SHHS PROTOCOL

February 23, 1996

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1. OVERVIEW

The Sleep Heart Health Study is a multi-center cohort study that has been implemented by the National Heart, Lung, and Blood Institute to determine cardiovascular and other consequences of sleep-disordered breathing. The study was motivated by the increasing recognition of the frequent occurrence of sleep-disordered breathing in the general population and mounting evidence that sleep-disordered breathing may increase risk for cardiovascular diseases, including coronary artery disease and stroke, and for hypertension and may reduce quality of life generally. Many clinical questions remain unanswered concerning sleep-disordered breathing as well: for example, we lack insight as to the point in the natural history of the disorder when intervention is warranted; and, while effective treatments for some forms of sleep-disordered breathing have been developed, information is still needed on who is at risk from sleep-disordered breathing so that these treatments can be applied in a cost-effective manner. Such questions can best be addressed by longitudinal epidemiologic investigations that are conducted in a population context. The Sleep Heart Health Study, implemented to obtain these needed data, will test whether sleep-related breathing is associated with an increased risk of coronary heart disease, stroke, all cause mortality, and hypertension.

The consequences of sleep-disordered breathing might best be addressed by enrolling a sufficiently large cohort of early middle-aged men and women who have not yet experienced cardiovascular disease and then prospectively following the cohort for cardiovascular and other events, having assessed risk factors and presence of sleep-disordered breathing on enrollment. However, this approach would be costly and currently needed information on the consequences of sleep-disordered breathing would not be available for many years. For efficiency and practicability, the Sleep Heart Health Study draws on a resource of existing, well-characterized, and established epidemiologic cohorts. The design adds assessment of sleep to data collection in ongoing cohort studies including the Atherosclerosis Risk in Communities (ARIC) Study sites in Washington County, Maryland, and Minneapolis Minnesota; the Cardiovascular Health Study (CHS) sites in Sacramento, California, Washington County, Maryland, and Pittsburgh, Pennsylvania; the Framingham Offspring and Omni cohorts in Framingham, Massachusetts; the Health and Environment and Tucson Epidemiologic Study cohorts in Tucson, Arizona; the Strong Heart Study sites in Arizona, Oklahoma, and South Dakota; and New York City populations assessed in studies of hypertension. Each of these populations is already established; some information on risk factors for cardiovascular disease has already been collected in each of the cohorts, and all but the Tucson and New York studies include ongoing and standardized monitoring for the occurrence of cardiovascular events.

The administrative structure of the Sleep Heart Health Study comprises the Coordinating Center at the University of Washington, the Sleep Reading Center at Case-Western Reserve University, the Project Officer of the National Heart, Lung, and Blood Institute, and six Investigative Centers (University of Arizona, Boston University, University of California-Davis/University of Pittsburgh, Johns Hopkins University, University of Minnesota, and New York University) which interact with the parent studies listed above. The Steering Committee is the main governing body of the study; specific subcommittees have been charged with aspects of the project including the Publications and Presentations Subcommittee, the Morbidity and Mortality Subcommittee, the Design, Sampling and Recruitment Subcommittee, the Comparability Subcommittee, the Polysomnography Subcommittee, the Questionnaire and Interview Subcommittee, the Quality Control Subcommittee, and the Operations Subcommittee. A Data and Safety Monitoring Board appointed by the Institute is

responsible for review of study data in order to insure quality and the safety of study subjects and to provide the Institute with advice on the progress of the study.

The Sleep Heart Health Study will add in-home polysomnography to the data collected in each of the parent studies. Using the Compumedics PS polysomnograph, a single over-night polysomnogram will be obtained at home for approximately 6,000 persons; the montage includes oximetry, heart rate, chest wall and abdominal movement, nasal/oral airflow, body position, EEG, EOG, and chin EMG. In-home monitoring can now be conducted feasibly, and this montage provides data on the occurrence of sleep-disordered breathing and on arousals. The sleep data will be collected during the second and third years of the initial five-year funding of the Sleep Heart Health Study, corresponding to Years 1 and 2 on the time line below. Follow-up will continue through Year 4, although initial analyses of the data will be implemented at the end of Year 3.

The study has a five-year funding period. The first year (Year 0 on the time line below) was devoted to planning the study and protocol development. Recruitment will occur during the second and third years of funding (Years 1 and 2 on the time line). Some Field Centers plan to complete recruitment within Year 1; other Field Centers plan to recruit over an 18 - 24 month time frame, depending on parameters of parent study contacts. All SHHS participants will be followed for events from their time of enrollment. The final year of funding will be used for data analysis and report generation.

SHHS Time Line

	Sept. 1994 ↓	Sept. 1995 ↓	Sept. 1996 ↓	Sept. 1997 ↓	Sept. 1998 ↓
Year	0	1	2	3	4
Month	1 --------- 12	13 ------- 24	25 ------- 36	37 -------- 48	49 -------- 60
<u>Phase I</u> Planning & Protocol	xxxxxxxxxx				
<u>Phase II</u> Subject Recruitment		xxxxxxxxxx	xxxxxxxxxx		
Follow-up of Events			xxxxxxxxxx	xxxxxxxxxx	
<u>Phase III</u> Data Analysis				(Baseline) xxxxxxxxxx	(Follow-up/events) xxxxxxxxxx
Report Preparation					xxxxxxxxxx

Approximately 1,000 participants will be enrolled from the parent cohorts of each of the six Investigative Centers. Recruitment approaches will be tailored for the requirements of the specific Field Centers. All participants will be at least 40 years of age and all minority members of each of the parent cohorts will be recruited. Individuals younger than age 65 years will be selected with stratification by history of snoring, as assessed by a standardized questionnaire to be administered to

all members of the parent cohorts; the sampling fraction for snorers will be greater than for non-snorers in order to increase the prevalence of sleep-disordered breathing. For persons older than age 65 years, snoring history does not predict the presence of sleep-disordered breathing and participants will be selected without reference to snoring history. There is no upper age limit for participants and the presence of prevalent cardiovascular disease will not exclude potential participants. The projected sample size of about 6,000 participants will provide sufficient power for some of the primary hypotheses by the end of Year 4, but further follow-up will be needed to have sufficient power for all primary and secondary hypotheses, both overall and within subgroups of *a priori* interest.

The extent of information available on key cardiovascular risk factors varies among the parent cohorts. Based on review by the Comparability Subcommittee, some additional data will be collected on covariates at enrollment into the Sleep Heart Health Study. However, the parent studies will be the principal source of information on risk factors for cardiovascular disease in the participants. The cardiovascular outcomes for all sites include hospitalized acute myocardial infarction, nonfatal coronary heart disease, stroke, and death due to cardiovascular or cerebrovascular disease. Additionally, change in blood pressure and diagnosis of hypertension will be considered and all participants will complete a standardized instrument on quality of life. The cardiovascular outcomes will be adjudicated by methods already in place for the ARIC, CHS, SHS, and Framingham Field Centers and by the CHS process for the New York and Tucson Field Centers. Ancillary studies will address other outcomes, such as cognitive functioning, that cannot be considered in the full Sleep Heart Health Study cohort.

Each participant in the parent studies will be asked to complete the Sleep Habits Questionnaire which covers usual sleep pattern, snoring, and sleepiness. Combining these responses with the ongoing outcome assessment of the full parent cohorts will permit the testing of hypotheses concerning the consequences of self-reported snoring and sleepiness in a combined sample of approximately 20,000 persons.

Although the Sleep Heart Health Study is a prospective cohort study, the cross-sectional findings will provide new information on patterns of sleep and sleep-disordered breathing in the general population. Consequently, initial analyses will be descriptive and also address cross-sectional associations of sleep-disordered breathing with prevalent cardiovascular disease and quality of life and with risk factors for cardiovascular disease. Longitudinal analyses will address sleep-disordered breathing as a predictor of cardiovascular outcomes and change in blood pressure.

2. BACKGROUND AND RATIONALE

Snoring, the most common symptom of sleep-disordered breathing, has been implicated as a risk factor for the development of hypertension, ischemic heart disease and cerebral infarction.(1-5) Many of these adverse cardiovascular effects of snoring have been attributed to the substantial prevalence of obstructive sleep apnea among habitual snorers.(2,3)

Obstructive sleep apnea is characterized by loud snoring and disrupted breathing during sleep. It is associated with a number of adverse clinical consequences, including daytime sleepiness, impaired

performance, accidents and cardio/cerebrovascular morbidity and mortality.(6,7) The relative risks of cerebrovascular accidents, ischemic heart disease and myocardial infarction range from 1.5 to 4 in snorers as compared to non-snorers. Sleep apnea is common in patients with hypertension, with studies suggesting that up to 40% of hypertensive patients may have significant sleep apnea. Improvement in hypertension control has been reported to occur in patients with both conditions following treatment of their apnea.(8) Cardiovascular mortality may be significantly higher among untreated or conservatively treated patients with sleep apnea compared to patients treated aggressively.(9)

In addition, patients with sleep apnea or heavy snoring may have up to a 50% decrease in brain blood flow during rapid eye movement (REM) sleep and as high as a 50% increase in the incidence of stroke.(2) These findings raise the intriguing possibility of an etiologic relationship between sleep apnea and thrombotic stroke. Sleep apnea may be an independent vascular disease risk factor, a concomitant of established vascular or cerebral diseases or other risk factors (such as obesity or hypertension), but this remains to be determined. Similarly, little is known regarding potential interactions between sleep apnea and other risk factors, or whether specific population subgroups may be particularly susceptible to adverse cardiovascular and cerebrovascular consequences potentially associated with sleep apnea.

Further elucidation of the relationship between sleep apnea and hypertension in African-Americans will receive emphasis. For uncertain reasons, severe hypertension is more common and its consequences more severe in African-Americans than in whites. Risk factors for sleep apnea such as obesity and macroglossia are also common in African-Americans, and preliminary data suggest that, among young subjects, sleep apnea may be more prevalent among African-Americans than among whites.(10) Sleep apnea may contribute to the marked racial differences in hypertension and its consequences. It is also known that obesity, a known risk factor for obstructive sleep apnea, is prevalent in Hispanics and Native Americans.(11) Sleep apnea is also known to increase markedly in prevalence following menopause.(12) Examining cardiovascular disease events and sleep apnea in post-menopausal women may provide insight into factors increasing cardiovascular disease risk among women.

Sleep apnea has been described in 30% or more of elderly subjects.(13) The basis for strong relationships between aging and increased apneic activity is not understood, but may be related to changes in sleep quality, cerebral function, muscle tone, obesity, cardiac function and lung function with aging. Due to their reduced functional reserves and co-existing morbidity, elderly persons may be at greatest risk for exacerbation of underlying cardiovascular and cerebrovascular disease when exposed to the physiologic stresses associated with apnea and arousal from sleep.

The profound physiological derangements (hypoxemia, severe hypertension, tachycardia, fragmentation of sleep, arrhythmias) that often occur in association with sleep-disordered breathing provide biologically plausible explanations for associations between sleep apnea and cardiovascular morbidity. The increased risk of cardiovascular events shortly after awakening has been linked to sympathetic discharge associated with arousal, which can occur dozens of times each night in patients with sleep apnea. The use of cardiovascular medications may also be an important effect modifier on the relationship of cardiovascular disease, its risk factors, and sleep-disordered breathing, since some of these agents have known side effects related to sleep and breathing.(14)

Therefore, it is particularly important to identify factors that predispose to increased risk for sleep-disordered breathing. Information on these factors is needed as a basis for public health policy, potentially enabling specific high risk populations to be targeted, as well as for developing an improved understanding of disease pathogenesis that may include interactions among a number of risk factors causing morbidity and mortality. This program seeks to accomplish this with an interactive, coordinated group of investigative centers, using existing epidemiological cohorts, working under a common protocol in a multidisciplinary setting. A Request for Applications was issued in February 1994, and in September 1994 the National Heart, Lung, and Blood Institute (NHLBI) funded six investigative centers and a coordinating center. This 5-year program was originally named "Cardiovascular Consequences for Sleep Apnea". In January 1995 the Steering Committee renamed it "Sleep Heart Health Study" (SHHS).

(References are listed in Appendix 1.)

3. HYPOTHESES

Study investigators have identified both primary and secondary hypotheses to be tested in the SHHS. The primary hypotheses are the main focus of analyses conducted on the entire cohort and have driven the study design specifications and sample size calculations. Secondary hypotheses will be tested either on the entire cohort or on subsets of the cohort for whom appropriate covariate data exist. Such analyses, which will be considered sub-studies of SHHS, are described in Section 3.3, below.

3.1 Primary Hypotheses

The primary hypotheses to be tested are:

1. Sleep-disordered breathing (SDB) is associated with an increased risk of incident coronary heart disease (CHD) events.

2. SDB is associated with an increased risk of incident stroke.

3. SDB is associated longitudinally with increased blood pressure.

4. SDB is associated with an increased risk of all-cause mortality.

3.2 Secondary hypotheses

Secondary hypotheses, which will be tested on either the entire cohort or on subsets of the cohort for whom data are available, are:

1. SDB is associated with an increased risk of recurrent CHD.

2. SDB is associated with an increased risk of recurrent stroke.

3. SDB is associated with impairment of health-related quality of life.

4. SDB is associated with a more rapid decrease in health-related quality of life.

5. SDB is associated with increases in left ventricular mass.

6. SDB is associated with changes in carotid measurements.

7. SDB is associated with an increase in arrhythmias.

8. SDB is associated with an increase in neuropsychological deficits (e.g., in attention, executive functions, learning and memory, and information processing) and with adverse effects on mood (e.g., irritability, anxiety, and depression).

9. SDB is associated with increased sleepiness.

10. SDB is associated with hemostatic dysfunction that promotes hypercoagulation and thrombosis.

11. SDB is associated with a distinct circadian pattern of cardiovascular (CVD) event occurrence.

12. SDB is associated with increases in nocturnal blood pressure and/or increasing 24-hour hypertensive load.

13. Level of lung function as measured by spirometry modifies CVD risk of SDB.

14. The impact of CVD risk factors differs with the presence or absence of SDB.

15. The impact of SDB on CVD risk is mediated by the effects of SDB on CVD risk factors, including blood glucose, insulin, and cholesterol levels, each of which may be increased via the effect of SDB on autonomic nervous system activity.

16. Self-reported sleep problems are associated with an increase in CVD events.

3.3 Sub-studies

The SHHS protocol provides a unique opportunity to study sleep-related breathing in a large number of subjects who would otherwise not be studied in sleep laboratories. The diversity of the cohorts from which the participants will be recruited and the wealth of additional measures being collected in those cohorts provides the possibility of addressing in subcohorts many secondary hypotheses which cannot be addressed in the entire study (see list of secondary hypotheses above). In addition, the original grant submissions for the RFA proposed studies motivated by the interests of the various principal investigators; although not part of the overall protocol of SHHS, these sub-studies are still possible in subsets of participants who have completed the sleep studies that are part of the main SHHS protocol. It is one of the strengths of this design that such studies can be accommodated, and the Steering Committee encourages such ancillary and sub-studies.

A partial list of proposed substudies is included in Appendix 2. These will be developed into formal proposals to the Publications and Presentations Committee and ultimately submitted to the Steering Committee. Collaboration between investigative centers is encouraged.

4. PARTICIPATING CENTERS

Participating Centers were selected based on their ability to conduct the study in an established cohort for which cardiovascular data were available. Six Investigative Centers were selected to participate in SHHS:

University of Arizona
Boston University

University of California at Davis/University of Pittsburgh
Johns Hopkins University
University of Minnesota
New York University/Cornell University

Each Investigative Center consists of one or more distinct Field Centers. Field Centers are distinguished within an Investigative Center by being either geographically separate or by representing a separate cohort. Boston University has one Field Center, the Framingham Heart Study in Framingham, Massachusetts. Participants will be included from both the Offspring and Omni cohorts. Johns Hopkins has two Field Centers, one consisting of CHS participants and one consisting of ARIC participants. Both Field Centers are located in Hagerstown, Maryland. The University of Minnesota has one Field Center which consists of ARIC participants. The NYU/Cornell site has 3 Field Centers, each representing a distinct cohort which is currently being studied. The UC Davis/Pittsburgh site has two Field Centers, one in Sacramento, California, and one in Pittsburgh, Pennsylvania, each consisting of CHS participants. The University of Arizona has four Field Centers. One represents two cohorts in Tucson, Arizona: the Tucson Epidemiology Study of Obstructive Airways Disease, and the Tucson Health and Environment cohort. The other three Field Centers consist of Strong Heart Study participants located in Phoenix, Arizona; Oklahoma City, Oklahoma; and in South Dakota.

In addition, a Coordinating Center was established at the University of Washington in Seattle, Washington, and a Sleep Reading Center was established at the Case Western Reserve University in Cleveland, Ohio.

5. SAMPLE SELECTION

5.1 Parent Cohorts

SHHS participants will be drawn from nine existing parent cohorts; ARIC, CHS, Framingham, three cohorts in New York City, SHS, and two cohorts in Tucson, Arizona. The parent studies for these cohorts are described below.

5.1.1 The Atherosclerosis Risk in Communities (ARIC) Study

5.1.1.1 Cohort Selection

ARIC was initiated by the NHLBI in the mid-1980s with the broad objective of studying prospectively "the etiology and natural history of atherosclerosis and the etiology of clinical atherosclerotic disease". ARIC is a multi-center population-based study in four communities: Jackson (Mississippi), Forsyth County (North Carolina), Washington County (Maryland), and suburban Minneapolis (Minnesota). Two ARIC field centers (Washington County and Minneapolis) participate in the Sleep Heart Health Study. ARIC has two complementary components: a cohort and community surveillance. The surveillance component of ARIC involves monitoring of coronary heart disease occurrence in the ARIC source communities and identifying cardiovascular endpoints (primarily acute MI and stroke) among the cohort members. For the cohort component, each Field Center recruited about 4,000 men and women, 45-64 years old, from a geographically-defined community. Recruitment and baseline measurements took place between 1987 and 1989 (exam 1). Cohort members were re-examined three years later, between 1990-1992 (exam 2), and are currently being re-examined for the third time (1993-1995). A fourth exam of the cohort is scheduled to be conducted between 1996-1998. For each participant, a three-year interval between exams has been maintained. ARIC exams are conducted in a Field Center Clinic and include a wide range of demographic, lifestyle, biochemical, physiological, and clinical measurements. In addition to the clinic exams, cohort participants are contacted every year by telephone to assess the occurrence of cardiovascular outcomes. The study investigators remain in contact with over 99% of the cohort using a number of tracing items from the baseline exam such as maiden name, social security number, driver's license number, and names of two contact persons.

In all ARIC centers, age-stratified random samples of individuals were selected, without replacement, in monthly cycles. A trained interviewer visited the home of the selectee, enumerated the household, and invited all age-eligible household members to attend a clinic exam. The sampling frames differed in the different centers.

ARIC Minneapolis Field Center

This population-based sample was selected from all residents of eight contiguous suburbs of Hennepin County: Brooklyn Center, Brooklyn Park, Crystal, Golden Valley, Medicine Lake, New Hope, Plymouth, and Robbinsdale. The sampling frame was the county's jury selection list, which is comprised of all persons with a driver's license, a state identification card, or a voter registration

card. A pilot study indicated that the sampling frame was more than 99% complete for non-institutionalized age-eligibles. Residents eligible for selection were identified by birthdate, zip code, and street address. The total number of eligibles was estimated at 6,021. Of these, 4,009 (67%) completed the first ARIC exam, including approximately 600 spouse pairs. At the time of second exam (1990-92), about 2% of the participants at baseline had died and 2% had left the Twin Cities area. A total of 3,828 (95%) returned for the second exam (1990-1992), the highest return rate among ARIC centers. So far, the return rate for exam 3 (currently in progress) has exceeded 90%.

ARIC Washington County Field Center

The sampling frame in Washington County, Maryland, consisted of a private census conducted by the Johns Hopkins Training Center in 1975 and driver's license records. Among 6,177 potential eligibles identified, 4,020 (65%) completed the baseline clinic exam. Among the participants who attended the baseline examination and were still alive, 93.4% returned for exam 2. Preliminary data from exam 3 shows that over 95% of cohort participants who attended the second exam and were scheduled to return to the clinic in 1993 did so.

5.1.1.2 Information Collected

ARIC's clinic examinations include numerous procedures and last about 3-4 hours.

Predictors

Ascertained at every examination
current medications
smoking and alcohol intake
medical history
anthropometric measures
2-lead electrocardiography
blood pressure
fasting lipid levels
hematologic and hemostatic factors
blood chemistry

Ascertained at some examinations
pulmonary function
cognitive function
diet
physical activity
retinal photography

Outcomes

hospitalized acute MI
coronary heart disease death
fatal and non-fatal stroke
silent MI
angina pectoris (Rose questionnaire)
transient ischemic attacks
intermittent claudication
incident hypertension
subclinical atherosclerosis (measured by B-mode ultrasound of the carotid arteries)

5.1.2 CHS

5.1.2.1 Cohort Selection

The Cardiovascular Health Study (CHS) is a population based study of risk factors for cardiovascular disease in adults ages 65 and older. A cohort of 5,201 men and women were recruited in 1989-90 from a random, age-stratified (65-74, 75-84, 85 and older) sample of the Health Care Financing Administration's (HCFA) Medicare eligibility lists in four U.S. communities: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh Pennsylvania. Three of these sites will be participating in SHHS. (California, Pennsylvania, and Maryland sites.) Sampled persons and age-eligible household members were recruited for the study. Those who were institutionalized, wheelchair bound or under active treatment for cancer were excluded. Of those who were eligible 57.6% agreed to participate. Participants were interviewed in their homes and examined in the field center clinics.

