the target area. Telephone numbers will be 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 will be 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 are defined as persons living within the defined geographic boundaries for each Field Center who are between the ages of 45 and 84 at enumeration, who are African-American, Chinese-American, Caucasian, or Hispanic, and who do 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 will not be recruited. Most other exclusion criteria relate to the long-term nature of the study or to incompatibility with certain components of the MESA exam. Eligibility (or ineligibility) status will be determined from self-reported information; no attempt will be made to validate the participant's response. MESA's exclusion criteria are shown in Table 12.

Table 12

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 respond "Don't know" to questions about medical conditions will not be considered ineligible.

4.5 Recruitment

4.5.1 Overview

Each site will recruit 1,100 participants, equally divided between men and women, and in the race proportions shown in Table 9. Desirable counts in age, gender, and ethnicity strata are shown in Table 11. Wake Forest, Johns Hopkins, Minnesota, and Northwestern all plan to start by creating community awareness of the study and enlisting the support and endorsement of community-based organizations and leadership. All sites will implement techniques that have been used successfully in other studies to recruit minority populations. Columbia will work closely with the 1199 National Benefit Fund during recruitment, including using study staff hired through the union for recruitment, retention, and study publicity. UCLA will recruit using random-digit dialing. All sites, which are recruiting Hispanics, will employ staff fluent in Spanish, and sites recruiting Chinese-Americans will employ staff fluent in Cantonese and Mandarin.

Prior to recruitment, the purpose, rationale, and design of the study will be publicized to residents of target areas at each site. Successive efforts will be directed at targeted individuals, and will include mailings of letters and brochures, followed by personal contacts via telephone or in person. Sites

will modify these materials slightly to meet unique aspects of the source population and recruitment strategy. Standard press releases will be written, and templates will be developed for participant letters, brochures, and scripts.

4.5.2 Screening

Since multiple eligible persons in a household can be recruited, the interviewer will first attempt 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 will be obtained, followed by an attempt to interview all age-eligibles on one or multiple calls. To determine MESA eligibility, the interviewer will administer a Screening Questionnaire that will provide basic information about the study and be 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 will help the interviewer introduce (or re-introduce) the study and stimulate interest. The questionnaire will usually be administered over the phone and sometimes during a home visit. The interviewer will be 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 might not be recruited in the interest of balanced recruitment, are provided with the Screening Questionnaire.

In this era of aggressive marketing and telemarketing, some contacted persons will terminate the interview before its completion, sometimes as early as the first sentence, or before household enumeration. In other cases, the respondent might terminate the interview after providing a certain amount of information but eligibility status might not be known. The first items to be ascertained by the interviewer are the absence of language barrier and age-eligible residents.

Once enumeration is completed (or at least one age-eligible is identified), each age-eligible person would be classified into one of the following mutually exclusive categories (also shown in Table 13).

Table 13

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 will be 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 clinic exam" is defined as 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) will be scheduled for eligible and consenting respondents. A follow-up call will be scheduled for eligibles who may want additional time to consider their decision. Whenever possible, a clinic visit should precede the CT exam and a CT exam should precede the MR exam. Two weeks prior to the clinic visit, the potential participant will be 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 will be phoned 48-72 hours prior to the appointment to remind them. Additional information about the CT and MR will be provided in-person during the clinic visit. No-shows will be contacted shortly after the missed appointment in an attempt to reschedule.

4.5.5. Recruitment Material

Studywide recruitment-related materials 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 will modify these materials slightly to meet unique aspects of the source population and recruitment strategy. For example, an abbreviated script might be used.

4.5.6 Recruitment Tracking and Progress

Given unique logistics of recruitment at each Field Center, some tracking will be done locally. A study-wide tracking form will be 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 will be 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 will be sent periodically to the Coordinating Center for centralized tracking.

The Coordinating Center will report, 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 will be made every four months on the basis of cumulative counts.

5 Overview of Study Methods

5.1 Timetable

The study is divided into three phases:

1.	Protocol development, training, pilot testing	January 15, 1999 - July 14, 2000
2.	Examinations, surveillance	July 15, 2000 - July 14, 2007
3.	Close-out, analysis/publication	July 15, 2007 - January 14, 2008

5.2 Overview of Examinations and Contacts with Participants

The first examination, scheduled for July 15, 2000 through July 14, 2002 (24 months) will include review of eligibility, signing of the informed consent, collection of questionnaire information on demographic characteristics, medical history, medications, lifestyle factors, physical activity, diet, and psychosocial factors, measurement of blood pressure in the arm, anthropometry, ankle-brachial blood pressure, carotid ultrasound, flow-mediated vasodilation in the forearm, and arterial wave forms in the radial artery, electrocardiography, magnetic resonance imaging of the heart, coronary calcification using computed tomography, phlebotomy, and a spot urine collection.

The second examination, scheduled for July 15, 2002 through January 14, 2004 (18 months), will include repeats or updates of questionnaire and history information, blood pressure in the arm, anthropometry, and electrocardiogram. In addition, half of the cohort will undergo repeat

measure of coronary calcification, one-fourth will undergo magnetic resonance imaging of the carotid artery to characterize plaque, approximately 200 will undergo repeat carotid ultrasound, and all of the cohort will undergo glucose tolerance testing.

The third examination scheduled for January 15, 2004 through July 14, 2005 (18 months) will likely include repeats and updates of questionnaire and history information, blood pressure in the arm, anthropometry, ankle-brachial blood pressure, electrocardiogram, and measurement of coronary calcification in the other half of the cohort.

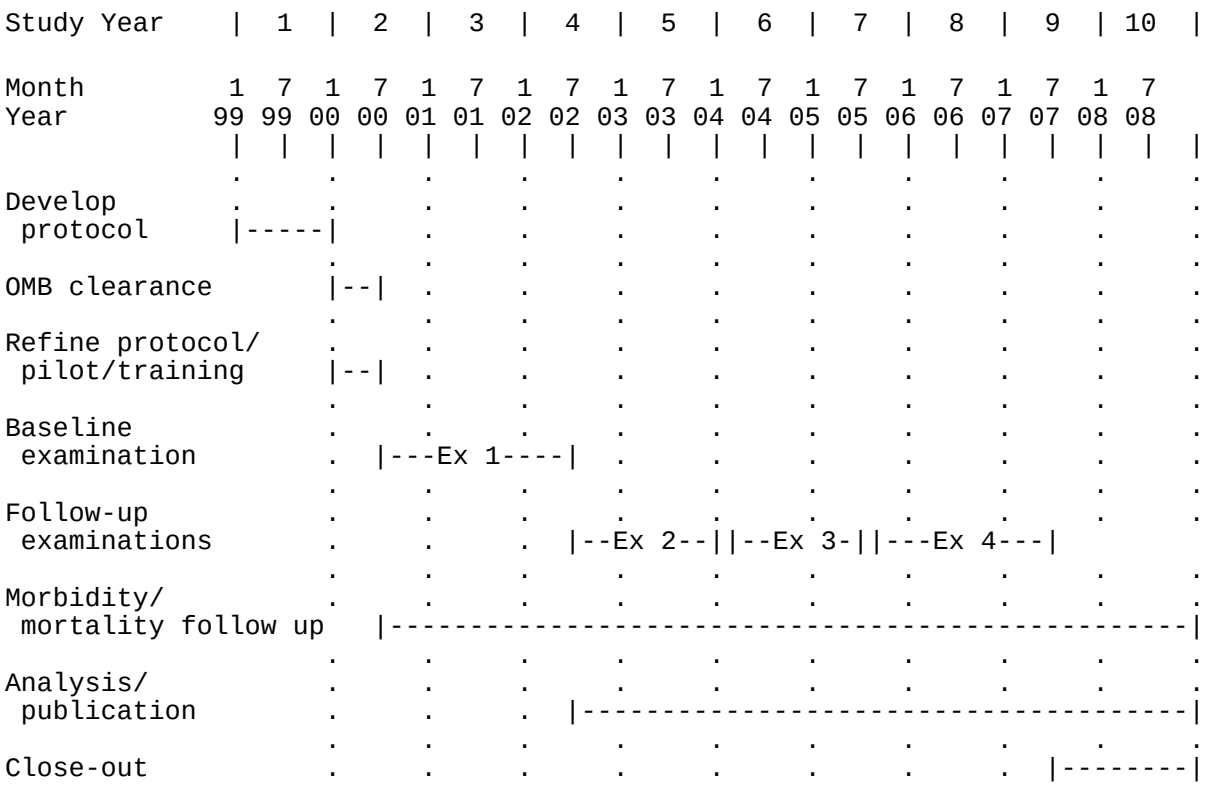
The fourth examination, scheduled for July 15, 2005 through July 14, 2007 (24 months) will likely include repeats and updates of questionnaire and history information, blood pressure in the arm, anthropometry, repeat measurement of coronary calcification in one-fourth of the cohort, and repeat cardiac MRI in one-fourth of the cohort. A general timeline for the study is provided in Table 14. During the surveillance period, participants will be contacted at 6-9 month intervals, including a combination of telephone and mail contacts.

5.3 Description of Field Center Clinics

Wake Forest: The primary clinic facility for examinations and interviews will be located on the first floor of the Piedmont Plaza Building located approximately 1/4 mile from the main campus. The clinic has eight examination rooms and ultrasound machines for measurement of carotid atherosclerosis. Magnetic resonance imaging scans will be done in the MRI Building, which also houses departmental offices of the investigators for the study. Computed tomography will take place in the Ardmore Plaza facility, located on Miller Street approximately 1/4 block from the main campus. Participants will park at the Piedmont Plaza Building and will ride a shuttle van to Ardmore Plaza and the MRI Building.

