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1. OVERVIEW

The Sleep Heart Health Study (SHHS) is a multi-center cohort study that was 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, 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 SHHS, implemented to obtain these needed data, is testing whether sleep-related breathing is associated with an increased risk of coronary heart disease, stroke, all cause mortality, and hypertension.

The design of the SHHS reflects these scientific questions and feasibility considerations. 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 SHHS drew on a resource of existing, well-characterized, and established epidemiologic cohorts. The SHHS design added 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 the Omni cohorts in Framingham, Massachusetts; the Health and Environment and the Tucson Epidemiologic Study cohorts in Tucson, Arizona; the Strong Heart Study sites in Phoenix, Arizona, Oklahoma City, Oklahoma, and in South Dakota; and New York City populations assessed in studies of hypertension - the New York Hospital cohort, the Harlem cohort, and the Work Site cohort. Each of these populations was already established as the SHHS was implemented in 1995; some information on risk factors for cardiovascular disease had already been collected in each of the cohorts, and all but the Tucson and New York studies included ongoing and standardized monitoring for the occurrence of cardiovascular events.

The organizational structure of the SHHS comprises the Coordinating Center (CC) at the Johns Hopkins Bloomberg School of Public Health, the Sleep Reading Center (SRC) at Case-Western Reserve University, the ECG Reading Center (ECGRC) at Cornell University (Years 6-10), the Project Office of the National Heart, Lung, and Blood Institute, and eight Investigative Centers (University of Arizona, Boston University, University of California-Davis, University of Pittsburgh, Johns Hopkins University, University of Minnesota, New York University, and the Strong Heart Study at MedStar. The Strong Heart Study Investigative Center includes 3 Field Sites which interact with the parent study).

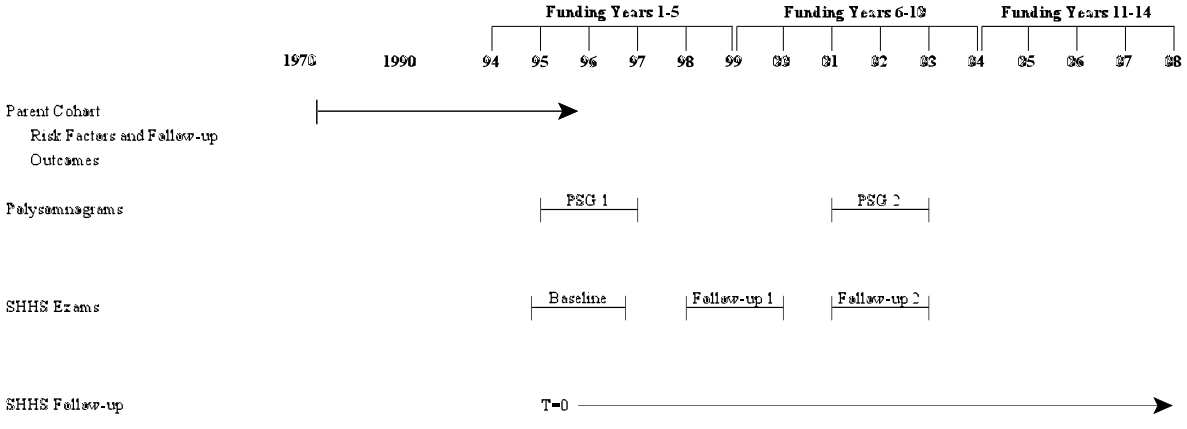
1. OVERVIEW

The Steering Committee is the main governing body of the study; specific subcommittees and working groups have been charged with aspects of design and operation of the project, including the Publications and Presentations Subcommittee, the Morbidity and Mortality Subcommittee, and Longitudinal Data Analysis Working Group. An Observational Study Monitoring Board (OSMB) appointed by the Institute is responsible for review of study data in order to insure data quality and the safety of study subjects and to provide the Institute with advice on the progress of the study.