In 1992 - 1993 a second cohort of African-Americans was recruited at three of the centers (California, Pennsylvania, & North Carolina) in order to increase the ethnic balance of the study. The same recruitment techniques were used as in the original recruitment but limited to those individuals who classified themselves as African-American to HCFA. A total of 687 new participants were recruited.

5.1.2.2 Information Collected

Predictors

current medications
smoking and alcohol intake
medical history
anthropometric measures
12-lead electrocardiography
blood pressure
fasting lipid levels
hematologic and hemostatic factors
blood chemistry
pulmonary function

cognitive function
diet
physical activity
echocardiograms
carotid ultra-sounds
abdominal ultra-sounds to detect aortic aneurysms
head MRIs
bone density and body composition (on a subsample at CA and PA sites)
ankle/arm index
orthostatic blood pressure
Holter monitors (on a subsample of 1432 participants)

Outcomes

Death
MI
Angina
CHF
Stroke
TIA
Claudication

Non-adjudicated data are available on all hospitalizations, including date, length of stay and the first ten ICD9 coded diagnoses.

5.1.3 The Framingham Heart Study (FHS)

5.1.3.1 Cohort Selection

The FHS is a longitudinal population-based investigation of the epidemiology of cardiovascular disease, with studies currently ongoing in three cohorts. The Original Cohort was established in 1948 with a random sample of residents of Framingham, Massachusetts aged 30-62 years. This group contained 5209 members including 1644 husband and wife pairs. In 1971 the children of these couples, and their spouses, were invited to participate in the study, and 5135 subjects became members of the Offspring Cohort. The clinical, biochemical and demographic features of the Offspring Cohort have been well characterized by data collected at "cycle examinations" conducted every 3.5 years. The presence of prevalent cardiovascular and cerebrovascular disease and congestive heart failure status was adjudicated at the outset of the cohort formation, and incident and recurrent events have been adjudicated at each subsequent cycle. Of the original 5135 members of the cohort, 4467 subjects are projected to be alive and 3570 to participate in the Cycle 6 examination, which began in January, 1995. Subject tracking has been excellent with only 47 (1%) subjects lost to follow-up.

The Omni Cohort, established in April 1994, is comprised of residents of Framingham, Massachusetts who are between the ages of 40 and 74 and members of minority groups. The racial and ethnic composition of the town has changed since the inception of the FHS. According to the 1990 US Census, 9.9% of town residents report a race other than white, and 8.1% report Hispanic origin. These figures include approximately 1340 Hispanic, 500 non-Hispanic black and 500 Asian residents in the targeted age range. Currently, 270 subjects have been recruited through multimodality efforts.

Prevalent cardiovascular and cerebrovascular disease and congestive heart failure will be adjudicated for these subjects in the identical manner as for the Offspring Cohort. The Omni Cycle 1 examination is similar to the Offspring Cycle 6 exam. Subjects for the SHHS will be drawn from the Offspring and Omni Cohorts.

5.1.3.2 Information Collected

Predictors

resting blood pressure
anthropomorphic measurements
spirometry
cardiac and carotid ultrasounds
biochemical analyses (glucose tolerance, lipoprotein subfractions, and clotting studies)
ankle/arm index
electrocardiography
bone density
dietary history
physical activity questionnaire
SF-36 Health status questionnaire
medications
alcohol and tobacco consumption

Outcomes

Angina pectoris
Coronary Insufficiency
Myocardial Infarction
Coronary Heart Disease, any
Coronary Heart Disease Mortality

Cerebrovascular Accident
Cerebrovascular Disease Mortality

Congestive Heart Failure
Intermittent Claudication

No sleep variables have been collected as yet.

5.1.4 New York

5.1.4.1 Cohort Selection

There are three cohorts, each of which is being studied in a separate project as part of our Program Project (HL 47540; Psychosocial Factors in Cardiovascular Disease, T Pickering PI), which is funded through August, 1998.

Project One (the Pickering NYH-clinic study) is a prospective study of the role of ambulatory blood pressure monitoring in the prediction of cardiovascular morbidity independently of other risk factors including clinic blood pressure. The central hypothesis is that ambulatory blood pressure will predict cardiovascular morbidity independently of other risk factors. The subjects are patients referred to the Hypertension Center for evaluation of their blood pressure, most of whom have mild hypertension or are normotensive. The first patients were enrolled in 1978, and more than 1000 have been studied since 1990.

The entry criteria are normotension or mild uncomplicated hypertension (clinic blood pressure less than 105 mm Hg diastolic), an absence of secondary hypertension or excessive obesity (BMI>30), and no other major medical condition. Patients are evaluated off medication with two clinic visits.

They are followed either at the Center with visits at least every six months, or by their local physicians, in which case they are followed by telephone contact. (Patients enrolled in SHHS will all have a clinic visit at the time of enrollment.) Follow-up evaluation includes medication use, blood pressure, and morbid events.

Harlem Substudy. A parallel group of subjects is being followed at Harlem Hospital. The initial evaluation is the same, but all the subjects are African-American. They are enrolled in the ratio of one normotensive for every two hypertensives.

Project Two (the Worksite Study) is a prospective study of occupational stress in employed men and women working at ten work sites in New York, which was started in 1986. The central hypothesis is that subjects in high strain jobs (defined as those combining a high workload with a low level of perceived control or decision latitude) will develop higher blood pressures and more target organ damage (echo LVH and carotid plaque) than those in less stressful jobs. Subjects are enrolled by first screening all eligible subjects at each work site and then randomly selecting subjects from those who meet the eligibility criteria. For this project, subjects must be normotensive or have borderline hypertension. Those with hypertension requiring treatment are not eligible, although subjects who subsequently are started on medication are still followed. Subjects are reevaluated every three years, with all the measures being repeated.

Project Three is an examination of blood pressure and hormonal changes occurring in association with the menstrual cycle and the menopause. In Study One, healthy women are evaluated on two occasions, once during the follicular and once during the luteal phase, with a 24-hour blood pressure recording, and urine collection for hormones of the reproductive system and renin-angiotensin systems. In Study Two, age-matched pre- and post-menopausal women are evaluated once with the same protocol. Study One is almost completed, and Study Two is just beginning.

5.1.4.2 Information Collected

Predictors

Variable	Project 1	Project 2	Project 3	
Medical history	Yes	Yes	Yes	
Demographics	Yes	Yes	Yes	
Life style (alcohol, smoking, etc.)	Yes	Yes	Yes	
Height, weight	Yes	Yes	Yes	
Routine blood test (include TC, TG, HDL)	Yes	Yes	No	
Anthropometrics (waist, hip, etc.)	Yes	Yes	Yes	
Clinic blood pressure	Yes	Yes	Yes	
24-hour blood pressure	Yes	Yes	Yes	
Electrocardiogram	Yes	Yes	No	
Echocardiogram	Some		Yes	Some
Carotid ultrasound	Some	Yes	Some	
24-hour urine (electrolytes, creatinine)	Yes	Yes	Yes	
Reproductive hormones	No	No	Yes	
Psychosocial questionnaires	Yes	Yes	Yes	

Outcomes

Pickering NYH clinic sample and Harlem sample:
- Myocardial infarction
- Coronary bypass surgery
- Coronary angioplasty
- Sudden cardiac death
- Completed stroke

Worksite sample:
- Ambulatory blood pressure
- Carotid artery atherosclerosis
- Left ventricular hypertrophy

Menopause sample (cross-sectional)

The outcome measures listed under the Pickering NYH clinic sample will be collected for SHHS participants from all 3 parent cohorts.

5.1.5 Strong Heart Study (SHS)

5.1.5.1 Cohort Selection

The SHS is a study of cardiovascular disease (CVD) among Native Americans. It involves 12 Native American communities in Arizona, Oklahoma, and North and South Dakota. The objective of the SHS is to employ standardized methodology to obtain estimates of CVD mortality and morbidity rates as well as to allow comparison of CVD risk factor levels among Native American groups living

in three different areas: Phoenix, Arizona, Southwestern Oklahoma, and the Aberdeen area of South and North Dakota. The study population includes members of the following tribes:

1) The Pima/Maricopa Indians of central Arizona who live in the Gila River Indian Community (GRIC) and the Salt River Indian Community (SRIC).

2) The Seven Tribes of southwestern Oklahoma: Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa and Wichita.

3) The Ogala Sioux Tribe (Pine Ridge),and the Cheyenne River Sioux Tribe (Eagle Butte) of South Dakota and the Devil's Lake Sioux Tribe (Ft. Totten) of North Dakota.

A mortality and morbidity survey using existing records was initiated on October 1, 1988 (Phase I). The SHS then entered its major phase (Phase II) involving clinical evaluations and follow-up of the population. Eligible to be enrolled were Native Americans aged 45-74 between July 1989 and January 1992 living in the aforementioned Indian communities. Tribal rolls were used; individuals who had died, moved, or were institutionalized were not included. Examinations (Exam 1) were performed on 4549 subjects with a 55-72% participation rate and at least 1500 from each area. Surveys included interviews, physical exams, blood pressure measurements, laboratory tests for cardiovascular risk factors, echocardiography and electrocardiograms. Exam 2 of SHS will be completed by November 1995 and Exam 3 is planned to start August 1996.

5.1.5.2 Information Collected by Cohorts:

Predictors

interviews
physical examination
laboratory tests
spirometry
electrocardiograms
echocardiograms
lipids and lipid proteins
fibrinogen
post-load fasting glucose
urinary albumin and creatinine
waist and hip circumferences
bioelectric impedance measurement of body fat
blood pressure
ankle/arm index

Outcomes

fatal and non-fatal myocardial infarction (MI)
fatal CHD
fatal and non-fatal stroke
fatal and non-fatal CHF
other fatal cardiovascular disease

5.1.6 Tucson Investigative Center

5.1.6.1. Tucson Epidemiological Study of Airway Obstructive Disease (TES)

5.1.6.1.1. Cohort Selection

The objectives of the TES Cohort are to investigate longitudinally the etiology and natural history of Airway Obstructive Diseases (AOD), including evaluations of cardio-pulmonary correlates and cardiovascular outcomes (i.e., mortality). The cohort was selected as a multi-stage stratified cluster sample of the Tucson urban area in 1971-73, stratified by age and socioeconomic status using census block statistics. The blocks also were clustered geographically, outside of the "Model Cities" area (as the Mexican-American Hispanics felt overstudied at the time), thus providing an essentially non-Hispanic white population. Households were enrolled within each block chosen through random sampling; the sample contained 3,805 individuals in 1,655 households. Comparisons of the participant sample enrolled (1972-73) with the census data demonstrated that the population under study was representative of the Tucson non-Hispanic white population. The TES is a project within a National Heart, Lung and Blood Institute (NHLBI) Specialized Center of Research (SCOR) grant under the directorship of Dr. Benjamin Burrows who is Director of the Respiratory Sciences Center at the University of Arizona.

In the greater than 20 years of this cohort's existence, there have been 12 surveys of the population. At the end of the twelfth survey in 1993, there were a total of 5,647 who had been under study, a result of enrolling new household members (e.g. spouses and newborns); 3591 (64%) were still active participants. Mortality amounted to 837 (16%), which was greater in the elderly, ever smokers and males. There were 844 (16%) permanent refusals who did not differ in characteristics from continuing participants. There were 375 (7%) permanently lost to follow-up, who differed from continuing participants only in that there were somewhat younger adults in this group, and they had less airway obstructive disease (AOD). The remainder are still being followed (including 1115 ages 40 and older); the current survey started with 3235 subjects. The refusal and loss rates in the total population has been smaller than expected, and the rate is stable; it is expected these trends will continue through current studies. Because no important differences can be found in sub-groups who have been lost to follow-up or in those who refused when compared to continuous participants, the sample is expected to be representative throughout the first 25 years of study.

5.1.6.1.2. Information Collected

The TES has been focused on pulmonary outcomes (25 years of pulmonary disease/ diagnoses morbidity and mortality follow-up, as well as different types of pulmonary function measurements and chest x-rays); It also has data pertaining to the prevalence of self reported cardiac and non- cardio-pulmonary diseases and diagnoses.

Predictors

questionnaires on medical history, including cvd history
family medical history
smoking
occupational and environmental exposures
exercise
socio-environmental characteristics
height, weight and other anthropometric measurements
blood pressure,
IgE determinations
surveys pertaining to sleep disorders
medication use
lung function tests
alpha one antitrypsin determinations
cholesterol
vectorcardiography
chest radiographs
electrocardiograms
ankle/arm index
6-minute walk with pulse oximetry

Outcomes

The TES also has obtained mortality information on its subjects with ascertainment of the cause of death by clinical follow-up and death certificate analysis using state agencies, the National Death Index computer files and the Social Security Administration.

5.1.6.2 Tucson Host Factors, Bronchial Reactivity, & Environmental (H & E) Cohort

5.1.6.2.1 Cohort Selection

This study is evaluating the role of bronchial responsiveness, host immunological status, smoking, environmental and occupational exposures in the acute and chronic processes in the etiology, natural history and type differentiation of airway obstructive diseases (AOD). One of its specific aims is to determine the important factors in the evolution of cardio-pulmonary problems and the prediction of mortality.

The population studied is derived from a multistage stratified cluster sample drawn from the municipal employees of Pima County (Arizona), in which Tucson is located. The first stage of the study screened 2323 employees to obtain demographic characteristics and location of residence in 1987-88. Their demographic characteristics (age, sex, ethnic group, educational level) were similar to the employed population of Tucson; Hispanics represented about 25% of the population, and others (Black, Asian/Pacific Islanders, Native Americans) below 5% each. Prevalence rates of major symptoms, including smoking rates and lung function, were similar between the non-Hispanic white participants in this and in TES (described above), except for small differences within sub-groups. Subsequent followup has consisted of the health evaluation surveys in those residing in the Tucson urban area. Currently there are over 2600 individuals in the study.

5.1.6.2.2 Information Collected

The H&E cohort has focused on pulmonary outcomes (diseases, diagnoses, morbidity and mortality as well as different types of pulmonary function measurements, including bronchial lability and responsiveness); it also has information pertaining to self reported cardiac and non-cardio- pulmonary diseases and diagnoses.

Predictors

Basic assessments of individual health have involved physiological, clinical, immunological and epidemiological techniques utilized in the TES cohort.

Individual characteristics were determined from the standardized health questionnaires.

Serum was obtained for IgE, IgG, IgG subclasses, blood counts (including eosinophils) and cholesterol.

pulmonary function tests (MEFVs & PEFs)
ankle/arm index
6-minute walk with pulse oximetry
electrocardiograms

Tables summarizing the data collected by all of the parent studies are included in Appendix 3.

5.2 Sampling Criteria

The parent cohorts for the Sleep Heart Health Study offer a sampling frame of approximately 20,000 individuals. In specifying criteria for sample selection from the parent cohorts, the Steering Committee carefully weighed the need to fully represent minorities and women and to cover the full age spectrum, recognizing that the cardiovascular consequences of sleep-disordered breathing may vary by age. The total sample size, which was generally fixed by the time frame and resources available to the investigators, was thus distributed in a fashion that assured that information would be gained on women and minorities and younger and older persons. In designing the sampling approach for selecting the Sleep Heart Health Study cohort, the Steering Committee agreed to the following criteria:

- **Each site will recruit all available minorities.**

    - **Rationale:** Guidelines of the National Institutes for Health specify that populations should be selected to assure representation of the population, including minority groups, to the fullest extent possible. To maximize representation of minority populations, all minorities will be recruited from the parent cohorts; 600 members of the Strong Heart Study, which includes only Native Americans, will be recruited such that over 10 percent of the full cohort for the Sleep Heart Health Study will be Native American. The other cohorts will contribute approximately 450 African Americans, 280 Hispanics, and 70 Asian Americans. Thus the total minority membership of the study will be approximately 1400 participants.

- **Each site will recruit equal numbers of men and women.**

    - **Rationale:** This criterion has also been implemented to assure representation of men and women equally.

- **Habitual snorers will be over-sampled in sites that recruit subjects younger than age 65 years.**

    - **Rationale:** At the anticipated population prevalence of sleep-disordered breathing, power can be increased by increasing the prevalence of sleep-disordered breathing among participants in the cohort. At younger ages, habitual snoring predicts sleep-disordered breathing and consequently the sample will be enriched with snorers in the age stratum of less than 65 years. With increasing age, snoring is not similarly predictive.

- **Persons with prevalent cardiovascular disease and hypertension will not be excluded.**

    - **Rationale:** The information on prevalent disease is variable among the cohorts and the presence of prevalent disease cannot be uniformly determined among the cohorts before recruitment begins. Moreover, cross-sectional analyses addressing associations of prevalent disease with sleep-disordered breathing will contribute substantially to existing literature, given the size of the Sleep Heart Health Study Cohort. The information gained from follow-up of persons with prevalent disease will provide clinically relevant information. Follow-up of persons with prevalent disease will provide insight into the impact of sleep-disordered breathing on the natural history of hypertension and on risk for recurrent myocardial infarction and stroke.

Additionally, all participants will be at least 40 years of age. This criterion, specified in the Request for Applications, excludes young persons at low risk for cardiovascular and cerebrovascular disease. The Steering Committee recognized that the resulting sample would not necessarily be representative of either the parent cohorts or of the general population. However, the sample should provide an internally valid assessment of the cardiovascular consequences of sleep-disordered breathing and of the impact of sleep-disordered breathing on quality of life. The findings will need to be generalized with caution and with careful assessment of the sampling that established the parent cohorts and of the subsequent sampling for the Sleep Heart Health Study cohort.

5.3 Sample Size Considerations

The target sample size is set at 6,000 subjects, or approximately 1,000 from each investigative center. This sample size was fixed by the time frame of the study and the resources available to the investigators. It is estimated that approximately a third of this sample will have prevalent cardiovascular or cerebrovascular disease, leaving 4,000 subjects available to test hypotheses regarding incident events.

The primary hypotheses regarding events can be specified as the relationship between two dichotomous variables in a two-by-two table (presence or absence of event by exposure to sleep apnea). The cell frequencies and, hence, the power for these hypotheses are determined by three parameters:

1) the prevalence of sleep-disordered breathing (SDB) in the sample: 15%, 20%, 25%, 35%
2) the event rates: 0.5%, 1.0%, 1.5%, 2.0%, 2.5%
3) the relative risk (RR) of an event (SDB vs. without SDB): 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0

The rationale for choosing the values listed for each parameter are outlined below.

Review of the literature indicates that the prevalence of sleep-disordered breathing depends on the age, body mass, and race distributions of the populations being studied. A recent study (6) estimated that the prevalence of sleep-disordered breathing (defined as an apnea/hypopnea index > 5) in middle-aged adults is 9% in women and 24% in men. The prevalence was estimated to be even higher in the elderly (20%-62%) (13). Data from the Cleveland Family Study, an epidemiologic study of more than 800 subjects, further suggested that the prevalence of sleep-disordered breathing may be twice as high in African-Americans as in Caucasians (9).

Event rates were estimated using data from the CHS cohort with an average of 3.5 years of follow up data. (unpublished data) To date, the incidence of myocardial infarction has been 3.7%, or approximately 1% per year. For strokes, the incidence was also 3.7%. All cause mortality to date has been 7.6%, or about 2% per year. Coronary heart disease mortality was 2.6%, or 0.75% per year. Thus, event rates range from 0.75% to 2% for each year of follow up. While the CHS cohort represents an older cohort (ages 65 years and older), this age group will comprise about 50% of the SHHS study. Assuming none of the younger group (40-64 years) experienced an event, then the yearly event rate in SHHS would be less than 0.4% up to 1%. If the event rate in the younger group is half the rate in the older group, then the yearly event rate would range from .6% to 1.5%. For the average follow up of two years expected for SHHS, these assumptions could yield event rates ranging between 0.8% to 3%. Thus power calculations used event rates between 0.5% and 2.5%.

Most of the evidence relating sleep-disordered breathing and myocardial infarction is based on studies of snoring, not specifically documented sleep apnea. For these studies relative risks ranged between 1.8 and 4.4 (2, 15, 16). Those few studies which considered sleep apnea specifically only evaluated the presence of apnea shortly after an MI had occurred and not longitudinally. The few studies relating stroke to sleep apnea found odds ratios of 2 to 3.2 for snoring (17, 18). For hypertension, marked increases in systolic (>200 mm Hg) and diastolic (>100 mmHg) have been observed with apneas (19, 20). The prevalence of sleep apnea in hypertensives is estimated to be at least three-fold higher than in subjects without hypertension (5, 21, 22).