Table 14

Timeline for the Multi-Ethnic Study of Atherosclerosis



Columbia: Exams will be held mostly at Columbia-Presbyterian Medical Center. Electron-beam computed tomography scanning will be performed at St. Francis Hospital, an approximately 40-45 minute drive. A van will be used to transport participants to and from St. Francis as required. Research Assistants will accompany participants throughout their visit to Columbia Presbyterian Medical Center and St. Francis.

Johns Hopkins: The office of the study will be on the East Baltimore Medical Campus, either at the Johns Hopkins Outpatient Center, or in the hospital. The Hopkins campus is at the end of the Metro line through Baltimore and thus provides easy access for those who prefer to come by Metro, and there is ample parking adjacent to the Outpatient Center. All examinations, interviews and other tasks will be completed in these offices. The examinations for MRI, CT, and ultrasound will be conducted in the research labs on the 5th floor of Johns Hopkins Hospital. Thus, participants may come to the main study office for baseline questionnaires, phlebotomy, anthropometry and blood pressure and then, later in the day, they will be escorted to the fifth floor of the hospital for the scan procedures.

Minnesota: The clinic exam will be conducted in a study clinic, to be located in a rented space in the West Side, whereas the CT and MR exams will take place at Fairview-University Medical

Center, approximately 15 miles away from the study community. Both a MESA clinic exam and a CT/MR will be scheduled at the time of recruitment but these components will likely be scheduled on different days. Attempts will be made to schedule the clinic exam before the CT/MR and to schedule the CT and MR on the same day "back-to-back".

Northwestern: Participants will choose whether to have the clinic exam in the Northwestern Center or the Loyola Center. Following completion of the baseline questionnaires and phlebotomy, participants will be transported via pre-arranged taxi service to University of Illinois for an EBCT examination. The MRI exam will take place in the Northwestern MRI Center, which may be scheduled with a separate appointment. A staff member will escort participants to the EBCT and MRI Centers.

UCLA: The Examination and ultrasound studies will be conducted at the research clinic in Culver City. The EBCT and MRI will be done in the Radiology Department at the UCLA campus (7 miles from the clinic). Participants will park at the clinic and be transported by UCLA shuttles to the Radiology Department and then back to the clinic after completion of the procedures.

5.4 Data Collection

Data collection activities are divided into six operational sections: (1) enumeration of households, (2) initial eligibility determination (by telephone), (3) final eligibility determination (in clinic), (4) examinations 1-4, (5) follow-up contacts, and (6) identification and classification of morbid and mortal events.

Once eligibility is determined, the study will be explained in detail in lay language to potential participants. Participants will be allowed enough time to think about the program and to consider the benefits and risks of participation. Informed consent and permission to release medical information will be obtained in writing in the clinic (Appendix B).

5.4.1 Examination Components

An outline of each of the four planned examinations is provided in the following sections, followed by a section of rationale behind the major subclinical disease measures obtained in the examinations. Most detail is provided for the first examination. Detail is provided for components included in later examinations that were not previously collected. Examination components, particularly for Exams 3 and 4, are subject to change, based on early findings and study priorities.

5.4.1.1 Examination 1

The Field Centers will schedule participants on a minimum of 5 days a week, with an average of 2.2 participants examined per day; however, some clinics will have heavy clinics on Saturdays, with an average of 4 participants. 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, electrocardiography, and urine collection will be measured in fasting state, before phlebotomy.

- Brachial reactivity will be performed before phlebotomy or at least 30 minutes after phlebotomy and will be performed fasting or at least 90 minutes after a no-fat snack.

- All participants will be scheduled fasting, with initial blood samples to be drawn before 10:00 AM.

Not all participants will be able to complete the examination in a single visit. Specifically, MRI and CT examinations may need to be performed on separate days. All participants who complete the clinic examination and a CT scan will be included in the cohort.

The first examination will start in July 2000 and will be completed in two years. All participants will undergo the following, also shown in Table 15:

- **Questionnaires**: Standard questionnaires will be used to collect information about demographics, socioeconomic and psychosocial status (see Table 15), medical and family history, medication use, dietary and alcohol intakes, smoking, and physical activity.

- **Anthropometry:** Height and weight will be measured to the nearest 0.1 cm and 0.5 kg respectively. Body mass index (kg/m^2) 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). The waist/hip ratio and waist circumference will be used as indices of body fat distribution.

- **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.

- **Ankle/Brachial Blood Pressure Index:** Systolic blood pressure will be measured in both the right and left brachial, posterior tibial, and dorsalis pedis arteries with a Doppler instrument. The average of the measures will be used to calculate ankle arm ratio for each side, which will be used as measure of peripheral vascular disease.

- **Electrocardiogram (ECG):** A 12-lead ECG will be obtained and transmitted to the ECG Reading Center via telephone lines for Minnesota coding.

- **Coronary Calcium Determination:** Coronary calcium will be determined with electron-beam or helical CT. Experienced and trained technologists will scan the hearts of each consenting subject twice in order to obtain an accurate and reproducible assessment of coronary calcium deposits. The technologist will transmit the scans of the Internet to the Reading Center. A list of the measures is in Appendix C.

- **Carotid Ultrasound:** High-resolution B-mode ultrasonography will be used for noninvasive measurement of intima-media thickness (IMT) of the carotid arteries and plaque characterization. A list of the measures is in Appendix D.

- **Arterial Wave Forms:** Arterial wave forms will be recorded by tonometry to measure compliance of arteries.

- **Flow-dependent Brachial Artery Vasodilation:** Arterial endothelial function will be assessed non-invasively by examining brachial artery response to flow-mediated vasodilation. Arterial diameter will be measured from B-mode ultrasound images at rest and in response to reactive hyperemia, 60 seconds after baseline (with increased flow producing endothelium-dependent vasodilation). The percent change in vessel diameter will be calculated.

- **Cardiac Magnetic Resonance Imaging:** Cardiac MRI will use used to obtain measures of left ventricular mass, wall thickness, ejection fraction, cardiac output, aortic atherosclerosis, and aortic distensibility. A list of the measures is in Appendix E.

- **Laboratory Measurements**: These will include lipids and lipid metabolism parameters, lipid oxidation markers, cytokines, adhesion molecules, nitric oxide, and hemostasis/fibrinolysis markers. White cells will also be cryo-preserved for future generation of cell-lines and isolation of DNA needed for genetic studies. (See Appendix F).

Table 15

COMPONENTS OF THE BASELINE CLINIC EXAMINATION

SECTION	PURPOSE
RECEPTION	Greet the participant. Review eligibility. Explain the schedule. Determine adherence to the fasting requirement. Obtain informed consent.
PERSONAL HISTORY/DEMOGRAPHICS	Obtain standard measures of education, income, wealth, occupation, smoking, and alcohol intake.
CHANGE CLOTHES	Standardize and facilitate anthropometric and other measurements.
BLOOD PRESSURES	Obtain measure of sitting blood pressure of the brachial artery, at rest, and of the posterior tibial artery and/or dorsalis pedis and brachial artery, to determine the ankle-brachial index.
ELECTROCARDIOGRAPHY	Obtain a 12-lead electrocardiogram.
ANTHROPOMETRY	Measure weight, height, waist and hip circumferences.
URINE SAMPLE COLLECTION	Obtain specimen for measurement of microalbuminuria.
PHLEBOTOMY	Obtain blood samples for lipids, chemistry, hemostasis, and other laboratory tests and for storage.
SNACK	Provide the participant with a snack which contains no fat or caffeine.
CAROTID ULTRASOUND	Measure intimal-media carotid wall thickness and identify echogenic lucencies.

Table 15, continued

COMPONENTS OF THE BASELINE CLINIC EXAMINATION

BRACHIAL ULTRASOUND	Measure flow-mediated brachial artery vasodilation.
ARTERIAL WAVE FORM	Measure compliance of arteries.
MEDICAL HISTORY	Obtain relevant medical history.
MEDICATIONS	Obtain information on types and dosages of all prescribed and over the counter medications.
DIET	Obtain information on usual intake of foods, including types and quantities.
PHYSICAL ACTIVITY	Obtain information on usual low, medium, and high-level activities during past month.
PSYCHOSOCIAL INFORMATION	Obtain information on anger, anxiety, social support, depression, chronic burden, discrimination, and neighborhood environment.
EXIT INTERVIEW	Explain next steps and answer questions and solicit comments about the exam. Discuss referrals. Obtain tracking information. Schedule CT and MRI exams. Thank participant.
CARDIAC MRI SCAN	Obtain MRI scan of the heart.
CHEST COMPUTED TOMOGRAPHY SCAN	Obtain CT scan of the heart.

5.4.1.2 Examination 2

The second examination will take place two years after the baseline examination, starting in July 2002, and will be completed in 18 months. Selected questionnaires (including psychosocial measures of optimism, religiousness and spirituality, hostility, job stress, and quality of life), anthropometry, blood pressure measurements, and laboratory tests will be repeated in all participants. All participants will also undergo provocative testing, such as an oral glucose tolerance test. A random half of the cohort will have a second CT for coronary calcium assessment. Twenty-five percent of the cohort will have a carotid MRI during this examination. Based on baseline findings which indicate the presence of plaque, approximately 200 participants who undergo carotid MRI will have a repeat carotid ultrasound during the second examination. Subsets undergoing carotid MRI will be preferentially selected from those undergoing repeat CT.

5.4.1.3 Examination 3

The third examination will start in January 2004 and will be completed in 18 months. Questionnaires, anthropometry, blood pressure measurements, ankle-brachial index, electrocardiography, and laboratory tests will be repeated in all participants. The other half of the cohort will have a second CT for coronary calcium assessment performed.