The SHHS added in-home polysomnography to the data collected in each of the parent studies. Using the Compumedics PS polysomnograph, a single over-night PSG was obtained at home for 6,440 persons at the baseline visit; the montage included oximetry, heart rate, chest wall and abdominal movement, nasal/oral airflow, body position, EEG, EOG, and chin EMG. This montage provided data on the occurrence of sleep-disordered breathing and on arousals. Sleep data were collected during the second and third years (1996-1997) of the initial five-year funding and during the second and third years of Years 6-10 of the SHHS.

The timeline for the SHHS is provided in the following figure. Enrollment and follow-up of the participants were initiated at varying times by the parent cohorts. The SHHS baseline visit was carried out between 12/95 and 2/98, so that follow-up in the SHHS began at this visit for study participants. The first follow-up visit (Follow-up 1) was two years after the baseline visit, over the calendar interval of 1997-1999 and did not include a polysomnograph. Follow-up 2 took place from 12/00 through 12/02 and included a repeat polysomnography approximately 5 years after the baseline PSG.

SHHS Participant Timeline



1. OVERVIEW

This Protocol – SHHS Protocol: Follow-up 3 – provides the template for follow-up, outcomes adjudication, and analysis, beginning in Year 11 of participant follow-up. The prior protocols – SHHS Protocol 1and 2 provides the original and followup design that were followed through Year 10. Together, the three documents constitute the protocol as of October 2004.

As initially planned, approximately 1,000 participants were to be enrolled from the parent cohorts of each of the then six Investigative Centers. Recruitment approaches were tailored for the requirements of the specific Field Sites. All participants were at least 40 years of age and all minority members of each of the parent cohorts were recruited. For American Indians, recruitment from the Strong Heart Study was to include 600 persons, 200 each from Phoenix, Oklahoma, and South Dakota. Individuals younger than age 65 years were selected with stratification by history of snoring, as assessed by a standardized questionnaire administered to all members of the parent cohorts; the sampling fraction for snorers was 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 in this age stratum were selected without reference to snoring history. There was no upper age limit for participants and the presence of prevalent cardiovascular disease did not exclude potential participants. The projected sample size of about 6,000 participants was originally estimated to provide sufficient power for the principal primary hypotheses by the end of Year 4, but further follow-up was needed to have sufficient power for all primary and secondary hypotheses, both overall and within subgroups of a priori interest.

The overall recruitment goal of the SHHS was met (see table 1.1). A total of 6,440 persons were recruited and completed an overnight PSG with usable data for Followup-1. For Followup-2, there were 4361 participants (97% of target) who completed a home visit with or without a PSG. The distribution of the participants by Investigative Center is given in the following table.

Participants by Field Site

Table 1.1

Field Site (Cohort)	SHHS followup-1 (Home visit with a successfully completed PSG)		SHHS followup-2 (Home visit with or without a PSG)	
	Frequency	Percent	Frequency	Percent
Framingham (Omni, Offspring)	1,001	15.5	804	18.4
Hagerstown (ARIC, CHS)	1,184	18.4	809	18.6
Minneapolis (ARIC)	1,085	16.8	765	17.5
New York (NYH, Harlem,Worksite)	758	11.8	238	5.5
Pittsburgh (CHS)	399	6.2	261	6.0
Sacramento (CHS)	502	7.8	347	8.0
South Dakota (Strong Heart)	201	3.1	161	3.7
Oklahoma (Strong Heart)	200	3.1	155	3.6
Phoenix (Strong Heart)	201	3.1	155	3.6
Tucson (TES, H & E)	909	14.1	666	15.3
Total	6,440	100	4,361	100

1. OVERVIEW

The extent of information available on key cardiovascular risk factors varied among the parent cohorts. Based on review by the Comparability Subcommittee, some additional data were collected on covariates at enrollment into the SHHS to have a comparable suite of risk factor data for all studies. However, the parent studies are to 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 are primary outcomes. Participants at all Investigative Centers other than the Strong Heart Study Center complete a standardized instrument on quality of life (the SF 36) as well. The cardiovascular outcomes are adjudicated by methods already in place for the ARIC, CHS, SHS, and Framingham Field Sites and by the CHS process for the New York and Tucson Field Sites. Ancillary studies address other outcomes, such as cognitive functioning, that cannot be considered in the full SHHS cohort.