The primary hypotheses regarding incident events (coronary heart disease or stroke) will be based on the smaller sample size of 4,000 participants without prevalent CVD at enrollment. Hypotheses which can be tested including prevalent cases (e.g., all-cause mortality) will be based on the 6,000 subjects. Power was determined for all 140 combinations of the three parameters, assuming sample sizes of N=4,000 subjects and 6,000 subjects, as well as an intermediate value of 5,000 subjects. The alpha level was specified at 5%. Table 5.3.1 illustrates the power for prevalences of 15% and 25% for sleep- disordered breathing. The lines in the table partition the tabulated values of power into those less than 60%, 60-79%, and 80% or better.

As the table shows, power increases with increasing prevalence, event rate, relative risk, and/or sample size. For a sample size of N=4,000, the power is limited for the lowest event rate of 0.5% or a relative risk of 1.5. For a mid-range event rate of 1.5% and a RR of 2.0 or greater, the power is at least 59% for a prevalence of 15% SDB and at least 71% for a prevalence of 25%. The power for a prevalence of 35% is only a few points higher than those for 25%. For all parameter combinations considered, a power of at least 80% can be achieved for 40% of the parameter combinations, with an additional 16% demonstrating power in the 60-79% range.

For a sample size of N=6,000, the power is still somewhat limited for an event rate of 0.5% , but is higher than those estimates for N=4,000 with power of at least 60% at the highest relative risks. For the mid-range event rate of 1.5%, there is approximately 80% power to detect a relative risk of 2.0 or greater. Again, the power for a prevalence of 35% is only a few points higher than a prevalence of 25%. For all parameter combinations considered, a power of at least 80% can be achieved for 59% of the parameter combinations, with an additional 15% demonstrating power in the 60-79% range. Thus, the power is sufficient (at least 80%) at this sample size for more than half of the parameter space considered.

Table 5.3.1 : Estimated Power based on N = 4,000 and N = 6,000

Event rate:		*.5%*	*1%*	*1.5%*	*2%*	*2.5%*
Prevalence of SDB	**RR**					
N = 4,000						
15%	***1.5***	11	17	23	29	34
	1.75	17	29	41	51	60
	2	25	43	59	71	81
	2.25	33	57	72	85	92
	2.5	42	69	85	93	97
	2.75	50	79	92	97	99
	3	58	86	96	99	100
25%	***1.5***	13	22	30	38	45
	1.75	21	37	52	64	73
	2	31	54	71	83	90
	2.25	41	68	84	93	97
	2.5	50	79	92	97	99
	2.75	59	87	96	99	100
	3	67	92	98	99	100
N = 6,000						
15%	***1.5***	13	23	31	40	47
	1.75	22	40	54	66	76
	2.0	37	63	79	89	94
	2.25	46	74	88	94	97
	2.5	58	86	96	99	99
	2.75	67	92	98	99	99
	3.0	75	96	99	99	99

25%	***1.5***	17	30	41	52	61
	1.75	29	51	67	80	87
	2.0	46	74	89	95	98
	2.25	56	84	95	98	99
	2.5	68	93	98	99	99
	2.75	76	96	99	99	100
	3.0	83	98	99	99	100

1) Prevalence = prevalence of sleep-disordered breathing (SDB) at baseline
2) RR = relative risk of event in those with SDB compared to those without SDB
3) Power calculations were done for logistic regression analyses.

6. SLEEP DATA COLLECTION

6.1 Sleep Habits Questionnaire

The Sleep Habits Questionnaire is a self-administered form assessing baseline sleep habits and problems as well as history and treatment of sleep-disordered breathing. It will be distributed to all members of all parent cohorts. This form was developed to serve 4 main purposes:

1. To survey the source populations on snoring frequency as a sample weighting factor. Enriching the cohort with habitual snorers (those who report snoring frequently [3-5 nights per week] or always or almost always [6-7 nights per week]) will increase the number of participants in SHHS with SDB and enhance study power.

2. To identify people who should not be included in the SHHS sample. The exclusions were: people treated for sleep apnea on a nightly basis (including CPAP or dental device but not surgery), and people on home oxygen therapy. Although individuals with a tracheostomy will be excluded, the very low prevalence of this exclusion factor did not warrant inclusion of this question on the Sleep Habits Questionnaire.

3. To characterize the SHHS sample participants and assess selection bias on key variables that would not be available from parent cohorts (sleepiness, snoring, etc).

4. To collect data from a very large sample (~20,000) for analysis of self-reported data on sleep problems and conditions and on cardiovascular endpoints and other data routinely collected on the parent cohorts. In order to minimize questionnaire length, the items included for this purpose were limited to those with established validity that were needed for *a priori* hypotheses determined by the Steering Committee.

6.2 PSG Study

All participants in SHHS will undergo EEG-based polysomnography in the home. Several other possible designs for the collection of sleep data were considered, such as a two-stage design employing a simpler montage of data collection in the home followed by sleep lab studies in a subset of participants. However, home monitoring of all participants was deemed the most practical way of obtaining a large amount of data on as many subjects as possible. Further, it has the advantage of allowing all data collection to occur in one visit, an important consideration with regard to participant load, as many SHHS participants experience considerable burden through their participation in parent studies. A feasibility study was conducted in March and April, 1995, to assess participant acceptance of EEG-based polysomnography in the home. (See Appendix 4).

Overnight sleep monitoring will be performed using the Compumedics Sleep Watch polysomnograph. This device was chosen out of many devices considered because it best met the study's needs in terms of providing the required data and having the best configuration and software combination for the study. A full description of the process of equipment selection is included in Appendix 4.

Data will be collected on twelve channels, as follows:

Oximetry
Heart Rate
Chest wall and abdomen movement
Nasal/oral airflow
Body position
Electroencephalogram (EEG) (2 central; one for redundancy in case of failure/loss)
Electrooculogram (EOG) (bilateral)
Electromyogram - chin (EMG)
Electrocardiogram (ECG)

The respiratory abnormalities which are the focus of the SHHS are apneas and hypopneas. An apnea is a complete or almost complete cessation of airflow, lasting at least 10 seconds, and usually associated with desaturation or an arousal. A hypopnea is a reduction in airflow (<70% of a "baseline" level), associated with desaturation or arousal.

Events (apneas or hypopneas) are also classified on the basis of the extent of the associated respiratory effort. Obstructive events, the most common form in sleep apnea, are associated with chest and/or abdominal respiratory effort occurring in the face of an obstructed upper airway. Central events are associated with insufficient or highly irregular breathing effort; an obstructed upper airway may or may not be a feature. This breathing pattern may be seen in heart failure and after strokes.

Apneas will be identified if the amplitude of the airflow or chest wall movement decreases to below approximately 25% of the amplitude of "baseline" (identified during a period of regular breathing with stable oxygen levels), if this change lasts for > 10 sec.

Hypopneas will be identified if the amplitude of the airflow or chest wall movement decreases to below approximately 70% of the amplitude of "baseline" (identified during a period of regular breathing with stable oxygen levels), if this change lasts for > 10 sec.

"Central" events will be noted if no displacement is noted on either the chest or abdominal inductance channels. Otherwise, events will be noted as "obstructive."

Computer analysis linking the data from multiple channels will provide the predictor variables listed below.

The main "predictor" variable considered will be apnea/hypopnea index (AHI), defined as the number of apneas and hypopneas per sleep hour, identified if at least a 3% desaturation or an arousal occurred in association with a change in breathing (as above). The other variables will be assessed as to any differences in their predictive ability to identify cardiovascular or other morbidities. Other measures:

Summary AHI values, based on requiring > 2%, 3%,4%, and 5% desaturation levels, occurring within 30 seconds of the termination of the event; based on an

associated arousal, occurring within 3 seconds of the termination of the respiratory event; and based on all combinations of arousal and the five levels of desaturation.

Percent sleep time in apnea (obstructive or central).
Percent sleep time in hypopnea.
Percent sleep time in desaturation (<95%, <90%, <85%, <80%, <75%).
Percent time in each sleep stage.
Arousal index.
Number/hour stage 1 shifts.
Number/hour wake shifts.
Sleep efficiency.
Maximum, minimum and mean heart rate noted with each event and over the entire recording period.

Teams of two technicians will travel to the participant's home in the evening to connect the polysomnograph. They will instruct the participant in how to move about while wearing the monitor so that no electrode connections are lost. The technicians will also complete other types of data collection during the home visit. (See Section 7.2.)

In the morning after the sleep study is completed, a technician will return to the home. The technician will disconnect the monitor if the participant has not already done so and collect the Morning Survey form which the participant should have completed.

When the technician returns to the Field Center, they will download the sleep data onto the Field Center computer and check to make sure that there are no gross errors in the data (e.g., blank channels, extremely noisy channels). The technicians will then transfer the data onto two zip cartridges, one to be kept at the Field Center and one sent to the Reading Center for processing.

Results of the polysomnography will be sent to the participant within six weeks of the monitoring visit.

7. COVARIATE DATA COLLECTION

7.1 Parent Cohorts

SHHS is designed to use existing data collected by the parent studies regarding health history, cardiovascular risk factors, and cardiovascular events. The Comparability Committee was charged with comparing data collected by the various parent studies to determine the data to be used.

The committee classified variables into ranks of priority as follows:

(A) Variables that are considered critical for the study; if any of the cohorts do not have comparable data in any of these variables, additional data are to be collected.

(B) Variables that could be important in specific or subset analysis: an attempt to achieve comparability will be made, but it is not required that all cohorts have comparable information.

(C) Other variables that could be used in cohort-specific analyses, or in ancillary studies, but no specific attempt to achieve comparability will be made.

The following table (Table 7.1) shows the list of variables according to the rated priority. The A-variables include those needed to define prevalent clinical and subclinical cardiovascular disease, in order to identify participants at risk of incident disease, as well as the main cardiovascular risk factors previously described as strong correlates of SDB (hypertension, smoking, anthropometric indices). Other cardiovascular risk factors that have not been clearly identified as correlates of SDB are also included, in order to study their role as possible confounders or effect modifiers. Finally, the list of A-variables included medications and other strong correlates or indicators of respiratory or sleep disorders (self-reported history of SDB and respiratory symptoms, caffeine and alcohol intake, spirometry).

For each of the A-variables, a maximum acceptable time window between the time of the home sleep study and the closest measurement is specified. That is, data previously collected by the parent study can be used for SHHS as long as they were collected within an acceptable time window. The acceptable window for each variable is included in the table below. A-variables collected outside the acceptable time window must be re-ascertained for SHHS.

Table 7.1 Priority List of Variables from Parent Studies

A variables	Maximum Window	B variables	C variables
Categorical covariates			
Prevalent CVD:	3 months	Non-cardiopulmonary medical history	
Prevalent MI		Family history of CVD	
Prevalent Stroke		Parental	
Angina		Sibling	
CHF			
Self-reported hypertension	3 years	Occupation	
Self-reported diabetes	3 years	Psychosocial status	
Self-reported respiratory symptoms	3 months	Access to health care	
Self-reported hx of SDB	3 months		
Cigarette smoking status	3 months		
Educational level	Any		
Marital status	3 years		
Race	Any		
Gender	Any		
Continuous covariates			
Age	Current	Hemostasis parameters:	Passive smoking (ETS)
Cigarettes/day	3 months	Fibrinogen	Diet:
Cigarette × years	3 months	Factor VII	Caloric intake
Usual alcohol intake	3 years	Physical activity	Fat intake
Usual caffeine intake	3 months	Family income level	Antioxidants
Seated blood pressure	Current		
Anthropometric indices:			
height	Any		
weight	1 month		
waist, hip girths	3 years		
neck girth	Current		
Total cholesterol	3 years		
HDL cholesterol	3 years		
Triglycerides	3 years		
Spirometry: FVC, FEV_1	Any		
Ankle-Arm Index	Any		
SF-36 Score	Any		
Other			
Medications	Current	Echocardiography	24h. blood pressure
ECG	Any		Carotid Ultrasound
			Holter
			MRI

7.2 Covariate Information Collected at the Home Visit

At the time of recruitment, a visit is scheduled to conduct the sleep study. Usually this visit will occur in the participant's home. However, under certain circumstances, such as over crowding or for safety reasons, the data collection may take place in a location other than the participant's permanent residence, such as a motel or a clinic. A few days prior to the home visit, the participant is contacted to confirm the visit date, time, place, and traveling directions, and to determine if any recent event, such as illness or a family emergency, has occurred which would impact their typical sleep pattern and thus require rescheduling of the PSG study. In addition, the participant's chart at the parent study clinic is reviewed to determine whether any A-variables have been collected within the acceptable time window, and packets are prepared for data collection including forms labeled with appropriate ID numbers and a token of appreciation to be given to the participant on the night of the sleep study.

The home visit is the key data collection point, with the majority of the baseline data collected at that time. The home visit is conducted by a team of two individuals (including at least one sleep technician) who have been specifically trained and certified to set up the Compumedics sleep monitor, obtain the necessary vital measurements, conduct Health and Medications interviews, and collect and review for completeness the other paper forms that are completed by the participant. The field team will be trained to be courteous, respecting the participant's home, family, and privacy, and to make their visit as unobtrusive as possible. They are also trained as to how to deal with medical alerts and emergencies.

In the home, one member of the team will set up the Compumedics monitor, while the other begins the data collection process. The sleep monitor is battery operated so the participant is not potentially in connection with any electrical outlets. Electrodes will be glued to the hair, face, and chest; a thermistor will be attached above the lip to monitor respiration; and an oximeter will be attached to one finger. During the evening visit, the participant's blood pressure is taken, he/she is weighed, neck circumference obtained, and Health and Medication interviews are administered. In addition, a Morning Survey is left for the participant to complete in the morning after the monitoring is completed. At some sites the self-administered SF-36 quality of life survey will also be left with the participant. This process should take approximately 1.5 to 2 hours.

The next morning a technician returns to the participant's home at a pre-arranged time to collect the sleep monitor and the Morning Survey regarding the sleep monitoring experience and the use of alcohol, tobacco, or medications. The technician thanks the subject for participating and indicates that a summary of the results of their sleep study will be sent to them in six weeks. This process will take approximately 10-15 minutes.

At the Field Center, the sleep technicians log in all data collected and evaluate the overall completeness and quality of the sleep study by reviewing it on a personal computer. The PSG data are then sent to the Reading Center for processing and the paper forms submitted for local data entry. A few days following the home visit, the study coordinator will personally call the participant to obtain feedback on the home visit and determine if there were any problems with the study personnel, paper form completion, or the sleep monitor. At sites where telephone calls are not feasible, an evaluation postcard will be left with the participant when the monitor is collected.

Table 7.2 lists all data to be collected at the home visit. The Health Interview includes those covariate data which were not collected by all the parent cohorts or not collected according to a common protocol. Thus, the Health Interviews vary slightly for the different field centers. Some of these data have time windows such that if the data have recently been collected within this window around the time of the sleep study, then those data need not be collected again. For example, if an individual was weighed at a clinic visit less than one month before the sleep monitoring visit, then weight need not be collected again.

Table 7.2 - Data Collected at Home Visit

Content
1. Health Interview (Interview administered by study personnel) a. History of heart disease: Angina, Myocardial infarction, stroke, heart failure. b. History of hypertension c. History of diabetes d. History of heart or cardiac surgery, or the insertion of a pacemaker. e. History of emphysema, chronic bronchitis, chronic obstructive pulmonary disease, or asthma. f. Current respiratory problems: coughs, chest congestion, runny or stuffy nose, sinus problems. g. Typical amount of caffeine consumed (coffee, tea, colas). h. Years of education i. Cigarette smoking history and current habits j. Typical alcoholic beverage consumption.
2. Blood pressure (three measurements taken)
3. Neck circumference
4. Weight
5. Medications taken in the past two weeks.
6. Quality of Life survey (self-administered, some sites collect this at another time)
7. Morning Survey - (self-administered) a. Medications taken in the four hours prior to bedtime. b. Assessment of previous night's sleep. c. Caffeine, alcohol, and tobacco use in the four hours prior to bedtime.

7.3 Medical Alerts and Participant Feedback

7.3.1 Medical Alerts

Certain findings made at the time of the home visit or during analysis of the sleep study may require medical intervention. Although the sleep study performed as part of the SHHS is not considered a diagnostic study, the SHHS investigators have an obligation to refer special cases to their local physicians.

Two levels of medical referrals will be identified. Immediate referrals are potential medical emergencies which may require immediate notification of both the participant and his/her primary care physician. Urgent referrals are findings which may require medical attention but not on an emergency basis.

Immediate referrals are findings made at the time of the sleep study setup in the participant's home. Because the technicians performing the setup are in general neither trained nor licensed to perform clinical diagnostic assessments, all findings requiring immediate referral will be referred by the technician to a physician-investigator of SHHS. The physician, based on information obtained from the technician and the participant, will determine whether immediate referral is in fact indicated.

Findings requiring immediate referral at the time of the sleep study setup are as follows, unless the parent study specifies different criteria:

Awake blood pressure:	Systolic > 200 (and not on bp meds)
	Diastolic > 120 (and not on bp meds)
Awake heart rate:	> 150 beats/minute for longer than 2 minutes at rest
	< 30 beats/minute for longer than 2 minutes at rest

Oxygen saturation at hook-up < 80% for longer than 2 minutes at rest

Urgent referrals are made for abnormalities detected at the time of hook-up or on review of the sleep study which require medical attention but not on an emergency basis. Notification of the participant and his/her physician will be sent by mail within 10 days.

Findings requiring urgent referrals are as follows, unless the parent study specifies different criteria:

Awake blood pressure:	Systolic > 170 (and not on bp meds)
	Diastolic > 100 (and not on bp meds)
Sleeping heart rate:	> 150 beats per minute for longer than 2 minutes
	< 30 beats per minute for longer than 2 minutes

Baseline awake oxygen saturation 80-85%
Oxygen saturation < 75% for more than 10% of total sleep time

Apnea-Hypopnea Index $\geq$ 50 events/hour

Details of the protocol for identifying and responding to Medical Referrals can be found in Section 6.10 of the Manual of Operations.

7.3.2 Participant Feedback

Participants will be sent a report summarizing the findings of their sleep studies. A copy of the report will also be sent to the participant's primary medical care provider. Included will be information regarding total sleep time, sleep latency, AHI, REM, and average heart rate during sleep. Additionally, some clinics may choose to include information on blood pressure and weight. Participants with an AHI $\geq$ 50 will be sent a different letter than those with lower AHI levels, recommending that they discuss the report with their personal physician. In addition, all participants will be told that they should contact their personal physicians if they have symptoms or experience daytime sleepiness.

Examples of participant reports are included in Section 6.10.5 of the Manual of Operations.

8. OUTCOMES DATA COLLECTION

8.1 Coronary Heart Disease events

8.1.1 Endpoints

The following *incident* events will be considered endpoints for the SHHS:

a. hospitalized acute MI (HAMI)
b. coronary surgical intervention -- percutaneous transcutaneous angioplasty (PTCA), coronary stent placement, coronary artery bypass grafting (CABG)
c. angina pectoris (AP) -- at CHS and FHS only
d. coronary heart disease death
e. any coronary heart disease (CHD) -- summary variable which includes a - d above.

The following *recurrent* events will be considered endpoints for the SHHS:

a. HAMI
b. coronary surgical intervention

8.1.2 Ascertainment

Cardiovascular events will be ascertained at least every two years and at least once by the end of Grant Year 3 (August, 1998). Each investigative center will identify potential outcome events and obtain the relevant hospitalization, outpatient procedure, and physician records. Protocols vary for the different parent study cohorts, and are summarized below.

8.1.2.1 Framingham

Very few of the FHS subjects participating in the SHHS will have a follow-up clinic visit prior to August, 1998, so the majority of events will be ascertained during a structured telephone or home interview. Subjects who undergo sleep studies between October, 1995 and August, 1996 will be visited in the home two years after the PSG. During this visit blood pressure will be measured in a standardized fashion and a modified ARIC Annual Follow-up Questionnaire form will be administered. Subjects who undergo sleep studies between September, 1996 and March, 1997 will not be due for their two-year-post-PSG BP measurement until Year 4 of the study; therefore, the modified Annual Follow-up Questionnaire Form will be administered over the telephone between June and September, 1998. Any potential outcome events identified will be referred to the FHS medical records department to complete data collection and allow the event to be adjudicated. Consent to obtain copies of medical records is granted by the FHS members as part of their participation in the parent study.

8.1.2.2 Johns Hopkins

In the ARIC portion of the cohort, events will be ascertained every twelve months either by annual phone calls with administration of the Annual Follow-up Questionnaire Form or during a structured history at the tri-annual clinic visit. Hospitalization records for potential outcome events will be obtained and abstracted by trained personnel. All DRG discharge codes are recorded. ECGs will be photocopied and classified by the Minnesota coding system. Consent to obtain copies of medical records is given as part of the overall consent for participation in ARIC.

In the CHS portion of the cohort, potential events will be ascertained every six months by phone calls alternating with clinic visits. Hospitalization and outpatient procedure records will be obtained and abstracted by trained personnel. ECGs will be photocopied and classified by the Minnesota coding system. Consent to obtain copies of medical records is given as part of the overall consent for participation in CHS.

8.1.2.3 Minnesota

Ascertainment procedures and abstraction forms for potential events will be identical to those used by the Johns Hopkins ARIC Cohort (see 8.1.2.2).