5.4.1.4 Examination 4

The fourth examination will start in July 2005 and will be completed in two years. Questionnaires, anthropometry, blood pressure measurements, and laboratory tests will be repeated in all participants. Twenty-five percent of participants will have CT for coronary calcium assessment performed for a third time. Twenty-five percent of the cohort will have a repeat cardiac MRI during this examination. These subgroups will be selected to allow studies of progression of subclinical disease.

An overview of the four planned examinations is provided in Table 16.

Table 16

Components, by Clinic Examination

Component	Exam 1	Exam 2	Exam 3	Exam 4
Reception, Review of eligibility, informed consent	X	X	X	X
Change clothes	X	X	X	X
Blood pressure	X	X	X	X
Electrocardiography	X	X	X	
Anthropometry	X	X	X	X
Urine sample collection	X			
Phlebotomy	X	X	X	X
Snack	X	X	X	X
Carotid ultrasound	X	X (n=200)		
Ankle brachial index	X		X	
Endothelial function	X			
Arterial wave form collection	X			
Medical history	X	X	X	X
Personal history, Demographics, Socioeconomic status	X	X	X	X
Medications	X	X	X	X
Psychosocial assessment	X	X	X	X
Diet assessment	X			
Physical activity	X	X	X	X
Family history		X		
Clinic Exit/Tracking	X	X	X	X
CT scanning	X	X (50%)	X (50%)	X (25%)
Cardiac MRI scanning	X			X (25%)
Carotid MRI scanning		X (25%)		

Note: Examination components, particularly for Exams 3 and 4, are subject to change.

5.5 Rationale for Subclinical Disease Measures

5.5.1 Computed Tomography for Measurement of Coronary Calcium

Coronary calcium is a specific, quantifiable marker for the presence of coronary atherosclerosis. Its presence closely follows epidemiologic patterns for coronary atherosclerosis, with marked increases with age and higher prevalence in men than women. It is associated with coronary risk factors and predicts coronary disease and mortality. Repeat measures over time are expected to provide a measure of progression of atherosclerosis.

5.5.2 Magnetic Resonance Imaging of the Heart and Carotid Artery

Magnetic resonance imaging is capable of determining soft tissue characteristics of the carotid artery wall, including wall thickness, plaque size, composition and lumen size. The potential for finding abnormalities related to small vessel disease of the heart represents a tremendous opportunity for enhanced understanding of ventricular dysfunction and congestive heart failure. MRI represents a relatively new imaging modality for epidemiologic studies. For established risk factors, MRI offers high degree of reproducibility and the ability to successfully image left ventricular mass on a greater proportion than echocardiography. MRI is also much more sensitive to the presence of disease.

5.5.3 Enhanced Grey-scale and Doppler Ultrasound of Carotid Arteries

The well-established methodology for carotid ultrasound imaging and current knowledge of its relationships to risk factors and disease will complement information obtained from different imaging modalities. Ultrasound can serve as a benchmark for determining whether risk associated with different measures of vascular disease is additive, multiplicative, or only confirmatory. Examination of gray-scale characteristics of carotid plaque will permit assessment of their relationship to disease in other vascular beds.

5.5.4 Flow-mediated Brachial Vasodilation

Endothelium-dependent vasodilation can be induced by reactive hyperemia and measured by ultrasound imaging of the brachial artery. It is related to coronary vasoconstriction, appears to precede clinical coronary heart disease, and demonstrates a wide range of response even in young persons. Treatment appears to improve endothelium-mediated vasodilation even in the absence of significant decreases in measured stenosis. The addition of this functional measure to strictly structural assessments will illuminate a critical aspect of the physiology of progression from subclinical to clinical disease.

5.5.5 Ankle-brachial Blood Pressure Index

The simple ratio of brachial systolic blood pressure to posterior tibial blood pressure has been found to reflect blood flow adequacy in the lower extremity and thus serve as an indirect measure of peripheral artery disease. Though peripheral vascular disease may have a distinct risk factor profile, ankle-arm index correlates strongly with prevalent cardiovascular disease and subsequent mortality.

5.5.6 Arterial Wave Forms

A tracing of the contours of the arterial wave form at the radial artery will be obtained to estimate compliance of the small and large arteries and the augmentation index, which may relate to atherosclerosis and left ventricular mass.

5.6 Cohort Surveillance and Follow-up

Periodic follow-ups of the cohort every 6-12 months will be used to maintain contact, to correct addresses of participants, and to ascertain medical events between the examinations. At the exit interview for the first examination, participants will be asked whether they prefer to be contacted for follow-up via telephone, surface mail, or electronic mail. Follow-up contacts will be made within a month of the target.

The follow-up contacts are comprised of an appropriate mail, electronic mail, or telephone interview. Affirmative answers to preliminary queries about new medical conditions will be followed up by a telephone interview 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.

5.7 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 exams 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.)

5.8 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 first clinic visit, such as height, weight, blood pressure, and preliminary findings of the electrocardiogram. 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 approximately two months after the clinic visit and will include a final electrocardiogram report and routine laboratory results (plasma glucose, lipids, and serum creatinine). A third report will be mailed 4-6 months after the completion of the examination and will include the coronary calcium score and the results of ultrasound and MRI studies. Similar reports will be provided after the subsequent examinations. The delay in reporting findings is dictated by the multicenter nature of the study and its complexity. Nonetheless, 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."

6 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:

- Data will be collected on coded forms which do 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.
- 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 recruitment and clinic data it collects. Data entry will be accomplished by scanning and then verifying data forms. The scanning software will be programmed for table lookups, range checks, skip pattern rules, consistency checking and ID check-digit confirmation. During the verification step, any fields which could not be successfully scanned will be highlighted for coding by the technician. Recruitment tracking data and data forms from the clinic exams and interim follow-up contacts will be processed in this manner, as will data forms for events. Local data will be kept on a local database at each Field Center, and Field Center personnel will be able to perform updates on their local databases.

Field Center personnel will electronically transfer scanned and verified data to the Coordinating Center once a week. This transfer will include recruitment data (during the recruitment phase), exam data, events data, tracking data (during the recruitment phase), and follow-up data (during the follow-up phase).

Routine backup of all data will be performed on a weekly basis at both the Coordinating Center and the Field Centers. Backed up data files will be stored on at least two separate devices, such as a hard disk and a floppy disk or magnetic tape.

Each Field Center will have a Data Manager who will be responsible for overseeing all tasks related to Field Center data. In addition to the tasks listed above, he/she will be responsible for working with the Coordinating Center to resolve any questions related to data completeness or accuracy, and maintaining the local computer system including ensuring that the most recent versions of programs and databases are being used.

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. 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 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 will establish 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 will develop a series of databases to store and manage data which will form a comprehensive system linked by unique participant ID numbers. Access to the data will be accomplished by our Intranet through separate databases for each main area of study (e.g., clinic exam data, MRI, EBCT/CT, ultrasound, tracking). There will be one raw database to which scanned data files from Field Centers and Reading Centers and Laboratory will be uploaded weekly. 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.

A recruitment tracking database will be developed to allow each Field Center to monitor recruited participants dynamically as well as to track current status information for each study participant. This database will monitor the age, gender, and race composition of the cohort as it is recruited, to ensure that study goals are achieved.

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 will also develop and maintain a database to track publications and presentations. The database will allow 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 will include: title, authors, manuscript proposal date, date for completion, submission date to journal, status of manuscript with the journal, publication date, and abstract. This database will be 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 either as compressed files ready to be transferred or as database files to be queried. Medical record security is a current topic of concern, and the Microsoft SQL Server 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 two web sites, an external site for the general public, and an internal site for study investigators and personnel.

External Web Site This external web site will inform its target audiences about the project, generate project support, and reduce mailing and printing costs. Specifically, the external web site will include: (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.

Internal Web Site This web site will provide a way for project staff to facilitate communication, share information, reduce mailing and printing costs, and increase efficiency. Staff will be 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) Data Analysis Manual; (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; (11) Search capability; and (12) Bulletin boards allowing investigators to post their own materials.

Passwords will be 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 RAID level 5 servers that are fault tolerant. "RAID" stands for Redundant Array of Inexpensive Disks, which means that all data are kept on 2 separate hard disks within the server, and so the first line of defense against hardware failure will be to restore the data from one of the other disks in the RAID server. The Coordinating Center will also maintain incremental system backups on a weekly basis using a magnetic tape backup unit. On a monthly basis, a full system backup is made and transferred to a secure location physically separate from the Coordinating Center. A rotation of these tapes is kept so that the Coordinating Center has backups on a monthly basis for the past quarter. The last backup of each year is also kept as a permanent archive throughout the study period. System backup tapes 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 on magnetic computer tape. Additional backup tapes will be made and kept for the duration of the study for databases, subfiles and retrieval and analysis procedures used to produce

reports for the Steering Committee or for endpoint analyses for publication of the results of the study. All backups will be verified to insure that they are usable and complete.

- Semi-annual backups of the all files will be made using an optical (laser) disk drive and will be stored off site. Optical disks provide the fastest access mass storage medium currently available. Important software and major study documents such as manuals of operation, protocols, and the texts for scientific reports will also be archived on the optical disks.

- Particularly 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 CT, Ultrasound, and MRI Reading Centers will receive data from the clinics transmitted electronically. Imaging studies will be stored on site at the Field Centers. After receiving the disks or tapes, 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.

The ECG Reading Center will receive selected electronic data files from the Coordinating Center. These will be ECGs with specified abnormalities as well as a 5% sample of ECGs without abnormalities. The Reading Center will code these ECGs and transmit the data to the Coordinating Center within 30 days. Additionally, hard copies of ECGs obtained from hospitalizations will be sent to the ECG Reading Center for coding. Data from these hard copies will be sent to the Coordinating Center within 60 days. Coded data will be stored in an organized manner and clinic ECGs will be easily distinguishable from Events ECGs.