To the extent possible as the cohort was enrolled, participants in the parent studies were asked to complete the Sleep Habits and Lifestyle 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 and provide insights into the bias that may have risen from the self selection into the SHHS cohort.

Although the SHHS is a prospective cohort study, the cross-sectional findings do provide new information on patterns of sleep and sleep-disordered breathing in the general population. Consequently, initial analyses have been 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 are addressing sleep-disordered breathing as a predictor of cardiovascular outcomes and change in blood pressure and the natural history of sleep-disordered breathing.

Aspects of the methodology of the SHHS are novel, particularly the performance of in-home polysomnography. To characterize the comparability and reliability of in-home tests to laboratory polysomnography, two substudies were carried out: one directed at night-to-night variability and the other at the comparability of testing in the home and laboratory settings. These substudies provide an understanding of the potential variability associated with a single night's sleep data and of any systematic differences between assessment in home and lab.

2. BACKGROUND AND RATIONALE

Sleep disordered breathing including 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 disordered breathing compared to patients treated aggressively. [9]

In addition, patients with sleep disordered breathing 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 disordered breathing and thrombotic stroke. Sleep disordered breathing 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 disordered breathing 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 disordered breathing and hypertension in African-Americans and other minority groups will receive emphasis in the SHHS. For uncertain reasons, severe hypertension is more common and its consequences more severe in African-Americans than in whites. Risk factors for sleep disordered breathing such as obesity and macroglossia are also common in African-Americans, and preliminary data suggest that, among young subjects, sleep disordered breathing may be more prevalent among African-Americans than among whites. [10] Sleep disordered breathing 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 disordered breathing is 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 disordered breathing has been seen in 30% or more of elderly subjects. [13] The basis for strong relationships between aging and increased apneic and hypoponeic 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 or hypopnea and arousal from sleep.

2. BACKGROUND AND RATIONALE

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 it 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 persons 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). A competing continuation application was funded for the interval September 2, 1999 through August 31, 2004. With that renewal, the Strong Heart Study was added as a seventh Investigative Center, independent of the University of Arizona Center. Through a competitive process, the CC was transferred to the Center for Clinical Trials at the Johns Hopkins Bloomberg School of and Public Health, following a decision by the University of Washington team not to continue as the CC. A competing continuation application was funded for the interval September 1, 2004 through August 31, 2008. With that renewal, the University of Pittsburgh was added as an eighth Investigative Center, independent of University of California at Davis.

(Updates and references are listed in Appendix.)

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 determined 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.

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.

4. PARTICIPATING CENTERS

Investigative Centers

Investigative 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 originally selected to participate in SHHS. The Strong Heart Study, originally a component of the University of Arizona, was established as separate Investigative Center with the first renewal. The University of Pittsburgh, originally a co-site with the University of California at Davis, is to be established as a separate Investigative Center as of this second renewal. The SHHS Investigative Centers are:

University of Arizona
Boston University
University of California at Davis
Johns Hopkins University
University of Minnesota
New York University/Cornell University
University of Pittsburgh
Strong Heart Study

Each Investigative Center consists of one or more distinct Field Sites. Field Sites are distinguished within an Investigative Center by being either geographically separate or by representing a separate cohort, if non-PSG data management functions are separated for those cohorts. Boston University has one Field Site, the Framingham Heart Study in Framingham, Massachusetts. Participants are included from both the Offspring and Omni cohorts. Johns Hopkins has two cohorts at the single Hagerstown, Maryland Field Site: one consisting of CHS participants and one consisting of ARIC participants. The University of Minnesota has one Field Site which consists of ARIC participants. The New York University/Cornell site has 3 geographically separated cohorts, but will have a central data management Field Site during the renewal period. The UC Davis has one Field Site in Sacramento, California and the University of Pittsburgh has one Field Site in Pittsburgh, Pennsylvania; each consisting of CHS participants. The single Field Site at the University of Arizona has two cohorts in Tucson, Arizona: the Tucson Epidemiology Study of Obstructive Airways Disease, and the Tucson Health and Environment cohort. The Strong Heart Study participants are located at three Field Sites in Phoenix, Arizona; Oklahoma City, Oklahoma; and in South Dakota.