8.1.2.4 NYU/Cornell

Potential CHD events in the New York City cohorts will be ascertained two years after PSG or at the end of Grant Year 3 (whichever is earlier). Participants who undergo PSG during Grant Year 1 will return to the clinic for follow-up blood pressure measurements and administration of a modified ARIC Annual Follow-up Questionnaire form during Year 3. Those participants who undergo PSG during Year 2 will be administered the follow-up questionnaire over the telephone in the last 4 months of Year 3, and return to the clinic for a blood pressure measurement during Year 4. Hospital and outpatient procedure records from any potential outcome event will be obtained and abstracted using the CHS forms. NYU and Cornell personnel will be trained in record abstraction for epidemiologic research. Subjects will give consent to obtain copies of medical records at the time of event ascertainment.

8.1.2.5 Pittsburgh/Sacramento

These CHS Cohorts will ascertain events, and obtain and abstract medical records in an identical fashion as the Johns Hopkins CHS Cohort (see 8.1.2.2).

8.1.2.6 Tucson/Strong Heart

Events occurring in subjects from the Tucson Epidemiologic Study of Obstructive Airways Disease (TES) and the Tucson Health and Environment Cohort (H&E) will be ascertained two years after the PSG or at the end of Grant Year 4 (whichever is earlier), using a modified ARIC Annual Follow-up Questionnaire form, administered either over the telephone or during a clinic visit. Hospital and outpatient procedure records from any potential outcome event will be obtained and abstracted using

the CHS forms. Tucson personnel will be trained in record abstraction for epidemiologic research. Subjects will give consent to obtain copies of medical records at the time of event ascertainment.

Events occurring in Strong Heart Study participants will be ascertained at the time of a follow-up clinic visit, using the protocols and forms established at SHS. Copies of medical records for potential events will be obtained and abstracted.

8.1.3 Adjudication

Each parent study will adjudicate potential cardiovascular events which occur among its participants. Based on the quality assurance procedures of the parent studies and the results of the HAMI Comparability Study (summarized below), it is expected that the adjudicated results from ARIC, CHS, FHS, and SHS will be both valid and in close agreement with one another. The NYU/Cornell and Tucson centers will establish their own Cardiovascular Events Adjudication Committees. A sample of events reviewed by these committees will be re-reviewed by the SHHS Morbidity and Mortality Committee to assure comparability with the other parent studies.

8.1.3.1 Results of the HAMI Comparability Study

The SHHS Morbidity and Mortality Subcommittee conducted a comparability study for the outcome HAMI during the May, 1995 Steering Committee meeting. A sample of hospital records and accompanying data abstraction forms which had been previously reviewed and adjudicated by the parent studies were re-adjudicated by nine SHHS physician investigators. FHS, CHS, ARIC, and Strong Heart Study sites each contributed 26 cases. Cases were selected which had a discharge diagnosis of MI or coronary artery disease. Three cases were excluded from the results of the review; for two cases the SHHS review committee did not have the complete parent study record, and one case was inadvertently missed during the adjudication session. The ARIC criteria for HAMI were used to guide event classification; however, clinical judgement could override these guidelines.

RESULTS	SHHS Adjudication	
Parent Study Adjudication	Not MI	MI
Not MI	45	7
MI	2	47

The observed agreement between the parent studies and the SHHS reviewers for the classification of HAMI was 91%, with a kappa statistic of 0.82, indicative of excellent agreement. Of the 9 disagreements, the SHHS reviewers classified as MI three uncomplicated post-CABG patients with elevated cardiac enzymes and two CPK bumps after a cardiac arrest which were not classified as MI by the parent studies. In the majority of disagreements, the parent study was more conservative than the SHHS committee, suggesting that by accepting the parent study adjudication we will maintain high specificity at the expense of missing a few potential cardiovascular events.

8.1.3.2 Cohort-specific protocols for cardiovascular event adjudication.

HAMI -- All parent studies rely on a combination of chest pain, ECG tracings and myocardial enzyme profiles to define MI. For the SHHS both incident and recurrent HAMI will be adjudicated at all sites. At ARIC sites, abstracted data including the Minnesota codes for serial ECGs will be entered into a computer algorithm; the result will then be reviewed by the Events Committee. CHS centers also will abstract the hospital record and Minnesota code the ECGs, but no computer algorithm will be used. Both CHS and ARIC code HAMI events as definite or probable (counted as MI in analyses), or suspect or no MI. FHS reviews will not use abstracted data (only a copy of the medical records), and ECGs will not be Minnesota coded; however, the ECG from the FHS clinic visits before and after the potential event will be considered. At FHS, HAMI is classified as definite (the only cases used in analysis), maybe and no MI. At Strong Heart, medical records are abstracted, but ECGs are not Minnesota coded; events are classified as definite MI (the only events used in analyses), suspect MI and no MI. The New York City and Tucson investigative center Adjudication Committees will adopt the CHS abstraction forms and event criteria. A random sample of records reviewed at these sites will be re-reviewed by the SHHS to assure comparability with the other sites.

Coronary Surgical Intervention -- All studies will review hospital records to identify incident and recurrent coronary interventions. Each parent study will likely adjudicate these hospitalizations for HAMI, angina pectoris or cardiovascular death; however, documentation of a CABG or PTCA during the hospitalization will be adequate to assign this outcome for the SHHS without specific adjudication.

Angina Pectoris -- Incident AP will be an adjudicated outcome only at CHS sites and at Framingham. In CHS, the outcome of angina is assigned to all subjects who have coronary disease. Criteria for "definite angina" include an exercise stress test diagnostic for ischemia, coronary angiography demonstrating 70% narrowing of an epicardial coronary artery, or the occurrence of a surgical intervention. Subjects who receive a diagnosis of HAMI are also classified as having "definite angina". At the inception of the CHS cohort, a classification of "possible angina" was made for those subjects in whom the diagnosis could not be confirmed. "Possible angina" will not be a SHHS outcome. At FHS syndromes of coronary ischemia are classified as either "angina pectoris" or "coronary insufficiency". For the SHHS these outcomes will be combined into the AP category. Both diagnoses rely on clinical criteria and ECG findings, augmented by catheterization and stress test results. These outcomes are coded as "definite" and "maybe" at FHS. Only the "definite" events will be utilized by the SHHS. Some of the adjudicated AP outcomes will not be available until after the FHS Offspring Cycle 7 or Omni Cycle 2 exams, after the end of the SHHS funding period.

Cardiovascular Death -- All participant deaths will be reviewed by the parent study Events Committees. At ARIC, CHS, and FHS copies of recent hospitalizations, death certificates and autopsy results are obtained, and abstracted at ARIC and CHS. In addition, the subject's physician and family or other proxy is interviewed to obtain additional data regarding the death. Each committee determines whether or not the death was due to coronary heart disease, and whether the death was sudden or not. The Tucson and New York City investigative centers will adopt the CHS abstraction forms and event criteria. The SHHS will perform a comparability study for mortality (all-cause, coronary heart disease and cerebrovascular disease) similar to the HAMI comparability study.

Any Coronary Heart Disease -- This will be a summary variable including all subjects who receive an adjudicated diagnosis of any of the other cardiovascular outcomes.

8.2 Congestive Heart Failure

8.2.1 Endpoints

Incident clinical CHF will be an endpoint for all SHHS subjects except for ARIC participants. In the CHS and FHS cohorts, routine echocardiograms are performed on all participants. The continuous variables of left ventricular mass and left ventricular ejection fraction will be endpoints for the SHHS participants from these parent studies.

8.2.2 Ascertainment

Ascertainment for potential CHF events will occur using the same forms during the same interviews as ascertainment of potential cardiovascular events at FHS and CHS. (See 8.1.2.1 and 8.1.2.2). At the NYU/Cornell and Tucson sites, medical records for any potential episode of CHF ascertained during the follow-up questionnaire will be obtained and sent to the Cardiovascular Events Adjudication Committee.

For FHS participants follow-up echocardiograms will be performed at the clinic visit following the PSG. The FHS Offspring Cycle 7 and Omni Cycle 2 exams will not be completed before the end of Year 4, so these data will not be available for all participants in this funding cycle.

8.2.3 Adjudication

Incident CHF will be adjudicated by the Events committees. CHS criteria for CHF include decreased systolic cardiac function, a report of cardiomegaly and pulmonary edema on chest X-ray, or an appropriate response to pharmacologic treatment for CHF. Framingham criteria include a combination of clinical signs and symptoms such as rales, edema, dyspnea, or orthopnea, and physiologic tests demonstrating decreased systolic function. For the SHHS endpoint of incident clinical CHF only measurements of systolic cardiac function obtained for clinical purposes will be utilized. NYU/Cornell and Tucson will adopt the CHS criteria.

The variables of left ventricular mass and left ventricular ejection fraction will not be adjudicated. Only the echocardiograms performed at the Field Centers and interpreted by CHS and FHS investigators (not tests performed for clinical purposes) will contribute to this data base.

8.3 Cerebrovascular Events

8.3.1 Endpoints

SHHS cerebrovascular endpoints will comprise all strokes, both incident and recurrent, and hospital admission for carotid endarterectomy. Strokes will be subclassified as hemorrhagic and non-hemorrhagic, and as fatal or nonfatal. Hemorrhagic strokes will be further subclassified as subarachnoid or intracerebral hemorrhage. Non-hemorrhagic strokes may be subclassified by specific etiology (such as embolic, lacunar, or atherothrombotic) if a planned comparability study demonstrates substantial agreement between studies on these details.

8.3.2 Ascertainment

Ascertainment of cerebrovascular endpoints will be conducted at the same time and with the same follow-up forms as ascertainment of cardiovascular endpoints (see 8.1.2).

8.3.3 Adjudication

Stroke is broadly defined as a constellation of neurologic symptoms with a sudden onset which lasts at least 24 hours or until death. The SHHS will use the parent study adjudication results for stroke (assuming that a planned comparability study reveals a high degree of agreement between sites). The NYU/Cornell and Tucson centers will establish their own Cerebrovascular Events Adjudication Committees. A sample of events reviewed by these committees will be re-reviewed by the SHHS Morbidity and Mortality Committee to assure comparability with the other parent studies.
For the carotid endarterectomy endpoint, documentation of this procedure during a hospitalization will be adequate to assign this endpoint without adjudication.

8.3.3.1 Site-specific protocols for cerebrovascular adjudication

ARIC (Johns Hopkins and Minnesota sites) -- Hospital records for potential cerebrovascular events will be obtained, and abstracted onto ARIC forms. A computer algorithm which includes symptoms, physical findings, the presence of a non-carotid embolic source, the results of CT scans, cerebral angiograms and lumbar punctures, and pathology reports will initially classify the event. Computer classifications will be reviewed by the Events Committee. ARIC classifications for stroke will correspond to the following SHHS endpoints:

ARIC Endpoint	SHHS Endpoint
Subarachnoid hemorrhage	Any stroke, hemorrhagic stroke, subarachnoid hemorrhage
Brain hemorrhage	Any stroke, hemorrhagic stroke, intracerebral hemorrhage
Thrombotic brain infarction	Any stroke, non-hemorrhagic stroke
Non-carotid embolic brain infarction	Any stroke, non-hemorrhagic stroke
Undetermined type	Any stroke

All fatal strokes will be classified both by the most specific etiology determined and as “fatal stroke.”

CHS (Johns Hopkins, Pittsburgh and Sacramento sites) -- When potential cerebrovascular events are identified, the medical records will be abstracted, the patient or family proxy will be interviewed, copies of brain images will be obtained, and all data will be reviewed by a study neurologist. If the diagnosis is not apparent from these data, the neurologist will discuss the case with the subject’s physician or examine the patient. The full record, including the report of the study neurologist and the MRI obtained as part of the

baseline CHS exam, will then be reviewed by the Cerebrovascular Disease Endpoint Committee. CHS classifications for stroke will correspond to the following SHHS endpoints.

CHS Endpoint	SHHS Endpoint
Hemorrhagic, subarachnoid	Any stroke, hemorrhagic stroke, subarachnoid hemorrhage
Hemorrhagic, intra parenchymal	Any stroke, hemorrhagic stroke, intracerebral hem.
Hemorrhagic, indeterminate	Any stroke, hemorrhagic stroke
Ischemic, lacunar	Any stroke, non-hemorrhagic
Ischemic, cardioembolic	Any stroke, non-hemorrhagic
Ischemic, atherosclerotic	Any stroke, non-hemorrhagic
Ischemic, other (arterial dissection or arteritis)	Any stroke, non-hemorrhagic
Ischemic, unknown	Any stroke, non-hemorrhagic

All fatal strokes will be classified both by the most specific etiology determined and as “fatal stroke”.

FHS -- When potential cerebrovascular events are identified, medical records will be obtained, and the subject will be invited to a special exam in the Neurology Clinic at the FHS. The findings of this exam, the medical record, copies of brain-imaging studies and results of spinal fluid analyses are reviewed by the Stroke Endpoints Committee. FHS classifications for stroke will correspond to the following SHHS endpoints.

FHS Endpoint	SHHS Endpoint
Subarachnoid hemorrhage	Any stroke, hemorrhagic stroke, subarachnoid hemorrhage
Intracerebral hemorrhage	Any stroke, hemorrhagic stroke, intracerebral hemorrhage
Embolic stroke	Any stroke, non-hemorrhagic stroke
Atherothrombotic	Any stroke, non-hemorrhagic stroke

All fatal strokes will be classified both by the most specific etiology determined and as “fatal stroke”.

NYU/Cornell -- When potential cerebrovascular events are identified medical records and copies of brain imaging studies will be obtained and abstracted onto CHS forms. The subject or proxy will be interviewed using the CHS protocol. The Cerebrovascular Endpoints Committee will then review the data and classify the event into one of SHHS categories.

Tucson and Strong Heart Centers -- When potential cerebrovascular events are identified medical records and copies of brain imaging studies will be obtained and abstracted onto CHS forms. The subject or proxy will be interviewed using the CHS protocol. The Cerebrovascular Endpoints Committee will then review the data and classify the event into one of SHHS categories.

A random sample of events reviewed by the Tucson and NYU Cerebrovascular Endpoints Committees will be re-reviewed by the SHHS Morbidity and Mortality Committee to assure a high degree of agreement between the parent studies.

8.4 Hypertension

8.4.1 Endpoints

SHHS will define incident hypertension as a new physician diagnosis of hypertension, beginning treatment with anti-hypertensive medications, or a systolic BP > 160 or a diastolic BP > 95. In addition, SHHS will use the continuous measures of blood pressure taken on the evening of the PSG as an endpoint in cross-sectional analyses and the change in blood pressure 2-3 years after the PSG in longitudinal analyses.

8.4.2 Ascertainment

During follow-up contacts, SHHS participants will be asked about physician-diagnosed high blood pressure and about all medications prescribed and taken. Both the initial and follow-up blood pressures will be measured with the subject in the seated position as detailed in Section 8.4.1.3 of the Manual of Operations. All of the initial blood pressure measurements will be performed in the subject's home, prior to setting up the PSG equipment. Follow-up blood pressures will vary by investigative site. In some centers, follow-up blood pressures will be measured in the subject's home two years after the PSG. In other centers, blood pressures will be measured in the clinic when the subjects return for their follow-up exams.

8.5 Mortality

8.5.1 Endpoints

Mortality endpoints will include all-cause mortality, cardiovascular mortality, cerebrovascular mortality and all vascular mortality.

8.5.2 Ascertainment

When subjects cannot be contacted for their scheduled follow-up, every attempt will be made to determine whether or not they are deceased. All known contacts for the subject will be called to determine the subject's vital status, and both local death registries and the National Death Index will be searched for their name or social security number. When a death has been ascertained, the parent study will obtain records from any hospitalization within one month of the death, a copy of the death certificate, and an autopsy report, if performed. In addition, the subject's physician and the family member or other proxy who was with the subject when they passed away will be interviewed to obtain details of the circumstances of the death. ARIC, CHS, and FHS centers will use their respective forms; Tucson and NYU will adopt the CHS forms and protocol.

8.5.3 Adjudication

All investigative centers will adjudicate all ascertained deaths using the forms and protocols established by each parent study. Events which meet the criteria for a cardiovascular or cerebrovascular outcome which also result in death will be coded as death due to cardiovascular or cerebrovascular disease. Tucson and NYU will adopt the CHS protocols.

8.6 Quality of Life

8.6.1 Endpoints

Quality of Life will be evaluated using the summary score and 8 specific domains of the SF-36 Health Survey.

8.6.2 Ascertainment

The SF-36 will be re-measured in SHHS participants two to three years after their PSG. Participants will complete the Health Survey themselves at most centers; however, some Strong Heart participants for whom an appropriate translation is not available will have the instrument administered by an interviewer.

8.7 Transfer of Adjudicated Results from the Field Centers to the Coordinating Center

During the follow-up phase of the study, self-reported and adjudicated events will be reported to the Coordinating Center every month. The Coordinating Center will issue to each Field Center a list of ID numbers of those participants whose PSG was completed two years earlier. The study coordinator will confirm that the follow-up contact has occurred or determine when follow-up is scheduled. Any self-reported symptoms or hospitalizations which have triggered parent study review and adjudication will be reported back to the Coordinating Center. Software will be developed to track these potential events from ascertainment through the collection of all relevant medical records to final adjudication for those centers which do not already have a tracking system. Periodically, each Field Center will determine the status of any incident outcomes for the whole SHHS cohort, as some events may be ascertained during earlier or later parent study contacts. The parent study coordinating centers will be asked to send parent study adjudication results for SHHS participants to the SHHS Coordinating Center annually.

9. PROJECT MANAGEMENT

The Coordinating Center has primary responsibility for study administration and data management. These are outlined below.

9.1 Study Administration

The Coordinating Center works with the Steering Committee and Project office to administer the study, including diverse tasks such as: 1) supporting the activities of the Field Centers by providing forms and manuals and by troubleshooting any problems that arise: and 2) monitoring overall study progress to ensure that goals are being met.

Many of these administrative activities fall under the rubric of communication, which is one of the Coordinating Center's most important functions. These communications are summarized in Table 9.1 below. The Coordinating Center is to be the primary conduit for communication between all participating sites, the Steering Committee, and the Data and Safety Monitoring Board (DSMB). Clear, frequent, and complete communications are vital to the successful operation of a collaborative study. In some instances communications will originate at the Coordinating Center, and in other instances communications originating from another site will be sent to the Coordinating Center to be disseminated to all other sites. Communications range from formal written documents such as manuals and steering committee reports to informal communication via telephone or e-mail. Communications facilitated by the Coordinating Center will be of several forms, including the following:

Routine communications: The Coordinating Center will routinely distribute announcements regarding deadlines, upcoming meetings, decisions made by the Steering Committee, minutes from Steering Committee and DSMB meetings, etc. Depending in the nature of a particular message, these communications may be sent to Field Center PIs or Study Coordinators, the Steering Committee, or the DSMB. In general copies of all communications will be sent to the Program Office.

Routine reports: During the recruitment and data collection phase of the study, the Coordinating Center will distribute reports to Field Center PIs and Study Coordinators and to the Program Office each week summarizing recruitment progress to date and data completeness. Monthly for the first year of the study and quarterly thereafter, the Coordinating Center will distribute Quality Control reports to Field Center PIs and Study Coordinators and to the Program Office. These reports will summarize technician performance and identify any potential problems. Outlying data values will also be returned to the Field Centers to be checked. Comprehensive reports summarizing study progress will be prepared and distributed before each Steering Committee meeting and each DSMB meeting, approximately 2-3 times per year.

Special reports: If problems arise with data completeness or quality, Field Center performance, or other areas, special reports will be prepared. Depending in the nature of the problem, these reports may be distributed to the entire Steering Committee or just to the PI involved, along with the Program Office. In unusual and infrequent circumstances these reports would be distributed to the

DSMB as well. Follow-up reports documenting the resolution of the problem will be prepared as well. Other special reports, including statistical reports and special progress reports will be prepared as needed or at the request of the Program Office or Steering Committee.

Documentation: The Coordinating Center will also prepare, duplicate, and distribute study manuals and other policy documents as needed.

Study Oversight: Another major function of the Coordinating Center is study oversight. This includes monitoring study progress in areas such as recruitment and data completeness, identifying problems that arise, and working with Investigators and Study Coordinators to resolve the problems. In its relationship with the Field Centers, the Coordinating Center views itself not as a policeman looking for wrongdoing but rather as a collaborative supporter whose job is to provide the FCs with the tools and support necessary to enable them to do their jobs efficiently.

Study oversight also includes quality assurance and control. The Coordinating Center will work with the Quality Control Committee and the Sleep Reading Center to establish quality assurance policies (activities undertaken before data are collected to assure high quality), including requirements for technician certification and observation, and equipment maintenance. The Coordinating Center will then take primary responsibility for monitoring that these policies are carried out. The Coordinating Center will also perform quality control activities (activities undertaken after data are collected to ascertain actual data quality). These will take the form of statistical reports in which data quality will be analyzed both as a whole and at the individual site and technician level. (See Section 10 for a description of Quality Assurance and Control activities.)