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

7 Participating Centers Organization, Roles and Responsibilities

7.1 Organizational Structure

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

7.2 Participating Organizations

The centers involved in the study and their principal investigators are listed in Table 17. All awards were made on January 15, 1999. All investigators are listed in Appendix H.

Table 17

List of Centers and Principal Investigators in MESA

Center	Site	Principal Investigator
Coordinating Center	University of Washington	Richard Kronmal, Ph.D.
Field Center	Columbia University	Steven Shea, M.D.
Field Center	Johns Hopkins University	Moyses Szklo, M.D. , Dr.P.H.
Field Center	Northwestern University	Kiang Liu, Ph.D.
Field Center	University of Minnesota	Aaron Folsom, M.D., M.P.H.
Field Center	University of California at Los Angeles	Mohammed Saad, M.D.
Field Center	Wake Forest University	Gregory Burke, M.D., M.S.
Central Laboratory	University of Vermont	Russell Tracy, Ph.D.
Computed Tomography Reading Center	University of California at Los Angeles (UCLA)	Robert Detrano, M.D., Ph.D.
Magnetic Resonance Imaging Reading Center	Johns Hopkins University	David Bluemke, M.D.
Ultrasound Reading Center	New England Medical Center	Daniel O'Leary, M.D.
ECG Reading Center	TBN	

The Project Office is in the Field Studies and Clinical Epidemiology Scientific Research Group, Epidemiology and Biometry Program, Division of Epidemiology and Clinical Applications, 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 followup procedures.

- Develop, implement and maintain a data base management system capable of: registration of participants and invited non-respondents; 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 designated laboratory measurements, specimen repository, and ECG Reading Center.

- 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.

- Recruit, examine, and maintain follow-up of approximately 1,100 noninstitutionalized participants aged 45-84 years in ethnic and gender strata designated by the Steering Committee.

- 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 at weekly intervals.

- Collect, process, and transmit recordings of electrocardiographic and carotid and brachial artery ultrasound examinations 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 Computed Tomography (CT) Reading Center

- Participate in the Steering Committee and its subcommittees in development of the study protocol.

- Develop, with assistance and input from the Computed Tomography (CT) Subcommittee and the Steering Committee, protocols for performance (scanning), reading and coding of CT studies of the heart.

- Recommend feedback to participants and their physicians regarding levels of coronary calcium and other findings from CT scans.

- Perform measurements of coronary calcium during each examination.

- Enter all data derived from CT scan measurements into computer storage and provide measurements to the Coordinating Center in a computer readable format.

- Design and implement quality control measures for performance of the CT scans at the Field Centers, and for reading of studies at the CT Reading Center.

- Train, certify, and oversee quality control monitoring of Field Center CT technicians in details of the CT examination of the heart, and of CT readers in making measurements.

- Participate in analysis and publication of study results.

7.2.5 Magnetic Resonance Imaging (MRI) Reading Center

- Participate in the Steering Committee and its subcommittees as needed in development of the study protocol.

- Develop, with assistance and input from the MRI Subcommittee and the Steering Committee, protocols for performance (scanning), reading and coding of MRI images of the heart and the carotid artery.

- Recommend feedback to participants and their physicians regarding findings from MRI examinations.

- Perform cardiac MRI measurements during examinations 1 and 4 and carotid MRI measurements during examination 2 or 3.

- Enter all data derived from MRI measurements into computer storage and provide measurements to the Coordinating Center in a computer readable format.

- Design and implement quality control measures for performance of the MRI examinations at the Field Centers, and for reading of studies at the MRI Reading Center.

- Train, certify, and oversee quality control monitoring of Field Center MRI technicians in details of the heart and carotid MRI examinations, and of readers in making measurements from these studies.

- Participate in analysis and publication of study results.

7.2.6 Ultrasound Reading Center

- Participate in the Steering Committee and its subcommittees as needed in development of the study protocol.

- Develop, with assistance from the Ultrasound Subcommittee and the Steering Committee, protocols for performance (scanning), reading and coding of B-scan, Doppler carotid and of flow-mediated brachial dilation examinations, and collection of arterial wave forms.

- Recommend feedback to participants and their physicians regarding findings from the ultrasound examinations.

- Perform carotid and brachial ultrasound and arterial wave form measurements during examination 1.

- Enter all data derived from measurements of the carotid and brachial ultrasound and arterial wave form examinations into computer storage and provide measurements to the Coordinating Center in a computer readable format.

- Design and implement quality control measures for performance of the carotid and brachial ultrasound and arterial wave form examinations at the Field Centers, and for reading of studies at the Ultrasound Reading Center.

- Train, certify, and oversee quality control monitoring of Field Center ultrasonography technicians in details of the carotid and brachial ultrasound and arterial wave form examinations, and of readers in making ultrasound and arterial wave form measurements.

- Participate in analysis and publication of study results.

7.2.7 Electrocardiogram (ECG) Reading Center

- Develop, with assistance from the Steering Committee and the Morbidity and Mortality Subcommittee, protocols for performance of ECGs and for reading and coding of both clinic and hospitalization ECGs.

- Recommend feedback to participants and their physicians regarding findings from the ECG examinations. Perform ECG measurements during all examinations.

- Enter all data derived from ECG measurements into computer storage and provide measurements to the Coordinating Center in a computer readable format.

- Design and implement quality control measures for performance of the ECG examinations at the Field Centers and for reading of studies at the ECG Reading Center.

- Train, certify, and oversee quality control monitoring of Field Center ECG technicians in details of the ECG examination and of readers in making ECG measurements.

- Develop a Field Center Manual of Operations for use by Field Center ECG technicians.

- Participate in analysis and publication of study results.

7.2.8 Central Lipid Laboratory

- Measure blood lipids and lipoproteins and other chemistries on specimens collected from MESA participants as directed by the MESA Steering Committee and Blood Laboratory Subcommittee.

- Recommend feedback to participants and their physicians regarding measurements.

- Enter all data derived from blood analyses into computer storage and provide measurements to the Coordinating Center in a computer readable format.

- Design and implement quality control measures for analysis of samples at the Central Lipid Laboratory.

- Train, certify, and oversee quality control monitoring of laboratory technicians in the analysis of samples.

- Participate in analysis and publications of study results.

7.2.9 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.

7.2.10 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; CT, MRI, and Ultrasound Reading Centers; Central Laboratory; and the Project Officer. Subcommittees include Design, Laboratory, MRI, CT, Morbidity and Mortality, Operations, Recruitment, 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 over the course of the study, repetition of the component, participant burden, and cost, along with scientific value.

7.3..3 Recruitment Committee

- In conjunction with Field Centers, evaluate and recommend modifications to recruitment strategies to assure consistency of procedures among Field Centers, as feasible.
- Evaluate status of recruitment, considering balance of relevant ethnic, gender, and age subgroups.
- Develop a standard description of recruitment procedures for use in study manuscripts.

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 a regular newsletter to keep participants informed about the study and foster good will.
- 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 Examination/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 Computed Tomography Committee

- Develop protocol to measure coronary calcium using electron-beam computed tomography or other computed tomography method.
- Develop protocol to read coronary calcium scans.
- In conjunction with the Quality Committee, 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 Ultrasound Committee

- Develop protocol to measure carotid intimal-media thickness and plaque using B-mode ultrasound.
- Develop protocol to measure flows-mediated vasodilation of the brachial artery, using ultrasound.
- Develop protocol to read ultrasound scans.
- In conjunction with the Quality Committee, develop and recommend methods to measure Reading Center quality and 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.

7.3.8 MRI Committee

- Identify and recommend to the Steering Committee measures of atherosclerotic plaque in the carotid or aorta, indices of cardiac anatomy and function and other measures appropriate to the technology, within the time constraints of the study, and according to the study goals.
- Develop protocols to make measurements and to read MRI scans.
- In conjunction with the Quality Committee, 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.

7.3.9 Laboratory Committee

- Recommend blood-based laboratory measurements, based on the study goals. Develop a protocol for Field Center phlebotomists.
- In conjunction with the Quality 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.

7.3.10 Morbidity and Mortality Committee

- Develop protocol for identifying, evaluating, and quantifying, as feasible and appropriate, cardiovascular events, including (1) clinical event manifestations of coronary heart disease, cerebrovascular disease, and congestive heart failure and (2) clinical diagnostic testing and interventions.
- Participate in classification of type and severity of cardiovascular events.

7.3.11 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.

7.3.12 Publications and Presentations Committee

- Develop, disseminate, 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.
- Develop and 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.

8 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.

8.2 Ultrasound Reading Center

Detailed and comprehensive quality control is very important with this procedure. Data from other studies such as CHS and ARIC indicate that the use of ultrasound is feasible in multicenter studies but that careful monitoring is necessary to watch for problems with sonographer and reader variability. Considerable training and experience are necessary before adequate ultrasound studies of the carotid system can be obtained in population studies. It will be particularly important to monitor for drift over time in all centers and laboratories.

Quality control procedures for ultrasound image acquisition and reading will include:

- Supervision of Field Center technicians by local ultrasonographer
- Ultrasound Reading Center staff visits to Field Centers
- Assessment of inter- and intra-technician variability (certification and examination periods)
- Assessment of inter- and intra-reader variability (certification and examination periods)
- Replacement or retraining of technician and readers
- Remeasurement periodically to assess drift over time

8.3 MRI and CT Reading Centers

Quality control activities will be very important for these procedures as well. Due to cost and radiation concerns, repeat scans will not be possible. Technician performance and machine calibration will be assessed with routine use of scanned phantoms. Other quality control activities will focus on the readers to ascertain that variability between and within readers is kept at a minimum level and that readers do not drift over time. Certification requirements will be established, and readers will be observed at regular intervals for adherence to the protocol.