Resource Centers

The Coordinating Center is at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. There is one central PSG reading center - the Sleep Reading Center at the Case Western Reserve University in Cleveland, Ohio.

5. SAMPLE SELECTION

5.1 Parent Cohorts

SHHS participants were drawn from nine existing parent cohorts: ARIC, CHS, Framingham, three cohorts in New York City, SHS, and two cohorts in Tucson, Arizona. The Atherosclerosis Risk in Communities (ARIC) Study provides two Field sites, one in Minneapolis, Minnesota, and one in Hagerstown, Maryland. The Cardiovascular Health Study (CHS) provides data from sites in Sacremento, California, Pittsburgh, Pennsylvania, and Hagerstown, Maryland. The Framingham Heart Study (FHS) has two cohorts that are involved, the Offspring and Omni Cohorts. New York City includes three cohorts, the Pickering NYH-clinic study, the Harlem Substudy, and the Worksite Study. The Strong Heart Study includes only Native Americans, located in Arizona, Oklahoma, and in South Dakota. The Tucson Investigative Center has two cohorts, the Tucscon Epidemiological Study of Airway Disease (TES), and the Tucson Health & Environmental (H&E) Cohort. Details regarding information collected by each parent cohort were provided in Protocol 1, and are summarized in Appendix 2.

5.2 Sampling Criteria

The rationale for the criteria was detailed in Protocol 1. The criteria included:

1. Each site will recruit all available minorities.
2. Each site will recruit equal numbers of men and women.
3. Habitual snorers will be over-sampled in sites that recruit subjects younger than age 65 years.
4. Persons with prevalent cardiovascular disease and hypertension will not be excluded.
5. All participants will be at least 40 years of age.

5.3 Sample Size Considerations

The target sample size was 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 was estimated that approximately a third of this sample would have prevalent cardiovascular or cerebrovascular disease, leaving 4,000 subjects to test hypotheses regarding incident events. During the first five years of the grant, the target was met, with a total of 6,440 participants, ranging from 200 to 1,085 according to site. The sample size calculations outlined in the first Protocol continue to be appropriate in guiding study design. Sample size is now fixed.

6. PARTICIPANT PROTOCOL FOR FOLLOW-UP 3

During the first data collection period the recruitment target was met, with a total of 6,440 participants who had an in-home PSG with associated non-PSG data collection. The target population for the second follow-up examination included all surviving members of the cohort who had a PSG at the baseline visit. In general, participants were sent a letter, announcing the continuation of the study, and indicating that a staff member would call them to inquire about their interest in undergoing a third data collection, preferably involving a second PSG, and to ask a limited set of questions to determine eligibility to undergo a PSG. At some sites, recruitment contacts took place at a study clinic if the SHHS schedule coincided with a parent study exam; in other sites, participants were recruited by telephone. It was expected that approximately 4,000 participants would undergo a second PSG. Exclusion criteria for the second PSG were similar to the criteria that were used at the baseline examination, i.e., conditions that pose technical difficulties for polysomnography:

- treatment of sleep apnea with continuous positive airway pressure or an oral device
- oxygen treatment at home
- open tracheostomy

Although not all participants had a second PSG, 4361 participants were recruited and completed a study visit (home visit with or without a PSG) in SHHS-2.

7. DATA COLLECTION

7.1 Parent study data collection

SHHS is designed to use existing data collected by the parent studies regarding health history, cardiovascular risk factors, and cardiovascular events. At the study's outset, 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 (key risk-factors for cardiovascular disease and outcomes) 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.