Table 9.1 Coordinating Center Communications

		Sent to:			
	Time frame	FC*	SC*	PO*	DSMB*
1. Routine communications: Deadlines, meetings, announcements, decisions, etc.	as needed**	X	X	X	X
2. Routine reports:					
Recruitment	weekly	X	X	X	X
Data completeness	weekly	X	X	X	
Quality Control	monthly	X	X	X	
Steering Committee	2-3/year	X	X		
DSMB Report	2/year	X	X	X	
3. Special reports: Problem identified, Problem resolved, Special progress report, Statistical reports, etc.	as needed	X	X	X	X
4. Minutes from meetings	as needed	X	X	X	
5. Documentation: Manuals, Other policy/procedure documents	as needed	X	X	X	X

* FC = Field Center; SC = Steering Committee; PO = Program Office; DSMB = Data Safety and Monitoring Board

** Communication types identified as “as needed” will be sent only to those groups to which that communication pertains. Under various circumstances, this may or may not pertain to all groups indicated. For example, Routine communications regarding meeting announcements would only be sent to the DSMB if the meeting being announced was the DSMB meeting.

9.2 Data Management

9.2.1 Data Management within the Coordinating Center

9.2.1.1 Field Center Data

Each week a set of data files will be transmitted from each Field Center to the Coordinating Center over the Internet. These raw files will be copied onto backup diskettes before any processing occurs. Next the files will be read into the Microsoft Access database. A set of routine programs will run to check the data for completeness, errors, and outlying values. Reports generated by these programs will be sent to the Field Centers weekly, along with recruitment status reports.

9.2.1.2 Reading Center Data

Each week, the Reading Center will send the Coordinating Center a list of all studies received that week. The Coordinating Center will match this list against the data received from the Field Center that week, to ascertain that all studies arrived as they should. If any problems are noted, lists will be generated and sent to the Reading Center and the Field Centers asking them to resolve the discrepancies. This will include both expected studies that did not arrive at the Reading Center and unexpected studies that did arrive.

In addition, the Reading Center will send the Coordinating Center data cartridges each week containing studies that have been read so that they can be permanently archived onto compact disc (CD) at the Coordinating Center. The Reading Center will also send the Coordinating Center data files each week containing participant results files. The participant results files will be read into the Coordinating Center database, again with programs checking for data completeness and errors. If any problems are noted, lists will be generated that will be sent to the Reading Center or the Field Center, as appropriate, for resolution.

Responses to these weekly lists are expected before the next weekly report is generated. Any problems not resolved will appear again on the next week's report. Any problems which remain unresolved after one month will be followed up with the PI and the Program Office.

9.2.1.3 Backups and Data Security

Backups: Raw PSG data will be sent to the Coordinating Center from the Reading Center on zip cartridges. These will be archived permanently onto CDs, with new CDs being created approximately twice per month for each site. Each CD will contain data from only one Field Center. One set of CDs will be kept in permanent storage at the Coordinating Center, and another set will be returned to each Field Center, containing only data from that site.

Home visit data, recruitment data, and participant result files from the Reading Center will be backed up onto tape weekly at the Coordinating Center. The Coordinating Center network is backed up every week. Some tapes are kept as permanent archives, others are rotated monthly. An updated backup tape is taken off site monthly. In addition, raw data transmitted from the Field Centers and Reading Center will be saved onto diskettes as a secondary backup.

Covariate information received from the parent studies will also be backed up onto tape and kept as a permanent archive.

Security: The Coordinating Center is located in a secured building which allows no access by unauthorized individuals after office hours. The computer network is secured by use of passwords so that no unauthorized individuals (including unauthorized staff) have access to the SHHS database. Sensitive information such as participant names and addresses are kept in a separate database accessible only to the database administrator. Any participant hospital records received at the Coordinating Center are kept in locked file cabinets.

9.2.1.4 Database Management and Reporting

Microsoft Access will be used for all database management functions at the Coordinating Center. A set of programs for data checking and reporting will be written which will be run weekly by a data processor. SPSS and SAS will be used to generate statistical reports.

9.2.2 Data Management at the Field Centers

The Coordinating Center will provide software to the Field Centers for data entry and management. Double-data entry will be required on all data entered at the Field Centers to reduce keying errors. Once a week, data will be transferred from the Field Centers to the Coordinating Center using the Internet. The Coordinating Center will return receipts to the Field Centers to verify successful data transfer.

The Field Center software will include components for tracking data sent to the Coordinating Center and the Sleep Reading Center. Receipts received from the Coordinating Center and the Sleep Reading Center will be read into the tracking system to verify all data transfers.

At the end of each day, data entered that day will be backed up onto floppy disks using backup utilities supplied by the Coordinating Center. Databases containing personal participant data such as names and addresses will be password protected.

9.2.3 Data Management at the Sleep Reading Center

Data will be transferred from the Field Centers to the Sleep Reading Center using magnetic cartridges. The cartridges will be logged in at the Reading Center and receipts returned to the Field Centers.

The chief polysomnologist will be directly responsible for training and certifying the polysomnology scorers and centrally trained field research assistants. She will review each PSG record within 72 hours of its receipt at the Reading Center, identifying medical alerts and providing quality codes. She will triage studies for formal scoring to the polysomnology scorers, monitor scorers' performance, and provide support for interpreting ambiguous studies. She will implement ongoing procedures for assuring accuracy and reproducibility of scored procedures.

The Compumedics software system will be used to process all records, and provide preliminary estimates of the apnea/hypopnea index (AHI). Scorers will review the record, on an epoch by epoch basis (on screen), marking each sleep stage, each arousal, and each respiratory event.

Analysis software will be used to link the various channels after scoring to provide summary measures of sleep disordered breathing and sleep staging. Sleep stages will be characterized by modified Rechtshaffen and Kales criteria (23), and arousals by the ASDA criteria (24). (See Reading Center Operations Manual.)

Computer analysis linking the data from multiple channels will provide the predictor variables described in Section 6.2.

10. QUALITY ASSURANCE AND CONTROL

In the Sleep Heart Health Study, quality assurance (QA) includes activities designed to assure data quality that take place prior to data collection. Quality control (QC) includes data quality monitoring efforts that take place at identified points during data collection and processing.

A Quality Control Subcommittee has been established to define, coordinate, and direct all SHHS QA/QC activities and to contact Field Centers, the Reading Center, or the Coordinating Center as needed to advise them of problems and to discuss corrective actions. The Coordinating Center monitors database logs and correspondence regarding data problems, conducts quality control analyses, and generates reports. The Reading Center assigns a quality grade to the PSG data, which the Coordinating Center uses to generate "quality grade" reports for each field center and technician.

Quality assurance includes the following activities:

1. Detailed protocol development and documentation, including study design and data collection activities.

2. Establishment of certification, recertification, and maintenance of certification requirements for technicians in order to ascertain and maintain an individual's expertise in executing study protocol and procedures.

3. Provision of training and training updates as the basis of continuing education involving the protocol.

4. Documentation of all changes in protocol or equipment.

For quality control purposes, SHHS data collection is monitored by observation, and by using quantitative QC procedures such as statistical analysis of data. SHHS quality control includes the following activities:

1. Regular observation by a QC Supervisor of staff performing specific protocols, such as taking blood pressure and use of the sleep monitors, is required to identify techniques that may need improvement. Remedial action taken as required. At times, retraining and recertification may be appropriate.

2. Early feedback and communication are used in monitoring and correcting problems such as data entry and data transmission errors. All data entry requires double-entry of values. The Coordinating Center provides monthly reviews of the data to detect outliers or unreasonable data. Questionable data are returned to the Field Centers to be verified or corrected. Study data are used to monitor performance of staff and field centers.

3. One site visit to each Field Center will occur during Year 1 to evaluate adherence to study protocol and procedures by all staff members, and will be repeated as needed in subsequent years.

4. Equipment will be calibrated and checked for accuracy and proper functioning on a monthly basis.

The following quality control data are sent to the SHHS Coordinating Center on a regular basis:

1. Field Centers send: contact/recruitment data and study data (weekly); calibration logs and quality control supervisor check lists (monthly); Responses to QA/QC reports as needed.

2. Reading Center sends: status of data upon arrival and study data (weekly); technician performance (monthly); internal QA/QC report (quarterly); site visit reports and responses to QA/QC reports as needed.

The Coordinating Center produces and distributes the following QA/QC reports:

1. Field Center recruitment status and data integrity reports (weekly).
2. Reading Center performance reports (monthly).
3. Field Center Technician QC Reports (quarterly)
4. Summary reports of all QA/QC activities that have occurred (as needed).

11. DATA ANALYSIS AND LIMITATIONS

11.1 Data Analysis

11.1.1 Baseline Data Analysis

During Year 3 the Coordinating Center in collaboration with the Field Center investigators will plan and execute a thorough statistical analysis of the baseline data. These analyses will take two forms. First will be a series of analyses to describe the sample in terms of the baseline variables collected. The descriptive analyses will be primarily composed of simple tabulations for discrete variables, and the calculation of a variety of summary statistics for the continuous variables such as means, medians, variances, maxima and minima, etc., and graphical displays such as frequency distributions or density estimates. Extensive data checking will be a crucial component of these early analytic activities. In addition, standard, study-wide definitions for many of the key analysis variables will be developed. Early assessment of the comparability of variables among the different parent study populations will result in the identification of important differences in some variables that will either be addressed by additional data collection or adjustment through data analysis.

The second type of analyses will also make use of tabular procedures to investigate the interrelationship between/within the sleep variables and a variety of risk factors measured during the baseline examination as well as with measures of preclinical cardiovascular disease. In analyses of binary variables such as the presence or absence of sleep-disordered breathing, the usual epidemiological statistical methods for categorical information will be used; namely, the Mantel Haenszel test, the Mantel Extension test for trend, and the computation of odds ratios and their confidence intervals. Tests for potential interactions and adjustment for possible confounders will be done with logistic regression in which the relationship between the various sleep variables and risk factors will be modeled. For variables measured on a continuous scale, multiple regression procedures, based on either the original or transformed variables, will be used to test for potential interactions, to adjust for confounders, and to identify important exposures and estimate their effects. In all cases, interpretation of the rather extensive modelling will be conservative because of the problem of multiple testing that is always present in research of this kind.
Multivariate analyses will be emphasized so that the complex relationships between groups of exposure variables, confounding variables, and outcomes of interest can be thoroughly examined.

Missing value procedures will be used to identify and estimate the effects of missing values especially when they are associated with a particular population or an important risk factor such as left ventricular mass.

Baseline analyses will include comparisons of the SHHS cohort with the parent cohorts using data available from the parent studies. These analyses will look at how representative those sampled for SHHS are of the parent cohorts and will analyze differences between respondents and non-respondents among those sampled.

11.1.2 Accumulated Follow-up Results

As will be done in the analysis of the baseline data, extensive descriptive displays of the results of the follow-up and endpoint data will be provided. These will take the form of tables, plots, and descriptive statistics. The primary goal at this stage will be analyses that address the primary study hypotheses. A preliminary assessment will be made of the power to test these hypotheses based on the number of events that have accumulated by the end of follow-up. The statistical methods available to appropriately model relationships between events and the length of time until events and various risk factors with adjustment for potential confounders are multiple logistic regression and the Cox proportional hazards model, respectively. Estimates of relative risks and confidence intervals associated with the important risk factors will also be obtained. The major challenge in the application of these methods in this study is the potential heterogeneity of the covariate data collected from different parent studies. Random effects models and other statistical techniques will be used to identify and adjust for these various sources of variability.

Similar statistical methods will likely be used to address the secondary hypotheses. However, determination of the appropriate statistical methods will depend on the study design selected to address a particular hypothesis. Substudies done in selected cohorts may be used for collecting information pertaining to one or more of the secondary hypotheses.

11.2 Limitations

Associated with any epidemiological study are inherent limitations due to the study design. Inferences about relationships between risk factors and disease must always be more cautious than those from clinical trials. Selection bias in the Sleep Heart Health Study may, among other things, be related to the extent to which potential participants are willing to undergo home sleep monitoring. It may be possible to estimate selection bias on important characteristics by using comparable information from non-participants in the parent populations.

Inferences based on analyses using baseline data will be subject to the usual limitations of cross-sectional studies. The disease and risk factor information may be subject to substantial recall distortion. Reliable information on prevalent cardiovascular disease in the participants will be obtained through the use of standard study-wide classification procedures. While this study-wide review will increase the reliability of the classification of cardiovascular disease for the study participants, it may reduce the comparability with non-participants in the parent populations and hence, decrease our ability to estimate selection bias associated with prevalent cardiovascular disease status.

Combining information from parent studies with major differences in their populations, sampling designs, protocols and procedures is one of the major challenges of SHHS. Efforts have been made to identify potentially important risk factors and confounding variables and to obtain the maximum level of comparability across the various parent studies. Information on a subset of the important variables will be collected on all participants using standard, study-wide procedures, while other variables may have to be adjusted statistically. Clearly, analyses based on statistically adjusted

variables will have to be viewed cautiously. In addition, additional variables not measured in some participants may be responsible for major differences in the samples and cannot be adjusted for in the analyses. Only a study design based on randomization procedures can protect against these unknown effects.

In analyses of the cross-sectional data no estimate of the time effect or dose response can be made for the potential risk factors or confounders unless retrospective information can be obtained from the parent populations. However, such information will be available for a portion of the follow-up data.

In the baseline data the heterogeneity of samples selected from different parent populations may overwhelm the power that is obtained from the increased sample size. The magnitude of the effects to be estimated will determine the ability of the study to detect significant differences and associations using the cross-sectional data.

Analyses of the primary hypotheses will be based on end point information obtained during follow-up. The greatest limitation in the study's ability to adequately address the primary hypotheses will be the number of events available for analysis at the end of the follow-up period. It is likely that the majority of end points obtained during follow-up will occur in older participants who represent only a subset of the parent populations. Thus, the primary study results based on short-term follow-up may be applicable primarily to older populations because there will be insufficient end point data to give reliable information about the effects of sleep apnea in middle aged populations. A longer follow-up period may be necessary to overcome this initial distortion. Furthermore, sample size limitations in the minority populations may restrict inferences that can be made about differences in these populations.

Again, the potential lack of comparability among risk factors and confounding variables resulting from the combination of sample information from different parent populations is also of concern in analyses of the primary hypotheses. However, the standardized collection of information over the follow-up period may reduce a portion of the heterogeneity expected in the baseline data.

12. PROJECT GOVERNANCE

The SHHS consists of several key components: the six Investigative Centers, the Coordinating Center, the Sleep Reading Center, and the NHLBI. Operational mechanisms include several subcommittees, procedural guidelines, and budgetary and fiscal management policies.

12.1 Components

12.1.1. Investigative Centers

The investigative centers of the SHHS have been established at six universities, including: University of Arizona, Boston University, University of California-Davis, Johns Hopkins University, University of Minnesota, and New York University. The Principal Investigator (P.I.) at each of the investigative centers bears overall responsibility for that center's participation in the SHHS. The P.I. hires and supervises relevant personnel; oversees data collection and participates in quality assurance activities; prepares budgets and annual reports; obtains IRB approval for the study protocol; and represents the investigative center on the Steering Committee. As a member of the Steering Committee, each P.I. participates in the planning effort, including setting priorities and developing strategies to develop and conduct the study within the 5 year project period.

A study coordinator is supported at each of the participating investigative centers, who functions under the supervision of the P.I. The coordinator certifies personnel, establishes procedures to ensure adherence to the protocol and high-quality data, and is responsible for data entry in the distributed data entry system. The coordinator maintains investigative center files; serves as the primary contact between the investigative center and the Coordinating Center; and participates in protocol subcommittees as necessary.

12.1.2. Coordinating Center

The Coordinating Center, at the University of Washington, is responsible for statistical planning and accumulation of quality data from the investigative centers, training of the investigative center personnel, and the management of technical aspects of Coordinating Center activities. The Coordinating Center has subcontracted with Case Western Reserve University to establish the Sleep Reading Center.

The Coordinating Center will participate in and coordinate the development of the study protocol and Manual of Operations. It will also coordinate the integration of data from the parent cohorts, all supported by the NHLBI: Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Strong Heart Study (SHS), the Framingham Study, the Cornell Cardiovascular Center, Tucson Epidemiology Study of Obstructive Airways Disease and Tucson Health and Environment cohort. Coordinating Center investigators will design, produce, and test forms to be used in the study, and will develop, test, and implement the data entry system. The Coordinating Center is also responsible for arrangements for the Steering Committee meetings and minutes from these meetings. There will be frequent meetings during the first year of the study, with the number of meetings decreasing in the four subsequent years.

Quality and quantity of data from the investigative centers is monitored and reported by the Coordinating Center to the centers and to the Steering Committee. The Coordinating Center prepares confidential reports for the Data and Safety Monitoring Board (DSMB), as well as interim and final analyses and other specific statistical analyses and reports. The Coordinating Center supports manuscript preparation through data analysis, statistical consultation, editorial tasks and coordination of meetings.

The P.I. of the Coordinating Center is a voting member of the Steering Committee; other statisticians participate in the study and are assisted by research assistants, programmers, and data clerks.

12.1.3 Sleep Reading Center

The Sleep Reading Center (Reading Center) at Case Western Reserve University will serve as a centralized laboratory to provide standardized scoring and interpretation and quality assessments of all sleep studies obtained as a part of this study. It will assist the Coordinating Center in establishing all procedures related to obtaining sleep data that best meet study objectives and in implementing these procedures. The Reading Center will be responsible for: assisting in protocol development; developing performance standards for sleep studies; developing a Manual of Operations for unattended and laboratory-based sleep studies; coordinating the purchase and maintenance agreements for sleep equipment; developing and maintaining software for sleep data processing; training sleep technicians centrally; providing technical support services to the field centers; ascertaining and reporting on the quality of sleep studies; providing centralized sleep scoring of unattended and laboratory-based sleep studies; interpreting sleep studies and providing sleep reports to the field centers; assisting in data analysis, and development of ancillary and nested studies. The Director of the Sleep Reading Center will be a voting member of the Steering Committee.

12.1.4 National Heart, Lung, and Blood Institute (NHLBI)

The NHLBI is responsible for organization and providing support for the SHHS in accordance with the allocation of resources that have been provided for this program. The administrative and funding mechanism is the cooperative agreement, an assistance mechanism. Under the cooperative agreement, the NHLBI assists, supports and/or stimulates, and is involved substantially with recipients in conducting a study by facilitating performance of the effort in a “partner” role. Consistent with this concept, the tasks and activities in carrying out the study will be shared among the awardees and the NHLBI Project Scientist. The NHLBI Project Scientist has substantial responsibilities in protocol development, quality control, interim data and safety monitoring, final data analysis and interpretation, preparation of publications, collaboration with awardees, and coordination and performance monitoring.

On behalf of the NHLBI, the Project Scientist has lead responsibilities in quality control and interim monitoring of data and safety and may recommend to the NHLBI modification or termination of the study based on advice from the Data Safety Monitoring Board. The NHLBI Project Scientist may, consistent with publication policy to be adopted by the Steering Committee, have lead responsibilities in the preparation of some publications. The NHLBI Project Scientist has voting membership on the Steering Committee and, as appropriate, its subcommittees.

12.2 Committees

12.2.1 Steering Committee

The Steering Committee is the main governing body of the SHHS with responsibility for setting priorities and for the design, implementation and interpretation of all investigations. The Steering Committee assures compliance with policies and procedures; facilitates the conduct and monitoring of the study, participates in analysis and interpretation of data; and assures that study results are reported in the scientific literature in a timely manner.

The Chairperson of the Steering Committee is elected by the Steering Committee by majority vote and need not necessarily be a P.I. from a participating investigative center. The Chairperson plans SHHS activities and oversees its functions. The Chairperson conducts meetings, casts tiebreaking votes and represents SHHS at the Data Safety Monitoring Board meetings.

Voting members of the Steering Committee include the P.I. from each investigative center (or the designated alternate); the P.I. from the Coordinating Center (or the designated alternate); the director of the Sleep Reading Center, and the NHLBI Project Scientist. Other, non-voting attendees at Steering Committee meetings may include other NHLBI staff; other Coordinating Center staff; other investigative center participants; other expert consultants invited to committee meetings as needed. The membership of Steering Committee is listed in Appendix 5.

After completion of the start-up phase of the study (typically after the first year), the Steering Committee meets two to three times each year, with additional meetings (or telephone conference calls) as needed.

12.2.2 Subcommittees of the Steering Committee

The Steering Committee is responsible for the formation and termination of various subcommittees which report back to the Steering Committee. The subcommittees accomplish their tasks in meetings and conference calls. Minutes are prepared for each conference call and are submitted to the Steering Committee. The membership of the subcommittees is listed in Appendix 5.

Publications and Presentations Subcommittee:

The Publications and Presentations Subcommittee is charged with developing publication and presentation policies. A P.I., elected by the Steering Committee, serves as the Chairperson (which may be a rotating position). A major responsibility of the committee is to develop a process for review of all publications and abstracts from SHHS studies that are undertaken within each of the investigative centers. All policies require approval of the full Steering Committee prior to implementation.