8.4 Central Laboratory

All blood and urine samples collected for MESA will be shipped to the Central Laboratory at weekly intervals. 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

8.5 ECG Reading Center

ECGs will be recorded on an electrocardiograph with built in computer for data storage and ECG interpretation. Data will be transmitted to the ECG Reading Center, where they will be interpreted via a computer algorithm. Selected ECGs will be further evaluated at the ECG Reading Center with greater specificity. Duplicate ECGs will be performed at the Field Centers on a small subset of participants to look for technician variability, and technicians will be observed by QC supervisors to monitor adherence to protocol. The duplicate ECGs will also be used at the ECG Reading Center to ascertain the reproducibility of the reading process.

8.6 Central Lipid Laboratory

The Lipid Analysis Laboratory will have in place an operating quality control program to assess and control within-run variability, accuracy, precision, and long-term drift for all blood measurements. Acceptable variation limits for each analyte shall be established prior to initiation of the study. Accuracy and precision standards will be maintained throughout the study, repeating determinations where quality control results are outside the acceptable range. Batch quality control results will be reported to the Coordinating Center monthly. Quality Control results will be reported to the Steering Committee quarterly. The CLL will participate in national standardization programs, such as the CDC standardization for measurements of cholesterol and triglycerides.

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.

9 Study Policies

9.1 Publications and Presentations

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

9.2 Ancillary Studies

The MESA investigators and NHLBI encourage ancillary studies, (substudies 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 J.

10 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 K.

Appendix A - References

Rates of and trends in cardiovascular disease

Aronow W. Prevalence of atherothrombotic brain infarction, coronary artery disease and peripheral arterial disease in elderly blacks, Hispanics and whites. Am J Cardiol 1992;70:1212-1213.

Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. New Engl J Med 1992;326:381-386.

Enriquez-Sarano M, Klodas E, Garratt KN, Bailey KR, Tajik AJ, Holmes Jr,D.R.. Secular trends in coronary atherosclerosis--analysis of patients with valvular regurgitation. New Engl J Med 1996;335:316-322.

Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Incidence and case fatality rates of acute myocardial infarction (1975-1984): the Worcester Heart Attack Study. Am Heart J 1988;115:761-767.

Higgins M, Thom T. Trends in CHD in the United States. Int J Epidemiol 1989;18:S58-S66.

Reed D. The paradox of high risk of stroke in populations with low risk of coronary heart disease. Am J Epidemiol 1990;131:579-588.

Traditional coronary heart disease risk factors

Burchfiel C, Shetterly S, Baxter J, Hamman R. The roles of insulin, obesity, and fat distribution in the elevation of cardiovascular risk factors in impaired glucose tolerance: the San Luis Valley Diabetes Study. Am J Epidemiol 1992;136:1101-1109.

Kuczmarski RJ, Flegal K, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Examination Surveys, 1960 to 1991. J Am Med Assn 1994;272:205-211.

Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, O'Leary DH, Savage PJ, Tell GS, Tracy R. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation. 1995;92:720-726.

Mitchell B, Stern M, Haffner S, Hazuda H, Patterson J. Risk factors for cardiovascular mortality in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. Am J Epidemiol 1990;131:423-433.

Sempos CT, Cleeman JI, Carroll MD, et al. Prevalence of high blood cholesterol among U.S. adults. An update based on guidelines from the Second Report of the National Cholesterol Education Program Adult Treatment Panel. J Am Med Assn 1993;269:3009-3014.

Simon JA, Hodgkins ML, Browner WS, Neuhaus JM, Bernet JT, Hulley SB. Serum fatty acids and the risk of coronary heart disease. Am J Epidemiol. 1995;142:469-475.

Cardiovascular disease and risk factors in minority populations

Fujimoto W, Bergstrom R, Boyko E, Leonetti D, Newell-Morris L, Wahl P. Susceptibility to development of central adiposity among populations. Ob Res 1995;2:179S-186S.

Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW. Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. Diabetes 1987;36:730-739.

Goff D, Ramsey D, LaBarthe D, Nichaman M. Greater case-fatality after myocardial infarction among Mexican Americans and women than among non-Hispanic whites and men. Am J Epidemiol 1994;139:474-483.

Gordon T. Mortality experiences among the Japanese in the United States, Hawaii, and Japan. Publ Health Rep 1957;72:543-553.

Klatsky A, Armstrong M. Cardiovascular risk factors among Asian Americans living in Northern California. Am J Publ Hlth 1991;81:1423-1428.

Markides KS, Coreil J. The health of Hispanics in the southwestern United States: an epidemiologic paradox. Public Health Rep 1986;101:253-265.

Marmot M, Smith G. Why are the Japanese living longer? Br Med J 1989;299:1547-1551.

Mitchell B, Hazuda H, Haffner S, Patterson J, Stern M. High prevalence of angina pectoris in Mexican-American men. A population with reduced risk of myocardial infarction. Ann Epidemiol 1991;1:415-426.

Mitchell BD, Stern MP, Haffner SM, Hazuda HP, Patterson JK. Risk factors for cardiovascular mortality in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. Am J of Epidemiol 1990;131:423-433.

Nichaman M, Wear M, Goff D, Labarthe D. Hospitalization rates for myocardial infarction among Mexican-Americans and non-Hispanic whites. Ann Epidemiol 1993;3:42-48.

Pappas G, Queen S, IIadden W, Fisher G. The increasing disparity in mortality between socioeconomic groups in the United States, 1960 and 1986. N Engl J Med 1993;329:103-109.

Wild S, Lawa A, Fortmann S, Varady A, Byrne C. Mortality from coronary heart disease and stroke for six ethnic groups in California, 1985-1990. Ann Epidemiol 1995;5:432-439.

Winkleby M, Fortmann S, Barrett D. Social class disparities in risk factors for disease: eight-year prevalence patterns by level of education. Prev Med 1990;19:1-12.

Winkleby MA, Fortmann SP, Rockhill B. Health-related risk factors in a sample of Hispanics and whites matched on sociodemographic characteristics. The Stanford Five-City Project. Am J Epidemiol 1993;137:1365-1375.

Yuh ES, Liu WT. US national health data on Asian Americans and Pacific Islanders: a research agenda for the 1990s. Am J Pub Health 1992;82:1645-1652.

Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JK, Tall AR. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J Clin Invest 1996;97:2917-2923.

Endothelial function

Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol 1995;26:1235-1241.

Celermajer DS, Adams MR, Clarkson P, et al. Passive smoking and impaired endothelial-dependent arterial dilatation in healthy young adults. New Engl J Med 1996;334:150-154.

Shireman PK, Pearce WH. Endothelial cell function: biologic and physiologic functions in health and disease. Am J Roentgenol 1996;166:7-13.

Non-traditional risk factors for coronary heart disease

Barrett-Connor E, Criqui MH, Witztum JL, Philippi T, Zettner A. Population-based study of glycosylated hemoglobin, lipids, lipoproteins in nondiabetic adults. Arteriosclerosis 1987;7:66-70.

Duncan BB, Heiss G. Nonenzymatic glycosylation of proteins--a new tool for assessment of cumulative hyperglycemia in epidemiologic studies, past and future. Am J Epidemiol 1984;120:169-189.

Folsom AR, Wu KK, Shahar E, Davis CE. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. Arterioscler Thromb. 1993;13:1829-1836.

Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease: The Atherosclerosis Risk in Communities Study. Arterioscler Thromb. 1994;14:1098-1104).

Singer DE, Nathan DM, Anderson KM, Wilson PW, Evans JC. Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. Diabetes 1992;41:202-208.

Coronary calcification

Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects. Circulation 1996;93:1951-1953.

Becker CR, Knez A, Jakobs TF, Aydamir S, Becker A, Schoepf UJ, Bruening R, Haberl R, Reiter MF. Detection and quantification of coronary artery calcification with electron-beam and conventional CT. Eur. Radiol. 1999;72:313-314.

Blankenhorn DH. Coronary calcification, a review. Am J Med Sci 1961;242:1-9.

Carr JJ, Burke JL, Goff DC, Crowe JR, D'Agostino RA. Coronary artery calcium scores correlate strongly between fast-gated helical and EBCT (abstract). 39th Annual Conference on CVD Epidemiology and Prevention, Orlando. March, 1999.

Rumberger JA, Schwartz RS, Simons DB, Sheedy PF, Edwards WD, Fitzpatrick LA. Relations of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. Am J Cardiol 1994;73:1169-1173.

Salomaa V, Stinson V, Kark JD, Folsom AR, Davis CE, Wu KK. Association of fibrinolytic parameters with early atherosclerosis: The ARIC Study. Circulation 1995;91:284-290.

Sorlie PD, Adam E, Melnick SL, Folsom A, Skelton T, Chambless LE, Barnes R, Melnick JL. Cytomegalovirus/herpesvirus and carotid atherosclerosis: The ARIC Study. Journal of Medical Virology 1994;42:33-37.

Toussaint JF, Southern JF, Fuster V, Kantor HL. T2-weighted contrast for NMR characterization of human atherosclerosis. Arterioscler Thromb Vasc Biol 1995;15:1533-1542.

Wong ND, Kouwabunpat D, Vo AN, et al. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. Am Heart J 1994;127:422-430.

Cardiac magnetic resonance imaging

Edelman RR, Warach S. Magnetic resonance imaging - Part one. N Engl J Med. 1993;328:708-716.

Edelman RR, Warach S. Magnetic resonance imaging - Part two. N Engl J Med. 1993;328:785-791.

Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Mag Res 1999;1:7-21.

Manning WJ, Li W, Edelman RR. A preliminary report comparing magnetic resonance coronary angiography with conventional angiography. N Engl J Med 1993;328:828-832.

Yuan C, Petty C, O'Brien KD, Hatsukami TS, Eary JF, Brown BG. Arterioscler Thromb Vasc Biol 1997;17:1496-1503.

Carotid ultrasound

Burke GL, Evans GW, Riley WA, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults--the Atherosclerosis Risk in Communities (ARIC) Study. Stroke 1995;26:386-391.

Ghaddar HM, Cortes J, Salomaa V, Kark JD, Davis CE, Folsom AR, Heiss G, Stinson V, Wu KK. Correlation of specific platelet activation markers with carotid arterial wall thickness. Thrombosis and Haemostasis 1995;74:943-948.

Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. Stroke 1993;24:1297-1304.

Rastam L, Lindberg G, Folsom AR, Burke GL, Nilsson-Ehle P, Lundblad A. Association between serum sialic acid concentration and carotid atherosclerosis measured by B-mode ultrasound. International J of Epidemiol 1996;25:953-958.

Woodhouse CE, Janowitz WR, Viamonte M. Coronary arteries: retrospective cardiac gating technique to reduce cardiac motion artifact at spiral CT. Radiology 1997;204:566-569.

Genetics

Diez-Roux AV, Nieto FJ, Tyroler HA, Crum LD, Szklo M. Social inequalities and atherosclerosis. Am J of Epidemiol 1995;141:960-72.

Fielding CJ, Havel RJ. Cholesterol ester transfer protein: friend or foe? J Clin Invest 1995;91:265-269.

Khoury MJ, Stewart W, Beaty TH. The effect of genetic susceptibility on causal inference in epidemiologic studies. Am J Epidemiol 1987;126:561-567.

Peterson ED, Shaw LK, DeLong ER, Pryor DB, Califf RM, Mark DB. Racial variation in the use of coronary-revascularization procedures: Are the differences real? Do they Matter? N Engl J of Med. 1997;336:480-486.

Sacco RL, Roberts JK, Boden-Albala, B. Gu Q, Lin IF, Kargman DE, Berglund L, Hauser WA, Shea S, Paik MC. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population: The Northern Manhattan Stroke Study. Stroke 1997;28:929-935.

Singer DRJ, Missouris CG, Jeffery S. Angiotensin-converting enzyme gene polymorphism: what to do about all the confusion? Circulation 1996;94:236-239.

Appendix B

Multi-Ethnic Study of Atherosclerosis (MESA)

Informed Consent

INVESTIGATORS:

Principal Investigator, _____

Co-Investigator, _____
Co- Investigator, _____
Co- Investigator, _____
Investigator/Project Director, _____

SPONSOR: NIH - NHLBI

INTRODUCTION/PURPOSE:

You are being asked to participate in a research study of risk factors for heart disease and atherosclerosis (also known as "hardening of the arteries"). The purpose of MESA is to study heart disease and diseases of the blood vessels in the early stages to determine why some people develop more serious conditions such as heart attack and stroke. People who have this early stage, known as "sub-clinical heart disease," often do not know it because they feel well. MESA investigators will use medical methods to determine if the early stages of heart disease can be identified. Also, this study will follow many people for several years in order to learn why this condition becomes more severe in some people.

MESA will include 6,500 subjects aged 45-84 years from four ethnic groups (African Americans, Caucasians, Chinese Americans, and Hispanics). Participants will be studied in six centers across the country. You are invited to participate in this study because you belong to one of these four ethnic groups and fall in the age group 45-84 years.

PROCEDURE:

Should you agree to participate in the MESA study, you will be asked to come to four clinic examinations over the next six years (approximately one visit every two years). During these visits, information about your health will be collected and medical tests will be performed. The first visit consists of two parts. The first part will take approximately 6 hours, and the second part will take approximately 2 hours. In the future, there will be three, less involved

examinations, that will take approximately 4 hours each. All clinic visits will take place at Northwestern University, but on some visits you will also travel to the University of Illinois at Chicago (UIC) where one of the tests will be done. Transportation will be provided for the trip to UIC at no cost to you. This study will include the following:

a) **Health Interviews:** This will include questions concerning your medical history; personal history; use of tobacco, alcohol, and medications; diet and exercise habits; and stressful factors in your life which may be important to your health.

b) **Physical Examination:** This will include measurements of your blood pressure, height, weight, and body girth.

c) **Electrocardiogram (EKG):** This is a recording of the electrical activity of your heart.

d) **Urine test:** A urine sample will be collected at the clinic to measure the amount of albumin, a substance that is sometimes secreted by the kidneys.

e) **Pregnancy test:** Women who have not reached menopause will have a pregnancy test done before undergoing the CT scan.

f) **Blood test:** A 75 ml blood sample (about 5 tablespoons) will be collected for measurement of blood sugar, cholesterol, and other substances.

g) **Genetic/DNA testing:** You will be asked to allow genetic testing on the collected blood samples. Your blood samples may be used to prepare DNA or cell lines. Cell lines are blood cells that have been treated so they will live for long periods of time. This genetic testing is necessary to study genes important to the development of heart and blood vessel disease. The DNA will be stored in a central site listed under a code number. Results of your genetic status will not be reported to you unless they have clinical meaning. If we happen to find a gene that is linked to a medically treatable genetic disease, we will contact you if you have given us consent to do so. Results from genetic testing will not be released, placed in your medical record, or shared in any way with your relatives, personal physician, insurance companies, or any other third party unless you authorize MESA staff, in writing, to do so.

h) **Ultrasound**: An ultrasound test will be performed on the arteries in your neck to measure artery size and function. This procedure uses sound waves. It is painless, involves no known risk, and takes about 20 minutes. You will lie on a table while a small hand-held ultrasound probe is placed lightly on the right and left side of your neck. You may hear some soft sounds as measurements of the blood flow are made.

i) **Endothelial function**: An endothelial function test (blood vessel function test) will be done to determine how the arteries in your arm respond to increased blood flow. After a 15-minute rest period, a blood pressure cuff will be placed on your arm and inflated periodically while recordings are made. The test should take about 30 minutes. You may experience tingling or

numbness in your arm during the inflation of the blood pressure cuff, but this will be temporary.

j) **Magnetic Resonance Imaging (MRI)**: The MRI exam will measure the size and function of your heart. The MRI machine uses magnetic fields to create images (medical pictures). During this examination, you will lie still on a table and be placed inside the large open-MRI device for approximately 30-40 minutes. Some of the participants will have a second MRI during the fourth (and final) clinic examination.

k) **Electron-Beam Computed Tomography (EBCT or CT)**: This test will be performed at the University of Illinois at Chicago. This special type of chest scan is done to measure the amount of calcium in the arteries of your heart. For this test, you will lie on a table and be moved through a large (approximately four feet in diameter) donut shaped x-ray machine. During the scanning process, your chest is in the "donut-shaped" portion, but your head is free. The scan will be done twice to increase accuracy. For each scan you will be asked to remain still and momentarily hold your breath twice, each time for 20 to 30 seconds, in order to get good quality pictures. There are no needles or catheters. The test should take no more than 20 minutes. Half of the participants in this study will have another CT scan done during the second clinic examination and the other half of the participants will have it done in the third clinic examination. About half of the participants will have a third CT scan in the fourth (and final) examination.

l) **Follow-up Information:** In the interest of this research, it is crucial for us to determine the long-term health status of the participants in this study. You will be contacted by phone or mail once a year and asked about your health over the past year. If you are hospitalized or admitted to a convalescent or nursing home, MESA staff will review your hospital or convalescent/nursing home records to determine the reason for your admission and verify the diagnosis. If you are unable to answer questions yourself, MESA staff may contact your physician or a person you indicate could answer questions for you. We would also want to access information about the cause of death, if anything unfortunate should happen during the study. We may therefore request death certificates or coroner's reports from the Chicago Department of Health or departments of health in other localities, and we may also contact the Illinois Cancer Surveillance System to verify any diagnosis of cancer. If you should change jobs and lose contact with the MESA study, we request your permission to contact you or your relatives or friends whose names and addresses you have provided and/or to utilize a commercial locator service to find your current address and telephone number.

RISKS:

The procedures to be used in this study are considered to be safe. The risks associated with the clinical exams are minimal. Risks associated with the drawing of a blood sample are discomfort at the site of needle insertion, bruising or inflammation at the site, and rarely, faintness or infection. Blood will be drawn by an experienced, certified technician using sterile procedures. There is no known risk associated with ultrasound and endothelial function measurements.

The MRI machine does not use radiation. Most people do not experience any ill effects, but some

experience dizziness, nausea, headache, metallic taste in the mouth, or sensation of flashing lights. If any of these symptoms occur, they will subside shortly after leaving the machine. You may need to wear earplugs or earphones since operation of the machine can produce high noise levels, which may cause discomfort. With earplugs, the risk to hearing is insignificant. Some people may experience psychological discomfort in the scanner if they are uncomfortable in tight places (known as claustrophobia). You will be able to communicate with a technician during the MRI and, if you wish, you can stop the test. The MRI machine generates magnetic fields. Therefore, you should not have the MRI done if you have any metal clips, fragments, implants or metal objects in your body. This includes pacemakers, artificial heart valves, ear implants, or spinal cord stimulators.

The CT scan, like medical x-rays, involves low doses of radiation. The estimated total amount of radiation is low and is equivalent to the amount a person is expected to receive each year from natural sources, such as cosmic rays from the sky and from radioactive substances that exist within the earth. No amount of radiation is considered to be completely safe. You should not participate if you have had more than one CT scan or radiation therapy in the past year. Pregnant women and women who are breastfeeding should not participate in this research.