Morbidity and Mortality Subcommittee

The Morbidity and Mortality Subcommittee is responsible for advising the Steering Committee on matters related to the choice of and operational definitions of cardiovascular, neurobehavioral, and quality-of-life outcomes. The Subcommittee will evaluate the comparability of the ascertainment methods and operational definitions used by the parent studies to determine the occurrence of

cardiovascular disease. On the basis of this evaluation, the Subcommittee will recommend whether or not the SHHS should rely on parent study determinations of cardiovascular outcomes. The Subcommittee will also develop specific recommendations regarding the choice of instruments for assessing neurobehavioral function and quality of life. During the course of the Study, the Subcommittee will monitor the quality of the data being collected for all of the relevant outcomes.

Design, Sampling and Recruitment Subcommittee

The SHHS cohort will be comprised of six site-specific cohorts selected from ongoing epidemiologic studies. For some of the sites, the cohort may be selected from more than one parent cohort. The Sampling Subcommittee is responsible for discussing and recommending to the Steering Committee general guidelines for selection of the SHHS cohort. The Sampling Subcommittee identifies priorities for sampling as well as inclusion and exclusion criteria. In addition, representatives from each site provide a site-specific plan for recruitment to be reviewed by the entire Sampling Subcommittee. Representatives from the Coordinating Center provide power calculations for the study. The Sampling Subcommittee contributes sections of the protocol on sampling of the SHHS cohort and, with contribution from the Coordinating Center, develops procedures for reporting progress in recruitment. As with all other subcommittees, final decisions and approval are the prerogative of the Steering Committee.

Comparability Subcommittee

This subcommittee is responsible for determining the comparability of data collected in the various cohorts, and reviewing and revising the prioritization list of covariates. This subcommittee will also request data and/or questionnaires and protocols from the parent studies as needed for comparison activities.

Polysomnography Subcommittee

The purview of this committee is selection of study equipment, determination of variables to be measured, definitions, and development of the protocol. Feasibility studies will be conducted at the Sleep Reading Center and possibly at some or all of the sites. Once subject enrollment has begun, this subcommittee will also be responsible for quality control of the sleep studies.

Questionnaire and Interview Subcommittee

This subcommittee is responsible for developing materials for self-report data collection and for communication with participants. These materials include questionnaires and documentation (such as coding guides) as well as such as consent forms, recruitment and retention materials, participant assessment forms, and sleep study results reports for participants and their physicians.

Quality Control Subcommittee

The Quality Control Subcommittee has been charged with coordinating and directing all SHHS quality assurance and control activities. Working with the specialty subcommittees and the Coordinating Center, the Quality Control Subcommittee determines the areas of emphasis for each

routine quality control report in response to priorities for quality assurance developed by the Steering Committee. The subcommittee also reviews all reports with specific attention to deviations from protocol, recurrent problems and trends, and shifts in data over time.

The Quality Control Subcommittee prepares recommendations to the Steering Committee concerning quality assurance and control and contacts Field Centers, the Reading Center or Coordinating Center as needed to advise them of problems and to discuss mechanisms for correction. The Quality Control Subcommittee will meet monthly during data collection years, and then periodically thereafter.

Operations Subcommittee

The Operations Subcommittee, which is comprised of a representative from each study site, discusses general operational issues, shares information on, and experience from, ongoing recruitment, and helps to solve site-specific problems. The Operations Subcommittee reports to the Steering Committee and, when deemed necessary, requests input of the Steering Committee on central operational issues.

12.3 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is responsible for review of study data in order to insure quality, and safety of study subjects and to provide NHLBI advice on progress of the study.

The DSMB members are appointed in accordance with established NHLBI policies. The members will be experts in sleep, pulmonary medicine, cardiovascular medicine, epidemiology, ethics, multi-center studies and basic science. Members of the DSMB will not be participants in the SHHS nor will they be associated with institutions participating in the SHHS. The Chairperson and all members will be appointed by, and responsible to, the Director, NHLBI. The P.I. of the Coordinating Center and/or other SHHS Investigators, as determined by the Steering Committee will attend DSMB meetings to present data. The NHLBI Project Scientist will serve as executive secretary of the DSMB. If necessary, the chairperson of the Steering Committee will be contacted (by mail or phone) to answer questions.

The DSMB will meet semiannually (twice a year) to ensure participant safety and/or study integrity. The DSMB will monitor data quality, including protocol adherence, and identify emerging operational issues. The DSMB may recommend protocol modifications or early termination of the study based on concerns for subject welfare or scientific integrity. All data and deliberations of the DSMB will be strictly confidential.

The DSMB will be privy to statistical data and case reports required for its deliberations. It will review interim reports of subject accrual and outcome measures provided by the Coordinating Center. Each report will include tabulations of study subject characteristics, major clinical events, and primary outcomes arranged by investigative center. After reviewing each such report, the DSMB will assess the need to perform further in-depth evaluation of the benefits and risks of continuing the study.

If it is determined that the study objectives have been satisfied based on data accrued to date; if subject safety would be compromised by continuation of the study; or if there are severe unanticipated problems with study conduct, that is, inadequate recruitment or problems with equipment, etc., the DSMB may recommend to the Director of the NHLBI that the study be terminated or suspended. The NHLBI would work with members of the Steering Committee to assure appropriate steps are taken to implement the recommendations of the DSMB.

A complete list of SHHS committees and an organizational chart are included in Appendix 5.

13. WOMEN AND MINORITIES

Guidelines of the National Institutes for Health specify that populations should be selected to assure representation of the population, including minority groups and women, to the fullest extent possible. To maximize representation of minority populations, all minority participants in the parent cohorts will be recruited for the SHHS; 600 members of the Strong Heart Study, which includes only Native Americans, will be recruited such that over 10 percent of the full cohort for the SHHS will be Native American. The other cohorts will contribute approximately 450 African Americans, 280 Hispanics, and 70 Asian Americans. Thus the total minority membership of the cohort will be approximately 1400 participants.

In order to assure adequate representation of women, equal numbers of men and women will be recruited, so that the cohort will be comprised of approximately 3000 women and 3000 men.

14. HUMAN SUBJECTS

The study is purely observational and therefore poses minimal risks to the participants. The chosen monitor (Compumedics) is battery-operated and therefore risk-free. While some subjects reported discomfort sleeping with the monitoring equipment during the feasibility study, most felt the experience was positive overall and that the information gained was worth the discomfort experienced. Any medical alert values noted for blood pressures, heart rate, or oximetry values will be reported according to the protocol outlined in the Manual of Operations.

IRB approval for the full protocol will be obtained by each Investigative Center locally. Site-specific consent forms will be used to meet the specific requirements of the IRB committee at each institution. The consent form will be signed either at the time of recruitment or on the night of the sleep study.

15. CONFLICT OF INTEREST

No participating investigator or their immediate family may hold a financial interest in, nor be employed by, any company which supplies equipment, drugs, or other materials for the study. Annual reports and certification of lack of conflict of interest will be submitted annually to the NHLBI. The complete conflict of interest policy is found in Appendix 6.

16. CONFIDENTIALITY

Each subject will be identified by the unique ID number assigned by the parent cohort. Personal identifiers will be kept at the corresponding Field Center. Participant names will not be used on any SHHS data files; only ID numbers will occur on paper forms, PSG data files, and all data files created from the paper forms or covariate data obtained from the parent cohort. Paper forms will be kept locked in file cabinets at the field centers. Only authorized study personnel will have access to the study data. The Coordinating Center will maintain only data files, not data collection forms. Results will be reported in an aggregate form without personal identifiers.

The Coordinating Center is located in an office building that has very good external security. The building has a 24-hour manned security desk, and key-cards keyed for a particular floor of the building are required in order to use the elevators outside of regular working hours. For internal

security, only staff working on SHHS will have access to the Coordinating Center computers. Passwords are required to access the databases maintained at the Coordinating Center. Data files are backed-up on a regular basis with an extra set stored off-site in a locked office. Only authorized users will have access to back-up files.

All study personnel will sign a statement of confidentiality.

APPENDIX 1

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APPENDIX 2

SUB-STUDIES

Sleep Disordered Breathing (SDB) is associated with abnormalities in hemostatic factors (hypercoagulation and thrombosis).

Secondary hypothesis # 11

Hypoxemia is associated with systemic vasoconstriction, which can trigger endothelial risk factors that are active in clothing and vasoconstriction. Nested exploratory studies on the association between SDB and hemostatic factors will be conducted, using data from SHHS cohorts that have collected hemostatic data (ARIC, CHS, FHS, SHS&&?).

SDB is associated with incident and progressive abnormalities in carotid artery atherosclerotic change as detected by ultrasound.

Secondary hypothesis # 6, 15

Hypoxemia may be involved in atherogenesis, and repetitive hypoxemic cycles caused by sleep apnea may accelerate the atherosclerosis process in a fashion similar to that demonstrated in animal models. Some of the SHHS cohorts have conducted repeated ultrasound examination of the carotid arteries (ARIC, CHS, FHS). Ancillary studies on the relation between SDB and carotid atherosclerosis prevalence and progression will be conducted in these cohorts.

SDB is associated with automobile and work-related accidents.

Data would be collected as to the number and timing of automobile and work-related accidents (number in the last 5 years, and ever) from a questionnaire which could be given after intake and at intervals (e.g., at time of follow-up for CV morbidity/mortality). This could be done in a mailing so as to be less threatening to the subjects.

Data will be collected on the burden, costs, and compliance with treatment of SDB. (Hopkins)

Based on the assessment of prevalence of SDB in the SHHS cohorts, the potential costs for treatment of undiagnosed sleep apnea in the population will be estimated.

Although the home sleep studies are research oriented and not aimed to the diagnosis of SDB, participants with severe sleep apnea will be alerted. In follow-up contacts with these participants, the compliance with the referral and recommendations, as well as the costs and burden in participants who underwent any treatment will be assessed.

The presence of SDB relates to the circadian timing of CVD events.

Secondary hypothesis # 12

SDB is associated with sleepiness, abnormalities in neuropsychological function and adverse mood.

Secondary hypotheses # 3, 8, 9, 10

This would be done as a nested substudy. Sampling would be based on the completed PSG and would be based on categorization of subjects as normal, hypopneic and apneic, with matching for sex, age and IQ (and possibly for weight). Testing would include a full battery

of psychometric tests with specific measures known to be affected by sleep fragmentation (sleepiness) and by hypoxia, to be administered by trained personnel. Testing would require approximately 3 hours per subject at a time near to the PSG.

SDB is associated with nocturnal hypertension and changes in the profile of 24 hour BP (ambulatory).

Secondary hypothesis # 13

Ambulatory BP would be categorized by presence/absence of nocturnal dipping, mean daytime BP and mean nocturnal BP. These outcomes would be examined in the subjects with sleep data using the measures of SDB as the "exposure," as in the primary hypotheses of the SHHS. This study requires no additional data collection in at least the NYU/Cornell Cohort, as all subjects in the cohort have a 24 hr BP monitoring session.

Upper Airway Resistance Syndrome (measured by the presence of flow limitation without apnea or hypopnia, detected by the nasal cannula technique) is associated with the same outcomes as proposed in the primary hypotheses of the SHHS.

Upper airway resistance syndrome would be defined by the presence of repetitive events of flow limitation (from the data collected by the nasal cannula, and detected by either visual inspection of the record or by an automated computer program provided by the NYU site). In effect, a new exposure variable for SDB is defined using the number of flow-limitation events (runs of 10-300 seconds of continuous flow-limited breaths ended by a series of 2 or more normal breaths), which can be used alone if apnea/hypopnia is absent (UARS), or added to the AHI if apnea/hypopnia is present. Another variation on defining the "exposure" is to quantitate the percent of breaths or total time during sleep spent in flow limited breathing (as defined above). Using these as the exposure variables, the primary hypotheses of the SHHS on CV mortality/morbidity will be re-examined. This study requires no additional data collection if the nasal cannula is used as the primary detector of airflow during sleep. If this detector is not used in the entire cohort, we propose it be used in a subset of subjects (eg the NYU/Cornell cohort).

Events of elevated upper airway resistance (measured by the presence of 10-300 sec runs of flow limited breaths detected by the nasal cannula technique) are predictive of arousal and disrupted sleep.

As in the above study, this is an analysis of the data on SDB as defined by the nasal cannula method of detecting air flow. The correlation between this index of SDB and measures of arousal from analysis of the PSG would be made using number and distribution (FACE) of arousals, time in Stage 1, etc. This study requires no additional data collection if the nasal cannula is used as the detector of airflow.

Actigraphy (number and pattern of movements during sleep) can be used as a surrogate for full polysomnography in characterizing the disruption of sleep.

Actigraphic data would be used to test the hypothesis that movements greater than a threshold value (25% of the amplitude of pre-sleep movement amplitude) indicate a brief or sustained arousal. The number and distribution of these movements would be related to the characterization of sleep from the PSG. Data collection consists of wearing an actigraph (a wrist watch sized device worn on the arm) for 1-3 days. These data are already collected in a

large subset of at least the NYU/Cornell cohort. If done simultaneously with the PSG, this would directly address the hypothesis above. Actigraphic data from non-PSG nights would also help evaluate night to night variability in sleep disruption if actigraphy is validated as being a surrogate for the full PSG. This could help address the issue of how representative the PSG night is of normal sleep in the subject. Actigraphic data can be obtained by placing the actigraph at the time of any patient contact (eg the PSG) and having the actigraph dropped off at a collection site or mailed back 3 days later in pre-addressed mailers.

Characterization of actigraphy in the present cohort is related to the outcomes proposed in the primary hypotheses of the SHHS.

Actigraphic data as defined in the previous substudy would be analyzed as the exposure variable (quantitating sleep disruption) in the SHHS primary hypotheses about CV mortality/morbidity.

Comparison/validation of the CompuMedics system with other modes of recording PSG data.

Comparison/validation of home vs. laboratory based PSG data collection.

Short term variability of PSG (repeat short-term studies).

Longitudinal change in home PSG (repeat long-term studies) and relationship to changes in CV disease status.

SDB is associated with incident and progressive abnormalities in LV dysfunction as assessed by cardiac ultrasound.

Secondary hypotheses # 5, 15

SDB is associated with incident and progressive abnormalities in cerebrovascular disease as assessed by MRI.

Secondary hypothesis # 15

SDB is associated with elevated urinary catecholamines.

SDB is associated with an abnormal ankle arm index.

Secondary hypothesis # 15

The ratio of the Ankle to Arm Systolic Blood Pressure (AAI) is usually greater than 1.0. A reduction usually indicates obstruction to blood flow in the leg due to atherosclerosis. It has been measured in all parent studies for SHHS except for the cohorts of the NYU/Cornell investigative center. The NYU/Cornell center will follow the protocol of CHS.

Participants at risk for incident cardiovascular disease will be classified as having subclinical CVD if the AAI is <0.9 in either leg. Other substudies may be done combining the AAI with other noninvasive/measures of atherosclerosis available including carotid ultrasound and echocardiography. The AAI is the only marker of subclinical disease that will be done in all SHHS participants.

We hypothesize that SRBD will be associated cross-sectionally with a low AAI. Another hypothesis that can be tested longitudinally is that subjects with a low AAI and SRBD are

more likely to develop clinical CVD than those that with a low AAI without SRBD, that is, that SRBD may precipitate clinical events in those with subclinical disease.

SDB is associated with abnormalities in the nocturnal ECG (arrhythmias and ST-T changes).

Secondary hypothesis # 7

Indices of SDB would be correlated with the prevalence of arrhythmias and ST-T wave changes observed on the nocturnal PSG. In addition, it would be determined whether individuals who have both SDB and nocturnal ECG changes have a higher incidence of CV adverse outcomes. This study would require no collection of additional data.

Restrictive, obstructive ventilatory impairment and low awake oxygen saturation increase the CV risk associated with SDB.

Secondary hypothesis # 14

Self reported sleep problems are associated with increased CV adverse outcomes.

Secondary hypothesis # 17

Indices from the existing SHHS Sleep Questionnaire would be used as the exposure variable in addressing the primary hypotheses of the SHHS relating to CV mortality/morbidity.

APPENDIX 3 **Outcome Variables Collected by Parent Cohorts**

Key: X = collected; --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
MI	X	X	X	X	X	---
CHD Death	X	X	X	X	X	---
Non-fatal Stroke	X	X	X	X	X	---
Fatal Stroke	X	X	X	X	X	---
Angina Pectoris	X	X	X	---	X	---
TIA	X	X	X	---	X	---
Intermittent Claudication	X	X	X	---	X	---
Incident Hypertension	X	X	---	X	---	---
Death	X	X	---	X	X	X
CHF	X	X	X	---	X	---
Pulmonary Disease	---	---	---	---	---	X
Coronary Artery Bypass	X	---	---	X	---	---
Coronary Angioplasty	X	---	---	X	---	---

Potential Risk Factors Collected by Parent Cohorts

Key: X = collected; --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
DEMOGRAPHICS						
Age	X	X	X	X	X	X
Gender	X	X	X	X	X	X
Race/Ethnicity	X	X	X	X	X	X
Marital Status	X	X	X	X	X	X
SES						
Education	X	X	---	X	X	X
Occupation	X	X	---	X	X	X
Family Income	X	X	---	X	X	X
OBESITY/OVERWEIGHT						
Weight	X	X	X	X	X	X
Standing Height	X	X	X	X	X	X
Skinfolds	X	---	X	---	---	---
Girths	X	X	X	X	X	X
Neck circum.	---	X	---	---	X	---
Bioelectrical impedence	---	X	X	---	---	---
BLOOD PRESSURE/HYPERTENSION						

Potential Risk Factors Collected by Parent Cohorts

Key: X = collected; --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
BP measured	X	X	X	X	X	X
Personal History	X	X	X	X	X	X
BP treatment	X	X	X	X	X	X
MEDICATIONS						
Current -- last 2 weeks	X	X	X	X	X	X
SMOKING						
Current/Past?	X	X	X	X	X	X
Current # cigs	X	X	X	X	X	X
Average past # cigs	X	X	X	---	X	X
Year Start	X	X	X	---	X	X
Year Quit	X	X	X	X	X	X
ALCOHOL INTAKE						
History	X	X	---	X	X	X
Habits	X	X	X	X	X	X
Type	X	X	X	X	X	X
SUBCLINICAL CVD						
ECG, 12-lead	X	X	X	X	X	X
B-mode Ultrasound						

Potential Risk Factors Collected by Parent Cohorts

Key: X = collected; --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
Carotid	X	X	X	Some	X	---
Popliteal	X	---	---	---	---	---
Abd. aorta	---	X	---	---	---	---
Holter	---	X	---	---	---	---
Echocardiogram	---	X	X	Some	X	---
MRI	---	X	---	---	X	---
Ankle-Arm Index	X	X	X	---	X	X
FAMILY HISTORY CVD						
Parents	X	X	---	X	X	X
Siblings	X	X	---	X	X	---
DIABETES						
Personal History	X	X	---	X	X	X
Fasting glycemia	X	X	X	X	X	---
Fasting insulin	X	X	X	---	X	---
Post-load insulin	---	---	X	---	---	---
Glucose tolerance	---	X	X	---	X	---
LIPIDS						

Potential Risk Factors Collected by Parent Cohorts

Key: X = collected; --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
Total cholesterol	X	X	X	X	X	X
Triglycerides	X	X	X	X	X	---
HDL	X	X	X	X	X	---
LDL	X	X	X	---	X	---
Personal history hypercholest.	X	X	---	---	---	---
RESPIRATORY DISEASES and SYMPTOMS						
Chronic bronchitis	X	X	X	---	X	X
Asthma	X	X	X	---	X	X
Emphysema	X	X	---	---	X	X

Variable	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
Snoring	---	X	---	---	X	X
Frequency of snoring	---	X	---	---	X	X
Loudness of snoring	---	X	---	---	---	---
Ever stopped breathing	---	X	---	---	---	---
Stopped breathing frequency	---	X	---	---	---	---
Epworth Sleepiness Scale	---	X	---	---	---	---
Often feel tired	X	X	---	---	---	---
Often have trouble falling asleep	X	X	---	---	---	X
Trouble staying asleep	---	---	---	---	---	X
Wake up repeatedly at night	X	X	---	---	---	---
Wake up feeling exhausted	X	X	---	---	---	---
Wake up breathless	X	X	---	---	---	---
Don't get enough sleep	---	---	---	---	---	X
Get too much sleep	---	---	---	---	---	X
Wake up too early and not being able to get back to	---	---	---	---	---	X
Falling asleep during the day	---	---	---	---	---	X

Variable	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
Nightmares	---	---	---	---	---	X

APPENDIX 4

Equipment Evaluation

The process of choosing sleep monitoring equipment involved: (1) defining the procedures and signals needed to most appropriately address the SHHS hypotheses; (2) evaluating the feasibility and trade-offs of alternative approaches for collecting these data (including a feasibility study); and (3) soliciting input from industry, including participation in local (Cleveland) and central (Steering Committee) demonstrations of equipment.

a. Defining the needs.

The Polysomnography (PSG) Committee, composed of William Bonekat (Sacramento), Paul Enright (Tucson), Daniel Gottlieb (Framingham), Conrad Iber (Minnesota), Mark Sanders (Pittsburgh), Philip Smith (Baltimore) and Susan Redline (Chair, Reading Center), met regularly by conference call and at Steering Committee meetings. (PSG member David Rapoport, New York, was not involved in these deliberations.) Based on data from the literature and personal experience, the following measurements were identified as needed for collection of the *minimally necessary* data for assessment of sleep disordered breathing and its relationship to cardiovascular morbidity:

[a] Oximetry (finger pulse): To gauge hypoxic stress, needed for event identification.