BENEFITS:

One benefit of participating in this study is that a free evaluation of certain aspects of your health will be performed using state-of-the-art technology. Information from the tests will be available to you and to your doctor if you choose. If a health condition is detected during this evaluation, your doctor or clinic will be notified, if you authorize the study staff to do so. However, the MESA study is not intended to provide medical care or interfere with your relationship with your own doctor. You will be referred to your own doctor for follow-up of all medical information obtained by the study. If you do not have a local doctor, you can be referred if you so desire.

An additional benefit of participating is that you may help to increase scientific knowledge about the characteristics and factors associated with sub-clinical atherosclerosis and its progression.

ALTERNATIVES:

You have the alternative to choose not to participate in this research study.

CONFIDENTIALITY:

Please understand that we will follow strict rules to protect your privacy at all times during and after this study. You will be assigned a unique ID number and only that number will be associated with your medical data. The ID numbers and matching names will be kept in a locked file in a secure area at the center where you are being seen. The coded data will be transmitted to a data center at another location for storage and analysis. This database will be available only to authorized staff of the study through a secure network.

We will ask for your social security number because data from this study will be linked with data supplied by the national Center for Health Statistics. It will be kept confidential according to the Privacy Act of 1974, and will be used only for research purposes. Providing this information to MESA is extremely important for the purposes of the study, but is entirely voluntary on your

part.

To help insure your privacy, a Certificate of Confidentiality has been obtained from the National Heart, Lung, and Blood Institute for this study. This Certificate means the researchers can not be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. However, if the researchers learned that you or someone else were in serious danger of harm, they would make disclosures, if necessary, to protect you and the other people. The information obtained, however, may be released to others for scientific purposes, only after removing your name, social security number, and any other items that could identify you. Study records may be kept indefinitely for analysis and follow-up.

FINANCIAL INFORMATION:

You will not incur any costs by virtue of your participation in this study. These tests, like the entire study, are paid for by the National Institutes of Health. You will be reimbursed for parking or public transportation costs associated with the clinical visits. You will not be paid for participating in this study.

RESEARCH-RELATED INJURY:

In the unlikely event of any injury or illness resulting from the research procedures, medical treatment for injuries or illness is available through McGaw Medical Center of Northwestern University. Payment for this treatment will be the subject's responsibility.

The Office for the Protection of Research Subjects of Northwestern University, at telephone number (312) 530-9338, can provide further information about rights as a research subject and is where any research -related injury should be reported.

SUBJECT'S RIGHTS:

You do not have to take part in this research study. Your decision to be in the study is voluntary. If you should change your mind about participating, you can withdraw from the study at any time. Any other current or future relations with Northwestern University will not be affected by your withdrawal. We would like to follow your health status by contacting you by phone or mail if you choose to no longer participate in the clinical examination portion of this study; however, you do not have to agree further contact once you have left the study. Any new findings developed during the course of this research, which may affect your willingness to continue, will be provided to you. You may be removed from the research study by the investigators in the event that they believe it is in your best interest.

CONTACT PERSON:

Further information regarding this study may be obtained from the MESA Project Director, Michelle Woods, at telephone number (312) 908-9372.

CONSENT:

I have been given the opportunity to ask questions about this research study and have received satisfactory answers. This study has been explained to me to my satisfaction and I agree to participate. Upon signing this form, I will receive a copy. I authorize the MESA study to obtain medical records from my physician, clinic, or from any hospitals or convalescent/nursing homes where I might be admitted; death certificates and coroner's reports from the appropriate city or state agencies; and information from state and other cancer surveillance systems. Furthermore, I give my permission to:

YES	NO	
_____	_____	Release the findings from tests and examinations to my physician.
_____	_____	Prepare DNA from my blood samples.
_____	_____	Create a cell line from my blood cells.
_____	_____	Test my DNA for genes related to the main goals of the study: heart and blood vessel diseases.
_____	_____	Test my DNA for genes related to the secondary goals of the study: other health conditions, such as diabetes, obesity, and cancer.
_____	_____	Notify me if a potentially treatable genetic condition is identified.
_____	_____	Allow researchers from private companies who wish to develop diagnostic lab tests or pharmaceutical therapies that could benefit many people to have access to my DNA (Note: you or your heirs will not benefit financially from this, nor will your cell line or DNA be sold to anyone)

_____ _____

Participant Signature Date

_____ _____

Witness Signature Date

Appendix C

CORONARY CALCIUM MEASUREMENTS TO BE PERFORMED FROM COMPUTED TOMOGRAPHY

- Agatston score, volume, volumetric score, and mass for the following arteries and for the sum of all arteries:

  Left main coronary artery
  Left anterior descending coronary artery
  Circumflex coronary artery
  Right coronary artery

Appendix D

CAROTID ULTRASOUND MEASUREMENTS TO BE PERFORMED

- Intimal-medial thickness measurements of left and right carotid arteries

- Lumen measurements for both left and right carotid arteries:
  - normal lumen diameter for common and internal carotid artery
  - minimum residual lumen diameter for common and internal carotid artery

- Lesion measurements for both left and right carotids:
  - maximum lesion width
  - density of plaque
  - homogeneity of plaque

- Doppler frequency shift or velocity at point of maximum disease

- Distensibility of the common carotid artery

Appendix E

MAGNETIC RESONANCE IMAGING MEASUREMENTS TO BE PERFORMED

Cardiac MRI:

- Left ventricular mass
- End diastolic volume
- End systolic volume
- Ejection fraction
- Stoke volume
- Cardiac output
- End diastolic wall thickness
- End systolic wall thickness
- Aortic distensibility
- Left ventricular wall motion.

Carotid MRI:

- Plaque characterization

Appendix F

BLOOD AND URINE MEASUREMENTS PLANNED OR UNDER CONSIDERATION IN MESA

Domain of study	Examples of possible measures
Lipids and lipid metabolism	HDL-cholesterol, membrane fatty acids
Insulin resistance	Insulin, glucose
Systemic inflammation	Acute phase proteins, pro- and anti-inflammatory cytokines, adhesion molecules, markers of infection
Oxidative damage/stress	Lipid oxidation makers, oxidized LDL, nitric oxide
Hemostatis/fibrinolysis	Coagulation and fibrinolytic markers of activity, platelet markers
Plaque destabilization	Matrix metalloproteinases, macrophage and lymphocyte activation, cellular response to endotoxins, tissue factor expression on monocytes
Endothelial cell function	Microalbuminuria, urinary prostaglandins and prostacylins
Calcium metabolism	Vitamin D and metabolites, bone metabolism markers
Endocrinology	Sex hormones

A Appendix G

STUDY ORGANIZATION

Director, NHLBI ---------- MESA Monitoring Board

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Project Office, NHLBI ----- Contracts Office, NHLBI

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MESA Steering Committee

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MESA Subcommittees

Appendix H

MESA SCIENTIFIC PERSONNEL

University of Washington Coordinating Center
Alice M. Arnold, Ph.D.
Annette L. Fitzpatrick, Ph.D.
Susan R. Heckbert, M.D.
Richard A. Kronmal, Ph.D.
Bonnie Lind, M.S.
William T. Longstreth, M.D.
Jennifer Nelson, Ph.D.
Bruce M. Psaty, M.D.
David Siscovick, M.D.
Patricia W. Wahl, Ph.D.

Columbia University Field Center
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Marco R. DiTullio, M.D.
Alan D. Guerci, M.D.
Shunichi Homma, M.D.
Daniel Rabinowitz, Ph.D.
Ralph L. Sacco, M.D. M.S.
R. Saouaf, M.D.
Steven J. C. Shea, M.D. M.S.
Alan R. Tall, M.D.
Arad Yadon M.D.

Johns Hopkins Field Center
Roger S. Blumenthal, M.D.
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Javier F. Nieto, M.D., M.P.H., M.H.S., Ph.D.
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Wendy S. Post, M.D.
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Willa A. Hsueh, M.D,
Michael F McNitt-Gray, Ph.D.
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Michael Jerosch-Herold, Ph.D.
Paul G. McGovern, Ph.D,
Pamela J. Schreiner, Ph.D.
Eyal Shahar, M.D.
Arthur E. Stillman, M.D., Ph.D.
Norbert Wilke, M.D.

Wake Forest University Field Center
Ronny A. Bell, Ph.D.
Gregory L. Burke, M.D.
John J. Carr, M.D.
John R. Crouse, III M.D.
Steve Folmar, Ph.D
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William G. Hundley, M.D.
Sharon A. Jackson, Ph.D,
Kerry M. Link, M..D.
Steve S. Rich, Ph.D.

University of Vermont Laboratory
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Robert C. Detrano, M.D, Ph.D.
Hans Fischer, M.D.
Angelo Secci, M.D.
Shaojun Wang, M.D.

Johns Hopkins Magnetic Resonance Imaging Reading Center
David A. Bluemke, M.D. Ph.D.

New England Medical Center Ultrasound Reading Center
Laurie Funk
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Joseph F. Polak, M.D., M..P.H.

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Teri A. Manolio, M.D., M.H.S.
A. Richey Sharrett, M.D., Dr.P.H.
Joanna Shih, Ph.D.

Appendix I

DRAFT 12/28/99

MESA Publications and Presentation 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) Subcommittee and select a chairperson.

The Publications and Presentations Subcommittee will report to the MESA Steering Committee on all matters relating to the publications or presentations of MESA material.

All communications to the P&P Subcommittee should be sent to the MESA Coordinating Center, Century Square Building, 1501 4th Avenue, Suite 2105, Seattle, WA 98101

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.
- To maintain a current Web-based list of all MESA presentations and publications;

III. Procedures

A. Papers

1. Submission of a Proposal for a Paper

This will consist of a formal proposal to the P&P Subcommittee and must include as a minimum: [FORM available on MESA Web site]

Full title
Abbreviated Title [Length, total of 26 letters + spaces]
Key Words [Selected from approved list on Web]
Lead Author & Proposed Co-authors
Introduction [Rationale and Background]
Research Hypotheses
Data [Variables to be used, sample inclusions/exclusions]
Brief Analysis Plan
Analysis [Coordinating Center or Local]
References
PI Approval [Yes or no]*

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

The P&P subcommittee will review the proposal to verify that the proposal format has been followed and to determine if there is potential overlap with any other papers or abstracts, proposed or in progress. In cases of potential overlap, the investigator will be encouraged to collaborate with the existing project.

Manuscript proposals will be available on the MESA Web site to help investigators determine available topics in advance.

After review by the P&P Subcommittee, a paper proposal will be submitted to the MESA Steering Committee for formal approval and nominations for additional Writing Group membership.

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

2. Formation of Writing Groups

In principal, each relevant study unit may nominate a representative on a Writing Group, although nomination is no guarantee of co-authorship. A second member of the Writing Group <u>from the same study unit</u> may be nominated if it is necessary to take advantage of unique expertise or to justify the amount of work performed on behalf of a manuscript.

The Publications and Presentations Subcommittee will review the nominees to ascertain if any

investigator able to significantly enhance the Writing Group should be added, or, when it is in the best interest of publication, a smaller Writing Group may also be recommended. In general, we expect there will be no more than eight in each writing group.

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 in which he\she is the Writing Group Chairperson.

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.

3. 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 Subcommittee;
- Assignment of tasks to Writing Group members with clear deadlines for completion of these tasks and determination that the tasks are completed on schedule;
- Manuscript approval by each member of the Writing Group before submission of its Penultimate Draft to the P&P Subcommittee 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 co-authors, communication with the Coordinating Center and the P&P Subcommittee, 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.

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 a letter to the P&P Subcommittee 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 and description should be submitted to the P&P Subcommittee. The same writing group members are usually retained on the second paper.

4. 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 Subcommittee. Failure to adhere to this schedule will prompt review of circumstances. If it is determined that a manuscript is delinquent, this could the basis for replacing either the Chairperson and/or replacing members of the Writing Group who may cause the delay, or for disbanding the Writing Group.

Draft. After notification by the P&P Subcommittee of manuscript approval, 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 with a copy to the P&P Subcommittee. 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 the MESA Steering Committee and to NHLBI for review. After review and approval of the penultimate draft by Writing Group members, the penultimate draft should be sent to the P&P Subcommittee with a cover letter stating that this penultimate draft is ready for review.

Review. The P&P Subcommittee has fourteen (14) days to review the manuscript. The P&P Subcommittee will review each manuscript followed by a discussion during a P&P Subcommittee 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 Subcommittee, 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 twenty-one (21) days. The Steering Committee members will vote to approve, approve with modifications or disapprove. No response within 21 days implies approval. Simultaneously, the manuscript will be sent to the NHLBI for review (See attachments 1 and 2 regarding NHLBI review).

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 Subcommittee. Completion of verification is expected within thirty (30) days and the P&P Subcommittee and Writing Group Chairperson will be notified.

Journal. Within thirty (30) days of receiving Steering Committee, NHLBI and P&P Subcommittee 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 subcommittee in addition to all co-authors.

The Writing Group Chairperson must keep the P&P Subcommittee and the co-authors 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 Subcommittee. If there are substantive (major findings or conclusions, alterations of the sample, exclusion/inclusion of major covariates) changes made in the manuscript during journal review, the revised manuscript should be submitted to the P&P Subcommittee for rereview.

5. 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 fall behind on the analyses, the Chairperson of the Writing Group should inform the P&P Subcommittee; if there is a problem, deadlines can be changed.

B. Abstracts

1. Preparation and Submission of Abstracts for Meetings

No abstract shall be submitted to any national or international organization for consideration prior to review by the MESA Publications and Presentations Subcommittee, approval by the MESA Steering Committee, clearance by NHLBI and sign-off from all co-authors. Any abstract submitted without these approvals may be asked to be withdrawn.

An abstract should be submitted to the P&P Subcommittee for review up to 10 days prior to the abstract submission deadline. If it is submitted too late for review, there is a risk of withdrawal if the abstract is not approved.

If the abstract is accepted, a copy of presentation materials (including tables and graphs) and text are to be submitted to the P&P Subcommittee.

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 P&P Subcommittee for review and approval.

Appendix J

Ver 2.3 Revised: July 27, 1999

THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

(MESA)

Ancillary Study Policy

An ancillary study is one that derives support 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).

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

1. Participation in an ancillary study is subject to the approval of the Steering Committee and the MESA Monitoring Board, upon the recommendation of the Ancillary Study Committee. The first level of review will determine whether the proposed study will interfere with other parts of the protocol, and whether the proposed study will hamper continued participation in the study. The scientific merit of a proposal will also be reviewed. Once an ancillary study is approved, if a change occurs in the structure or concept of the study, the Steering Committee will review and approve the alterations.

2. The Monitoring Board will similarly judge the scientific merit, the demands the proposed study places on participants, and the likely acceptability of the proposed study to participants.

3. If the ancillary study meets the test of non-interference with MESA, it may still compete with other proposed ancillary studies for limited additional time, blood, subject matter, etc. Ordinarily such competition can be resolved according to the preferences of each center. However, if this question arises for studies requiring more than one center, the competing

applicants should try to combine their efforts. If this is not possible, the Steering Committee members will individually assign priority scores to the competing proposals. Because the baseline MESA examination is very long, it should be understood that only proposals of exceptional merit are likely to be implemented in the first exam cycle. Acceptable proposals not of sufficient priority can be resubmitted to compete again for a subsequent cycle. Reviewers will use this information to assess the priority of the study in relation to MESA objectives, and most importantly, determine its potential impact on the main study. Highest priority will be given to studies which:

- do not interfere with the main MESA objectives,
- have the highest scientific merit,
- produce the least burden on MESA participants and the least demand on MESA resources such as blood samples, and
- require the unique characteristics of the MESA cohort.

5. The investigator applying for an ancillary study must supply all additional funds needed for it. 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, etc).

6. Confidentiality of individually identifiable data about MESA subjects must be assured.

7. A MESA investigator would usually be expected to be a principal investigator and must be at least a co-investigator on an ancillary study. This individual would be responsible for presenting the study to the Ancillary 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 would generally be expected to include a MESA investigator, except under circumstances that should be stated and rationalized as part of the original submission to the Ancillary Studies Committee.

8. All the publications, presentations and abstracts from an ancillary study must be reviewed and approved by the Steering Committee prior to submission or presentation, in accordance with the general rules for publications and presentations.

9. As a general rule, no personal identification will be provided to ancillary studies staff. There are no assurances that ancillary studies will be able to identify and contact subjects in the future, particularly after MESA ends.

All proposed ancillary studies must be submitted to the Ancillary Study Committee in time for review, circulation to appropriate committees, and consideration by the Steering Committee and the Monitoring Board prior to submission to a funding agency. If the proposed ancillary study involves the use of an imaging modality or other technical component it will be reviewed by the appropriate sub-committee (e.g., CT). Studies submitted for review less than 8 weeks prior to a funding application deadline may not receive approval.

1. The following are the elements to be included in an ancillary study proposal:
   - A. A description of the goals and methods of the ancillary study, preferably not to exceed three single-spaced pages.
   - B. Specific data collection methodology, including questionnaires and coding forms, if available.
   - A. Specific answers to the following questions:

     1 What is the expected burden to participants? What are the time burdens, discomfort and expected participation rates? What MESA core data and/or analyses are needed for the ancillary study?

     2. Are blood or other biologic samples (from MESA's repository of stored samples) required?

     3. What collaboration with MESA investigators is planned? With whom?

Have the collaborating investigators approved the proposal?

4. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
5. Which MESA centers have agreed to participate?
6. How many participants are required?
7. When will data be collected? Could the ancillary study be deferred to a later exam cycle?
8. How will the ancillary study be funded? Would any additional un-reimbursed work or personnel time be expected of MESA?
9. Where will the data analyses be conducted?
10. How will the confidentiality and other aspects of protection of human subjects be maintained?

The ancillary study's PI should provide evidence that adequate support for carrying out data analysis is available at his/her institution; if not, the coordinating center will conduct the analyses using resources provided by the ancillary study.

The data collected by the ancillary study are first to be provided to the MESA Coordinating Center for integration into the main database. After that has been done the ancillary investigators will receive the integrated file containing data from the main study. The ancillary study PI will be given the first and 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 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. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Steering Committee access to the data will be honored or some

compromise will be worked out.

A member of the Coordinating Center staff will be identified to assist the investigator in the preparation and processing of the proposal. The proposal will generally be discussed by the Ancillary Committee within 2-4 weeks by conference call. The investigator may be asked to make him/herself available at that time to address questions that may arise. A copy of the final proposal as submitted for funding should be submitted to the Ancillary Studies Committee.

Appendix K - MESA MONITORING BOARD ROSTER

Richard Devereux, M.D. (Chair)
Cornell Medical Center
Division of Cardiology

Warren J. Manning, M.D.
Harvard Medical School
Division of Cardiology

Lewis Wexler, M.D.
Stanford University School of Medicine
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James H. Chesebro, M.D.
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Helen P. Hazuda, Ph.D.
University of Texas Health Sciences Center
Department of Medicine

Gervasio A. Lamas, M.D.
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Division of Cardiology

Elisa T. Lee, Ph.D.
University of Oklahoma Health Sciences Center
College of Public Health

David Williams, Ph.D.
University of Michigan
Institute for Social Research

Richard Fabsitz, M.A. (Executive Secretary)
Division of Epidemiology and Clinical Applications
National Heart, Lung, and Blood Institute