Heart Rate (ECG): To identify autonomic variability, bradytachycardia (i.e., cardiac outcomes).

Chest wall and abdomen movement (piezoelectric or inductance bands): To distinguish central from obstructive events.

Nasal/oral airflow (thermistry and/or pressure-flow): essential for the identification of respiratory events.

Body position (mercury gauge): To identify positional apnea.

A more complete montage, that would permit precise measurement of sleep time, allow sleep staging, and permit arousal detection, would additionally require measurements of:

[b] EEG (2 central; one for redundancy in case of failure/loss)

EOG (bilateral); chin EMG (identified after pilot work indicated the difficulties in identifying REM-specific arousals without these data.)

These additional measurements would improve the classification of apneic activity by providing an accurate determination of how much of the monitoring time was spent asleep; by gauging the impact of sleep apnea on sleep continuity (fragmentation); and by collecting data on physiological responses thought important in the pathogenesis of apnea-associated heart disease.

These measurements were determined to be needed in at least a sample of subjects studied with the "minimal" montage, to establish the validity and/or define the limits of the non-EEG studies, and, possibly, to resolve ambiguous non-EEG studies.

Other measurements, often considered part of full sleep studies, which were not recommended for collection were: snoring (poorly standardized collection and analysis procedures); and leg movements (cumbersome in free living subjects, not directly relevant to the SHHS hypotheses).

Either the "minimal" ([a], above) or the more complete montage, would require data collection with systems that were comparable across clinical sites and were capable of storing data electronically in a format compatible with a single software analysis system. The home was determined to the optimal setting for the majority of studies because of participant acceptability, cost, and (possibly) for minimization of a "first-night" effect. The sleep laboratory was identified as a potential setting for the EEG-based studies. However, a survey of the participating sleep laboratories revealed the lack of common computer-based sleep data acquisition units. Thus, all studies (including those with EEG) would require the purchase of equipment with EEG capacity specifically for use in the SHHS.

b. Trade-offs and feasibility.

The advantages/disadvantages of collecting all data with a single home visit with EEG-based equipment (Approach 1) was compared to home collection of (a) above, with EEG data collection in only a sample (with either a second home or in-laboratory study) (Approach 2).

Approach 1 (collect the full montage in the entire cohort using in home, EEG capable systems.

Advantages:

Use of a widely-accepted montage, producing study results that likely would have good credibility in the larger scientific community.

Would minimize misclassification of apneic activity due to either: overestimation of sleep time (very relevant in older populations who often have fragmented sleep), or underestimation of respiratory events which cause arousals without desaturation (possibly common in the general population, and also associated with the newly recognized "upper airway resistance syndrome."

Would allow assessment of stage-specific respiratory events (i.e., to pursue hypotheses about REM-specific apnea).

Would minimize the number of contacts/participant (compared to a 2-stage sampling strategy), possibly saving costs and reducing subject burden.

Would provide a large amount of data useful for defining the abilities of different types of sleep measures to predict morbidity, thus, contributing to a much needed literature on criteria for sleep study procedures.

Disadvantages:

Few precedents for collection of these data in a large scale study (little known about feasibility and acceptability).

Longer time needed for hook-ups.

Immense data storage requirements.
Larger data processing costs.

Increased subject burden, associated with longer hook-ups and use of more cumbersome equipment.

Approach 2

Advantages:

Previous experience in research settings.

Simpler hook-ups, potentially higher technical success rates, and less hook-up time.

Disadvantages:

Less data and potentially more misclassification (poorer ability to estimate sleep time, and limited arousal and sleep data.

Potentially more complicated sampling frames, and more subject contacts (for secondary EEG studies).

PSG Feasibility Pilot Study: Assessment of Multichannel Testing in the SHHS Cohort

A pilot study was undertaken to evaluate the use of two different in-home PSG machines, the MiniSomno (Approach 1) and the Edentec (Approach 2), to gauge whether the subject burden would be minimal enough to justify the increased information obtainable with the MiniSomno. In addition, the recruitment process and the sleep habits questionnaire were piloted.

The pilot study was planned in February, 1995, with sleep studies to be scheduled in March, 1995.

Objectives

The objects of the evaluation of the in-home machines were to determine:
(1) subject acceptability of multichannel in-home sleep and respiratory recording in the SHHS cohorts,
(2) an EEG system alters subject acceptability,
(3) time requirements for hook-up and downloading of each system,

(4) any gross differences in subject acceptability and technical failure rates according to age, gender, site and cohort effects, and
(5) the willingness of participants to participate in a second assessment, in the eventuality of a poor initial technical study.

Other issues that were identified for exploratory analyses:
(1) technical failure rates, and
(2) time/technician costs.

Subjects

Participants were recruited from the following sites: Sacramento, Pittsburgh, Minnesota, Baltimore, Washington County -ARIC and Hagerstown, South Dakota, and Tucson. A target of 10 participants per site was set. Subjects were to be randomly assigned to one of the two machines, resulting in approximately 35 evaluated on each machine. However, for logistical reasons some subjects were not randomly assigned, some used volunteers instead of parent study subjects, and one site only piloted the Edentec. Technicians were trained on equipment use and on the protocol at the Reading Center in Cleveland, OH.

Data Collected

A "contact form" was developed for the recruitment process of this pilot study. This form provided the demographic characteristics of those contacted and their interest in participation. However, different sites used different methods for recruiting their subjects. Some sites completed contact forms for only those who agreed to do a PSG study, some sites returned all recruitment contacts attempted, and one site did not use the contact form for recruitment.

Before and after the PSG study, the technicians completed "worksheets" to collect data on hook up and pickup times and made notes on problems encountered while doing the PSG study. In addition, an "assessment" survey was completed by the participant regarding their experiences with the sleep study equipment and components, and how the equipment may have impacted their usual waking and sleeping activities.

A "sleep habits" questionnaire was also administered to participants. This questionnaire inquired about typical sleeping habits (e.g., sleep time, problems sleeping, problems with daytime sleepiness, etc). This data was collected on all those who consented to a PSG study. In addition, some sites used this questionnaire as a recruitment form, thus including additional data on nonparticipants as well.

RESULTS

Overview

The total number of subjects contributing data to the study was 138. Of these, 78 agreed to do an in-home sleep study (32 using MiniSomno and 46 using the Edentec). Of these 78, five studies could not be evaluated due to data errors/equipment failures. Two of the study participants actually had physical disabilities which precluded them from completing a PSG study. Thus, there were 71 PSG studies to evaluate.

Initial contact and recruitment (Table 1)

Contact forms were completed and returned for 128 individuals. This group was comprised of 59% females and an average age of 69 years. The contact forms yielded 68 participants for home sleep studies. Of the remaining subjects, 30 refused, 24 were unlocateable, and 4 were unable to participate due to illness. Most of those unlocateable were a result of the telephone recruitment strategy and most occurred in the Tucson cohort.

Technician worksheet results (Table 2)

Those participating in the home sleep studies were an average of 68 years of age and 52% were females. Each site contributed anywhere from 10 to 15 participants per site. There were 46 Edentec studies done and 32 MiniSomno studies scheduled. Two of these 78 sleep studies could not be done due to physical limitations of the participants. The required hook up time for the Edentec was an average of 37 minutes, 8 minutes less than the average of 45 minutes for the MiniSomno. The average pick up time the next morning were similar for both machines, about 18 to 22 minutes.

Sleep Habits Questionnaire (Table 3)

This questionnaire was administered to more subjects (18 more) than those who consented to do a sleep study. Most people did not have difficulty completing the questionnaire. There were only a few missing values, except on the snoring and stopped breathing questions.

There was a very wide range in habits in terms of when people go to sleep at night and when they wake up in the morning. Most people (80%) fell asleep within 20 minutes of going to bed and average about 7 hours of sleep per night. About two-thirds of the sample took naps with an average of 4 naps per week. About 10 to 20% of the participants reported troubles with falling asleep or falling back to sleep. Less than 10% reported problems with feeling sleepy during the day or that they don't get enough sleep at night. Eight percent reported use of sleep medications.

Key questions of interest regarded snoring status and characteristics and problems of stopped breathing while sleeping. Seventy-eight percent of the sample answered yes to "have you ever snored." The remaining were split between "no" (12%) and "not sure" (11%). Many people indicated they were unsure as to "how often" they snored (21%), the "loudness" of their snoring (25%), the number of "years of snoring" (70%), and whether their snoring is increasing or decreasing over time (42%). Thirteen percent of the entire group (n=96) had indicated they had "stopped

breathing" while sleeping. But, 38% were unsure as to whether this had ever happened to them. Only 3 subjects indicated they'd actually been told by a doctor that they had sleep apnea.

Twenty-six percent of the participants were often or almost always awakened from their sleep by pain in the joints, muscles, or back. Many (61%) were often or almost always awakened by the need to go to the bathroom.

Participants had moderate to high likelihood of dozing off while in the following situations: sitting and reading (45%), watching TV (47%), sitting in public place(18%), as a passenger in the car (24%), lying down to rest (63%), and after lunch (23%). Only a small percentage (1-3%) had moderate to high chances of dozing off while sitting and talking to someone, stopped in traffic for a few minutes, at the dinner table, while driving, or during routine activities.

Comparison of Edentec to MiniSomno (Table 4)

There were 46 Edentec and 32 MiniSomno studies scheduled. The Edentec had slightly less problems associated with it than did the MiniSomno. In terms of the hook-up procedures, 87% of the MiniSomnos and 91% of the Edentec had very little or no difficulty with this. Both machines had very little or no discomfort reported for the attachment of lead wires, ECG pads, gluing sensors, taping of oxygen sensor on finger, and taping of eye sensors.

Eighty-nine percent of the Edentec wearers had little or no interference with normal evening activities compared to 81% of the MiniSomnos. Thirty-one percent of the MiniSomno users reported moderate to a great deal of difficulty in falling asleep while wearing the equipment (as compared to 15% for Edentec). Staying asleep was more difficult for the MiniSomno users (37% compared to 11% in Edentec) and were more likely to be awakened by the discomfort of the system, tossing and turning, and getting comfortable in bed. Participants, in general, worried about the equipment causing the participants to wake up.

In general, for either machine, the different parts of the system did not cause much discomfort. The only exception was the sensor over the lip, where 24% of the MiniSomno users reported moderate to a great deal of discomfort (compared to 8% of the Edentec users). Most participants had very little or no discomfort when the ECG pads or paste from hair were removed. When asked to compare this procedure to other procedures they had undergone, 20% of the Edentec versus 43% of the MiniSomno users said it was less comfortable than those other procedures. About seventy percent of the participants, for both types of equipment, said they would be willing to do the sleep test again.

On a more informal level, study coordinators and Investigators conducted unstructured interviews to gauge overall attitude toward the study. The majority of participants, in each equipment group, reported the experience to be positive, expressing interest in sleep information.

On the basis of this, it was concluded, that although subject burden is greater with use of more complicated equipment, the burden did not generate negativity about overall study participation. Approach 1 was chosen.

PSG Results (Table 5)

Of the 78 studies attempted, two were not doable due to physical disabilities of the subjects and five others were lost due to mechanical/data transfer errors (9%). In terms of overall quality of the

remaining studies (n = 71), 51% yielded excellent results with all channels good. The results were OK with at least 1 channel problematic in 23% of the studies. Ten percent of the studies were OK but had more than 50% of the channels problematic. Five percent of the studies were uninterpretable.

The apnea-hypopnea index (AHI) ranged from 0.29 to 64.38. Twenty-three percent of the completed studies had AHI scores of five or less. Five subjects (8%) had AHI scores greater than 40 points. The mean AHI score was 16.5 (SD = 17.1) and the median score was 10.4.

The arousal index, only available from the MiniSomno studies, ranged from 0.14 to 21.79. The mean response was 8.6 (SD = 7.6) and the median response was 8.5. The correlation between the arousal index and the AHI score was not significantly different from zero (r = 0.14; p-value = 0.54).

Table 1
SHHS PSG PILOT STUDY: Results of Contact Form
(N=128)

1. Age of Participant	Mean	SD
(years; 44% missing)	69.15	13.77

2. Gender

	n	%
Female	73	59
Male	51	41
(Missing)	4	
Total	128	100

3. Parent Study

	n	%
CHS**	69	54
SHS	15	12
Tucson	44	34
Total	128	100

[** CHS: 10 ARIC, 27 Pittsburgh, 21 Sacramento, 11 Hagerstown]

4. Type by Result of Contact

		Type of Contact							
						In-person,		In-person,	
Result of Contact		Missing		Telephone		at clinic		at home	
		n	%	n	%	n	%	n	%
Scheduled sleep study		6	86	27	44	25	51	10	91
Refused				12	20	17	35	1	9
Unable to participate due to illness				1	2	3	6		
Contact later, after Unable to locate									
All other				21*	34	3	6		
(Missing)		1	14			1	2		
	Total	7	100	61	100	49	100	11	100

5. Result of Contact by Study

Result of Contact	Parent Study: CHS n	CHS %	SHS n	SHS %	Tucson n	Tucson %	Total n	Total %
Schedules sleep study	43	63	15	100	10	23	68	53
Refused	19	28			11	25	30	23
Unable to participate due to illness	3	4			1	2	4	3
Contact later, after Unable to locate	3	4			21*	48	24	19
All other (Missing)	1	1			1	2	2	2
Total	69	100	15	100	44	100	128	100

*The 21 correspond to 10 with “no answer/bad #/busy” and 11 “left message”

Table 2
SHHS PSG PILOT STUDY: Results from Technician Worksheet

(N=78 : 46 Edentec, 32 MiniSomno)

1. Age of Participant

	Mean	SD
(years; missing 15%)	66.76	13.23

2. Gender

	n	%
Female	37	50
Male	37	50
(Missing)	4	
Total	78	100

3. Parent Study

	n	%
ARIC - Minn.	10	13
CHS**	43	55
SHS	15	19
Tucson	10	13
Total	78	100

[** CHS : 10 ARIC, 10 Pittsburgh, 12 Sacramento, 11 Hagerstown]

4. Required hook up time (minutes)		Mean	SD	n
	Edentec	37	29	40
	Minisomno	45	32	28
	Combined	40	30	68

5. Required pick up time (minutes)		Mean	SD	n
	Edentec	22	18	29
	Minisomno	18	10	17
	Combined	21	16	46

Table 3
SHHS PILOT STUDY: Results of the Sleep Habits Questionnaire
(N=96)

(NOTE: Results are numbered according to the question number on the survey.)

1. At what time do you fall asleep?

Range: 8:30 p.m. to 1:30 a.m. work days (n=94)
8:00 p.m. to 2:00 a.m. weekends (n=92)
Median = 11 p.m. on work days and weekends

2. How many minutes does it take to fall asleep at bedtime?

Minutes	n	%
1 to 5	29	33
6 to 10	17	19
11 to 15	15	17
16 to 20	10	11
21 to 25		
26 to 30	11	13
31 to 35		
36 to 40	1	1
More than 40	5	6
Missing	8	
Total	96	100

3. At what time do you wake up?

Range: 3 a.m. to 9:00 a.m. on work days (n=93)
Range: 3 a.m. to Noon on week ends (n=91)
Median = 6:15 a.m. on work days
Median = 7:00 a.m. on weekends

4. Hours of sleep? Mean = 7.1 hours, SD = 1.2 (n=92)
Median = 7 hours; Range: 4 to 9 hours

5. Take naps?

	n	%	
NO	35	37	
YES	60	63	If YES, Mean=4 naps Median = 3 ; SD =2.7
Missing	1		
Total	96	100	

6. How often do you have each of the following?

		Never (0)	Rarely (1/mo)	Sometimes (2-4/mo)	Often (5-15/mo)	Almost Always (16-30/mo)
a. Trouble falling asleep	n	12	39	31	10	4
	%	13	41	32	10	4
b. Wake up at night, hard time getting back to sleep	n	16	34	30	10	6
	%	17	35	31	10	6
c. Wake up early, cannot get back to sleep	n	20	42	23	10	0
	%	21	44	24	11	0
d. Don't feel rested during day, even with lots of sleep	n	18	38	32	6	2
	%	19	40	33	6	2
e. Feelings of too much sleepiness during the day	n	20	45	27	4	0
	%	21	47	28	4	0
f. Not getting enough sleep	n	17	50	21	6	2
	%	18	52	22	6	2
g. Take sleeping pills/ other meds. to help sleep	n	72	6	10	2	6
	%	75	6	10	2	6

7. Have you ever snored?

	n	%
NO	11	12
YES	73	78
Not sure	10	10
Missing	2	
Total	96	100

Questions 8 - 11 are FOR THOSE WHO HAVE or MIGHT SNORE

8. How often do you snore?

	n	%
Don't snore anymore	4	5
Rarely (< 1 night / week)	14	19
Sometimes (1-2 nights / week)	17	23
Frequently (3-5 nights / week)	11	15
Always/almost always (6-7 nights / week)	12	16
Unsure	15	21
Missing	12	
Total	85	99

9. How loud is your snoring?

	n	%
Only slightly louder than heavy breathing	20	28
About as loud as mumbling or talking	22	31
Louder than talking	7	10
Extremely loud - can be heard through door	4	6
Unsure	18	25
Missing	10	
Total	81	100

10. How many years have you snored?

	n	%	
Years	21	30	Range: 2 to 50 years
			Median = 10 years
Unsure	49	70	
Missing	11		
Total	81	100	

11. Is your snoring?

	n	%
Increasing over time	6	9
Decreasing over time	7	10
Staying about the same	27	39
Unsure	29	42
Missing	12	
Total	81	100

12. Have you ever stopped breathing while sleeping?

	n	%
NO	47	49
YES	12	13
Unsure	36	38
Missing	1	
Total	96	100

13. How often do you stop breathing? FOR THOSE WHO HAVE STOPPED & UNSURE

	n	%
Rarely (< 1 night / week)	3	6
Sometimes (1-2 nights / week)	2	4
Frequently (3-5 nights / week)	2	4
Always/almost always (6-7 nights / week)	1	2
Unsure	40	83
Missing	1	
Total	49	99

14. Have you ever been told by a doctor that you have sleep apnea?

	n	%	
NO	89	96	
YES	3	3	These 3 YESes do not sleep with a CPAP or mouthpiece
Unsure	1	1	
Missing	3		
Total	96	100	

15. How often have you been awakened by?

		Never (0)	Rarely (1/mo)	Sometimes (2-4/mo)	Often (5-15/mo)	Almost Always (16-30/mo)
a. Coughing or wheezing	n	36	43	11	2	0
	%	39	47	12	2	0
b. Chest pain or tightness	n	76	12	5	0	0
	%	82	13	5	0	0
c. Shortness of breath	n	67	16	4	1	3
	%	74	18	4	1	3
d. Sweats or hot flashes	n	63	16	10	3	0
	%	68	17	11	3	0
e. Noise in your surroundings	n	34	39	10	4	5
	%	37	42	11	4	5
f. Pain in joints muscles, back	n	28	23	17	12	12
	%	30	25	19	13	13
g. Heartburn or indigestion	n	45	35	9	3	1
	%	48	38	10	3	1
h. Leg cramps or leg jerks	n	22	42	16	9	4
	%	24	45	17	10	4
i. Need to go to the bathroom	n	5	11	21	20	38
	%	5	12	22	21	40

16. Anybody sleep near you?

	n	%
Never	18	19
Sometimes	13	14
Usually	63	67
Missing	2	
Total	96	100

17. How likely are you to doze off or fall asleep in the following situations?

		Never	Slight	Moderate	High	Doesn't Apply
a. Sitting & reading	n	16	36	34	9	0
	%	17	38	36	9	0
b. Watching TV	n	12	38	32	13	0
	%	13	40	34	13	0
c. Sitting, inactive	n	50	25	15	2	3
in a public place	%	53	26	16	2	3
d. As a passenger	n	39	32	15	8	1
in a car for 1 hr.	%	41	34	16	8	1
e. Lying down to	n	15	20	35	25	0
rest in afternoon	%	16	21	37	26	0
f. Sitting & talking	n	77	14	2	1	0
to someone	%	82	15	2	1	0
g. Sitting quietly	n	52	20	17	5	1
after lunch	%	55	21	18	5	1
h. In a car, stopped	n	80	11	2	0	2
in traffic for a	%	84	12	2	0	2
few minutes						
i. At dinner table	n	89	4	1	0	1
	%	94	4	1	0	1
j. While driving	n	74	14	0	1	6
	%	78	15	0	1	6
k. During routine	n	81	11	2	1	0
activities	%	85	12	2	1	0

Table 4
SHHS PSG PILOT STUDY : Comparison of Edentec to MiniSomno
Edentec (N=46) and the MiniSomno (N=32)

1. How much difficulty did you have, if any, with the hook-up procedure?

	None	Very Little	Moderate	A Great Deal
Edentec (n)	27	13	4	0
(%)	61	30	9	0
MiniSomno (n)	21	6	3	1
(%)	68	19	10	3

2. After the monitor was attached, how much difficulty did you have, if any, with your normal evening activities?

	None	Very Little	Moderate	A Great Deal
Edentec (n)	28	12	3	2
(%)	62	27	7	4
MiniSomno (n)	18	8	5	1
(%)	56	25	16	3

3. How much discomfort, if any, did the following aspects of the hook-up cause you?

a. Rubbing my head prior to attaching the lead wires

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	25	5	2	0
(%)	78	16	6	0

b. Rubbing my chest prior to attaching the ECG pads

	None	Very Little	Moderate	A Great Deal
Edentec (n)	39	5	0	0
(%)	89	11	0	0
MiniSomno (n)	25	5	1	0
(%)	81	16	3	0

c. Gluing the sensors to my hair

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	22	8	2	0
(%)	69	25	6	0

d. Taping the oxygen sensor to my finger

	None	Very Little	Moderate	A Great Deal
Edentec (n)	38	5	1	0
(%)	86	11	2	0
MiniSomno (n)	27	3	2	0
(%)	84	9	6	0

e. Taping the eye sensors to my face

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	27	4	1	0
(%)	84	13	3	0

4. How much difficulty did you have, if any, falling asleep while wearing the equipment?

	None	Very Little	Moderate	A Great Deal
Edentec (n)	22	16	6	1
(%)	49	36	13	2
MiniSomno (n)	12	10	7	3
(%)	38	31	22	9

5. Once asleep, did you have more difficulty than usual in staying asleep?

	None	Very Little	Moderate	A Great Deal
Edentec (n)	26	13	4	1
(%)	59	30	9	2
MiniSomno (n)	12	8	8	4
(%)	38	25	25	12

6. Once asleep, did any of the following cause you to wake up?

	Edentec		MiniSomno	
	No	Yes	No	Yes
a) Discomfort from the sensors or vest	42	1	26	5
b) Tossing and turning	39	4	20	12
c) Worrying about the equipment	33	11	23	8
d) Problems getting comfortable in bed	40	3	23	9

7. How much discomfort, if any, did the following equipment cause you?

a. Wires on the head

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	26	5	1	0
(%)	81	16	3	0

b. Sensor over the lip

	None	Very Little	Moderate	A Great Deal
Edentec (n)	26	14	2	2
(%)	59	32	4	4
MiniSomno (n)	11	12	5	2
(%)	37	40	17	7

c. Vest or belt

	None	Very Little	Moderate	A Great Deal
Edentec (n)	38	6	1	0
(%)	84	13	2	0
MiniSomno (n)	21	6	2	2
(%)	68	19	6	6

d. ECG pads on chest

	None	Very Little	Moderate	A Great Deal
Edentec (n)	41	4	0	0
(%)	91	9	0	0
MiniSomno (n)	23	6	0	1
(%)	77	20	0	3

e. Finger sensor

	None	Very Little	Moderate	A Great Deal
Edentec (n)	29	13	2	1
(%)	64	29	4	2
MiniSomno (n)	24	5	2	0
(%)	77	16	7	0

f. Straps around chest and stomach

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	24	4	1	2
(%)	77	13	3	7

8. How much discomfort, if any, did the following aspects of the study cause you?

a. Removing the ECG pads

	None	Very Little	Moderate	A Great Deal
Edentec (n)	28	12	3	2
(%)	62	27	7	4
MiniSomno (n)	18	11	1	1
(%)	58	36	3	3

b. Removing the paste from your hair

	None	Very Little	Moderate	A Great Deal
MiniSomno (n)	22	6	1	2
(%)	71	19	3	7

9. Would you be willing to do this sleep test again?

	Yes	No	Unsure
Edentec (n)	32	6	8
(%)	70	13	17
MiniSomno (n)	22	3	7
(%)	69	9	22

10. Compared to other procedures you have undergone in this study (e.g., _____), how would you describe the sleep study?

	Edentec		MiniSomno	
	n	%	n	%
1) Much more comfortable	11	31	3	10
2) Slightly more comfortable	6	17	2	7
3) About the same	11	31	12	40
4) Slightly less comfortable	6	17	9	30
5) Much less comfortable	1	3	4	13

Table 5
SHHS PILOT STUDY: Results of the PSG studies
(n = 78)

1. Overall Study Quality

	MiniSomno		Edentec	
	Frequency	Percent	Frequency	Percent
Uninterpretable	5	16	0	0
OK, but > 50% channels with problems	3	9	5	11
OK, but at least 1 channel with problems	14	44	4	9
Excellent, all channels good	8	25	32	70
Not completed:				
Subject disability	0	0	2	4
Mechanical/data failure	2	6	3	6
	32	100	46	100

2. Apnea-Hypopnea Index (AHI)

Value label	Value	Freq.	Percent	Valid Percent	Cum. Percent
LE 5	1	15	19.2	23.1	23.1
GT 5-LE 10	2	15	19.2	23.1	46.2
GT 10-LE 20	3	19	24.4	29.2	75.4
GT 20-LE 30	4	6	7.7	9.2	84.6
GT 30-LE 40	5	5	6.4	7.7	92.3
GT 40	6	5	6.4	7.7	100.0
Missing	.	13	16.7	Missing	
Total		78	100.0	100.0	

3. Arousal Index

Value	Freq.	Percent	Valid Percent	Cum. Percent
0.14	1	1.3	4.2	4.2
0.15	1	1.3	4.2	8.3
0.16	1	1.3	4.2	12.5
0.20	1	1.3	4.2	16.7
0.23	1	1.3	4.2	20.8
0.28	1	1.3	4.2	25.0
0.51	1	1.3	4.2	29.2
0.57	1	1.3	4.2	33.3
1.14	1	1.3	4.2	37.5
6.64	1	1.3	4.2	41.7
6.65	1	1.3	4.2	45.8
7.87	1	1.3	4.2	50.0
9.18	1	1.3	4.2	54.2
10.44	1	1.3	4.2	58.3
10.64	1	1.3	4.2	62.5
11.00	1	1.3	4.2	66.7
14.77	1	1.3	4.2	70.8
14.78	1	1.3	4.2	75.0
16.26	1	1.3	4.2	79.2
16.86	1	1.3	4.2	83.3
17.11	1	1.3	4.2	87.5
19.49	1	1.3	4.2	91.7
19.55	1	1.3	4.2	95.8
21.79	1	1.3	4.2	100.0
Missing	54	69.3	Missing	
	---	---	---	
Total	78	100.0	100.0	

Choice of Equipment

The interest of the SHHS investigators in purchasing equipment for this study was advertised in a commercial publication. The system requirements (both for Approach 1 and 2) were summarized and distributed to 22 equipment manufacturers (all known major suppliers of sleep equipment and any others who contacted us). Fifteen companies contacted the Sleep Reading Center by writing or telephone. An evaluation process was developed which included assessment of: commercial specifications (size, computer requirements, sampling and storage rates, storage medium, electrical supply), channel characteristics (amplifiers, filters, etc.), construction (sturdiness, bulk), sensor descriptions, and software. A decision was made to exclude equipment that required a bedside stand-alone computer (because of bulk, electrical requirements, and the complexity of presenting such a system in the home.) Eight companies, producers of equipment that appeared to most closely meet study requirements, made equipment demonstrations (to the Steering Committee and/or to members of the PSG committee). Five different devices were also evaluated (with hands-on testing) at the Sleep Reading Center or one of the participating clinical sites. Finally, three companies were identified as making equipment that met minimal study requirements for Approach 1. Of these, one was excluded because of AC electrical requirements and inflexibility in adjusting sampling rates. The final choice of the CompuMedics PS polysomnograph was based on the following considerations:

1. Most robust and flexible hardware, with up to 24 channels for data acquisition (compared to 9 for the alternative system);

2. Fully developed software (in contrast to incompletely developed software for the alternative, necessitating a separate software agreement with another company);

3. Ability to do in-home set-up procedures without a separate laptop computer;

4. Attractive pricing.

5. A high level of enthusiasm by the company in participating in the study, customizing hardware and software, and providing technical support.

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APPENDIX 5

SHHS COMMITTEE ORGANIZATION

STEERING COMMITTEE

Chairperson:	Jonathan M. Samet, M.D.	Baltimore
Investigative centers:	F. Javier Nieto, M.D., Ph.D.	Baltimore
	George T. O'Connor, M.D., M.S.	Boston
	Stuart F. Quan, M.D.	Tucson
	David M. Rapoport, M.D.	New York City
	John A. Robbins, M.D., M.H.S.	Sacramento
	Eyal Shahar, M.D., M.P.H.	Minneapolis
Sleep Reading Center:	Susan Redline, M.D., M.P.H.	Cleveland
Coordinating Center:	Patricia W. Wahl, Ph.D.	Seattle
NHLBI Project Scientist:	James P. Kiley, Ph.D.	Bethesda

SUBCOMMITTEES

Polysomnography / Quality Control Subcommittee
Chairman: Susan Redline
Members: William Bonekat, Paul Enright, Daniel Gottlieb, Conrad Iber, Philip Smith, Mark Sanders, Stuart Quan

Morbidity and Mortality Subcommittee
Chairman: George O'Connor
Members: Thomas Pickering, Bruce Psaty, David Siskovick, Joyce Walsleben, Stuart Quan

Sampling, Design, and Recruitment Subcommittee
Chairman: Eyal Shahar
Members: Michael Lebowitz, Anne Newman, F. Javier Nieto, John Robbins, Joseph Schwartz, Pat Wahl, Terry Young

Comparability Committee
Chairman: F. Javier Nieto
Members: Daniel Gottlieb, Michael Lebowitz, Bonnie Lind, Anne Newman, Thomas Pickering

Questionnaire and Interview Subcommittee
Chairman: Terry Young
Members: Vishesh Kapur, Stuart Quan, Susan Redline, Eyal Shahar, Joyce Walsleben

Publications and Presentations Subcommittee
Chairman: John Robbins
Members: James Kiley, George O'Connor, Stuart Quan, David Rapoport, Patricia Wahl

Quality Control Subcommittee

Chairman: F. Javier Nieto

Members: Paul Enright, Joel Hill, Conrad Iber, James Kiley, Joyce Walsleben, Coralyn Whitney, Terry Young

Operations Subcommittee

Chairman: Eyal Shahar

Members: Rachel Givelber, Jamie Goodwin, Joel Hill, Gary James, Bonnie Lind, Anne Newman, Sherri Nooyen, Bobbie Moyer

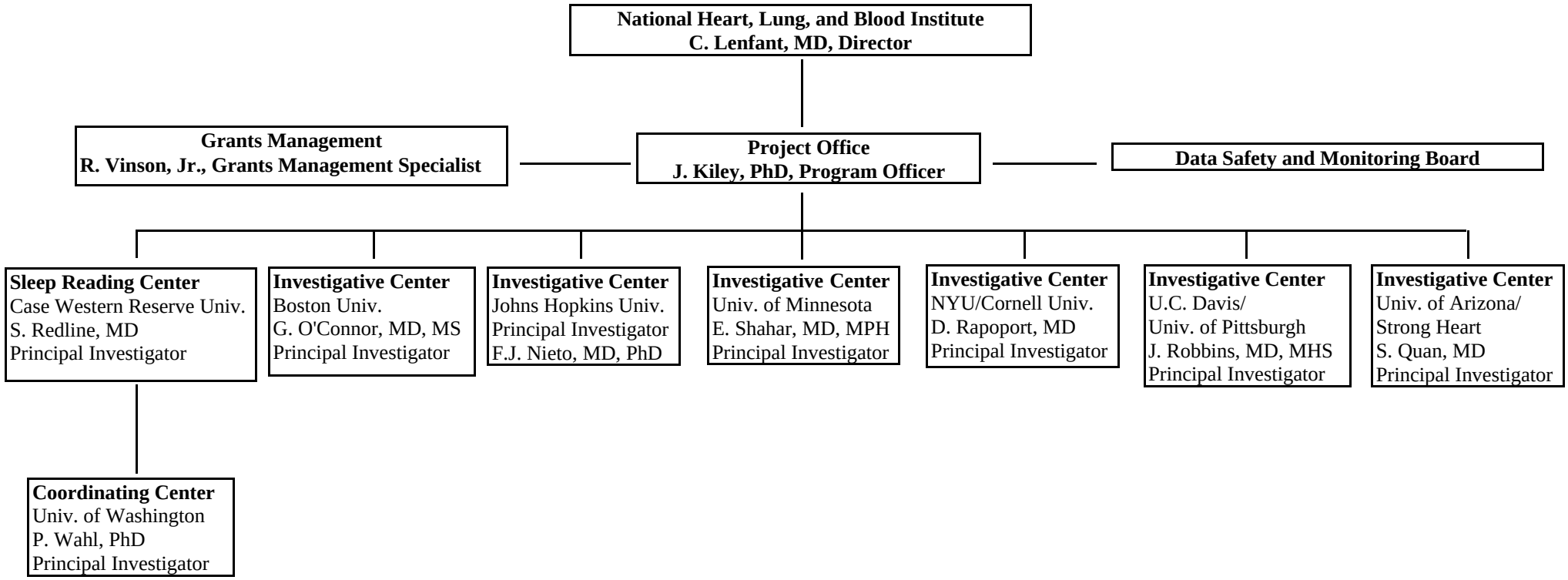
NHLBI APPOINTED COMMITTEE

Data and Safety Monitoring Board (DSMB)

Chairperson:	John V. Weil, M.D.	Denver
Board Members:	Sonia Ancoli-Israel, Ph.D.	LaJolla
	Julie E. Buring, Sc.D.	Boston
	Vernon M. Chinchilli, Ph.D.	Hershey
	June M. Fry, M.D, Ph.D.	Philadelphia
	Otelio S. Randall, M.D.	Washington, D.C.
	Joe R. Rodarte, M.D.	Houston
	Wolfgang W. Schmidt-Nowara, M.D.	Albuquerque
	James Woodrow Weiss, M.D.	Boston

APPENDIX 5 (cont.)

ORGANIZATIONAL STRUCTURE OF THE SLEEP HEART HEALTH STUDY



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APPENDIX 6 6/7/95

Sleep Heart Health Study
POLICY ON CONFLICT OF INTEREST

In a collaborative activity, investigators have responsibilities in relation to the collaborative effort as well as to their individual institutions. Investigators must adhere to individual institutional policies, but these may vary among institutions. The collaborative effort dictates the need for a commonality of standards that are in addition to, rather than substitutes for, individual policies.

In the instance of the Sleep Heart Health Study (SHHS), the policies must recognize that over the course of the study new topics and new potential sources of conflict of interest may be encountered.

DEFINITIONS

Investigator means the principal investigator and any other person at the institution who is responsible for the design, conduct, or reporting of research. For the purposes of financial interest, "investigator" includes the investigator's spouse and dependent children.

Study-related entity means an entity with an active or potential interest in the conduct or outcome of the SHHS because:

a) a drug, biological, device, or other product ("product") of the entity is a primary focus in the SHHS (a ***"Type A" relationship***),

b) a drug, biological, device, or other product of the entity is a direct alternative or substitute for the product used by the SHHS (a ***"Type B" relationship***), or

c) a drug, biological, device, or other product of the entity is being used in the study (e.g., as a tool or as an adjunct, but not as a primary study drug or device) at a time in its scientific or commercial development that would play a substantial role in its commercial viability and success (a "***Type C" relationship***).

Financial interest means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interest (e.g., stock, stock options, or other ownership interests); intellectual property rights (e.g., patents, copyrights, and royalties from such rights). It does not include indirect financial interest through broadly diversified investments, e.g. in broadly diversified mutual funds, and retirement plans.

Significant financial interest means financial interest in a business enterprise or entity if:

1) the value of the interests plus payments for services (but not the reimbursement of reasonable directly incurred costs) exceeds $5,000 per annum, or

2) the ownership interest exceeds 5% of the total, or

3) the impact of the use of its product by SHHS or the outcome of the SHHS research may reasonably be expected to have a very significant impact (e.g., twofold or greater change) upon the value of the investment.

Other significant relationships with a study-related entity includes:

4) research, training, or other support from the entity for the SHHS investigator, or in which the SHHS investigator is involved, or over which the SHHS investigator has control, responsibility for conduct, responsibility for making appointments, or the like, even if funding is not to the SHHS investigator,

5) possible other relationships in which there is or seems to be a dependency relationship of the SHHS investigator to the study-related entity.

POLICY

This policy and its definitions (e.g., financial interest, significant financial interest, other significant relationship, and study-related entity) shall be public information.

The existence (but not the amount or details) of any financial interest, any significant financial interest, any other significant relationship of any SHHS investigator or any exception to the standard policy shall be public information. The existence of financial interest shall routinely be acknowledged in publications and in the program of presentations.

A SHHS investigator with a significant financial interest in a study-related entity of Type A shall not have the responsibilities of an investigator in the SHHS (e.g., decision-making, analysis, reporting, management, etc.); he/she shall not participate in the decision to undertake, continue, or terminate the study or to participate in discussions or negotiations with the entity related to the potential or actual use of the product(s) of the entity.

A SHHS investigator with a significant financial interest in a study-related entity of Type B shall have the same general limitations as in a Type A relationship. However, exceptions may more readily be made, because consideration is given to multiple factors (see below), which also include the degree to which the product of the Type B entity might reasonably be expected to be impacted by the study, and the importance of that product to the Type B entity.

A SHHS investigator with a significant financial interest in a study-related entity of Type C may exercise all the responsibilities of an investigator in the study, except that he or she shall not participate in the decision to undertake, continue or terminate the use of the specific product, or to participate with the entity in any discussions or negotiations related to that entity.

Other significant relationships of SHHS investigators will be reviewed individually by the Governance Board, but it is anticipated that most will result in no restrictions on SHHS activity.

Relationships of investigators with study-related entities (and representatives of these entities) shall also adhere to the following principles:

- SHHS-related activities shall be discussed only as needed by the study and in the role of, or on behalf of, the SHHS activity, but never in the context of other discussions, relationships, or interest that the investigator and that entity may have.

- SHHS study protocol and policies relating to the release of information dictate the confidentiality of non-publicly released information, as well as the release of certain confidential information to certain interested entities. Investigators must adhere to these policies. Except in a formal role, on behalf of the study, they must scrupulously avoid transmitting information to any entities that have interest in the study and they must be particularly scrupulous in avoiding such release of information to an entity in which the investigator has a financial interest.

- As a tangential point, investigators must be cognizant of and adhere to Federal regulations on the prohibition of "insider trading."

PROCESS

The potential for conflict of interest shall be considered routinely on an annual basis and whenever new products are considered or relationships with new entities are considered by the SHHS, or if an investigator develops or terminates an SHHS significant (or potentially significant) financial interest or such interest changes.

The principal investigator at each SHHS center shall be responsible for transmitting to the Governance Board not only his or her own disclosure statement, but those of others at his or her institution who may fulfill the criteria of investigator as defined here.

The disclosure material must include a list of study-related entities in which there is a financial interest or with which there is another significant relationship, the basis and nature of the interest or relationship, and its classification as "significant financial interest" and/or "other significant relationship."

The investigator is responsible for identifying for review any related financial interests that do not meet criteria (1) or (2) under significant financial interest, but for which reasonable persons might have differing judgements as to meeting criterion (3). Any other significant relationships with study-related entities must be described at least briefly, but in sufficient detail so that their acceptability can be assessed.

If an exception is sought to the stated policy, the base for it must be indicated. Exceptions may be made in circumstances where both the substance and the appearance of conflict are each sufficiently small and benefits to the study and the public outweigh these factors. Participation by exception to standard policy shall be public information.

Recommendations on potential conflicts of interest will be the responsibility of the Governance Board. The SHHS Governance Board is comprised of the eight SHHS principal investigators and the Steering Committee chair. The Board shall elect a chair and vice-chair who will supervise the review of disclosure documents and who will serve throughout the duration of the grant term. The vice-chair presides in the case of a potential conflict involving the chair. Board members shall neither review nor rule on disclosures from their own SHHS center.

The recommendations of the SHHS Governance Board shall be conveyed by the chair to the Director, National Center on Sleep Disorders Research (NCSDR), NHLBI. In granting a waiver to the policy, the chair and/or the Director, NCSDR, may seek independent review and advice from outside sources, if that process is deemed necessary.

Disclosure statements shall be reviewed and kept on file in the offices of the Director, NCSDR after review by the Board.

DISCLOSURE STATEMENT FOR INVESTIGATORS OF THE SLEEP HEART HEALTH STUDY

This statement is provided in accordance with the disclosure requirements specified in the "Sleep Heart Health Study Policy on Conflict of Interest."

The following is a list of SHHS study-related entities in which my spouse, dependents, or I have a financial interest or other significant relationship, the basis and nature of the interest or relationship, and its classification as "significant financial interest" or "financial interest" and/or "other significant relationship."

I (We) have no relationship with any organization related to this study. ❒

Name of Entity _____

Significant Financial Interest ❒ Financial Interest ❒ Other Significant Relationship ❒

Basis/Nature of Relationship _____

_____

Name of Entity _____

Significant Financial Interest ❒ Financial Interest ❒ Other Significant Relationship ❒

Basis/Nature of Relationship _____

_____

Name of Entity _____

Significant Financial Interest ❒ Financial Interest ❒ Other Significant Relationship ❒

Basis/Nature of Relationship _____

_____

(If additional space is required, please use separate form)

Signature: _____ Date: _____

Name Typed: _____

SHHS Center Named: _____