7. DATA COLLECTION

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 PSG and the closest measurement was specified. That is, data previously collected by the parent study could 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. For cohort members refusing or ineligible for a second PSG, the reference date will be the date of the home visit. In the absence of a home visit, the observation closest in time to the screening interview will be used.

As the SHHS is now in a phase of longitudinal data collection, the A-variables also need to be considered in a time-dependent fashion. A number of the A variables might change over time; diabetes status, lipid levels, alcohol intake, and smoking. SHHS will track self-report of diabetes and smoking.

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		Occupation	
Self-reported hypertension	3 years	Psychosocial status	
Self-reported diabetes	3 years	Access to health care	
Self-reported respiratory symptoms	3 months		
Self-reported hx of SDB	3 months		
Cigarette smoking status	3 months		
Education level	Any		
Marital status	3 years		
Race	Any		
Gender	Any		
Continuous covariates			
Age	Current	Hemostasis parameters:	Passive smoking
Cigarettes/day	3 months	Fibrinogen	(ETS)
Cigarettes/years	3 months	Factor VII	Diet:
Usual alcohol intake	3 years	Physical activity	Caloric intake
Usual caffeine intake	3 months	Family income level	Fat intake
Seated blood pressure	Current		Antioxidants
Anthropometric indices:			
height	1 year		
weight	Current		
waist, hip girths	Any		
neck girth	Current		
Total cholesterol	Any		
HDL cholesterol	Any		
Triglycerides	Any		
Spirometry: FVC, FEV_1	Any		
Ankle-Arm Index	5 years		
SF-36 Score	Any		
Other			
Medications	Current	Echocardiography	24h. blood pressure
ECG	3 months prior through 2 months after F2		Carotid Ultrasound
			Holter
			MRI

7.2 Outcomes data collection

Plans for cardiovascular disease (CVD) outcome ascertainment and adjudication during years 11-14 of the Sleep Heart Health Study

7.2.1 Overview of outcome ascertainment and adjudication in years 1-10.

SHHS was designed to include subjects participating in multiple existing cohort studies and to take advantage of ongoing mechanisms of CVD outcome ascertainment and adjudication in place in these parent studies. Specifically, the ARIC, CHS, FHS, and SHS studies have had mechanisms in place for determining CVD outcomes since the start of SHHS. Outcomes data for SHHS subjects belonging to these cohorts have been provided to SHHS by the parent studies. The SHHS subjects recruited in Tucson and New York were members of research cohorts that did not include ongoing assessment of CVD outcomes. In these two sites, SHHS investigators have implemented their own procedures for ascertaining and adjudicating CVD outcomes among SHHS participants. These procedures have been closely modeled on those of CHS.

Key outcomes for SHHS include the following incident or recurrent CVD events or diagnoses occurring subsequent to the first SHHS polysomnogram:

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
c. stroke

A summary of CVD outcomes data received to date (June 2004) by the SHHS Coordinating Center is provided in the table below (Table 7.2). These data are most up-to-date for the New York (outcomes through Sept 2003) and Tucson (outcomes through January 2004) sites, where SHHS investigators ascertain and adjudicate CVD outcomes themselves. For ARIC, CHS, FHS, and SHS, outcome status is available (i.e., received in Coordinating Center) through dates ranging from December 1999 through December 2002.

Table 7.2 SHHS 1 cohort outcome status as of June 2004

	ARIC	CHS	FHS	NY	SHS	Tucson	Total
Num. in SHHS 1	1920	1248	1000	760	602	911	6441
Death reported at SHHS II visit N (rate/1000 p-y)*	78 (8.2)	217 (37.8)	33 (6.7)	32 (8.6)	95 (32.6)	42 (9.5)	497 (15.9)
Num. with adjudicated outcomes from parent studies:	1920	1248	699†	554†	602	911	5934
Outcomes through (date)	31 Dec 01	30 Jun 00	31 Dec 02	30 Sep 03	31 Dec 99	8 Jan 04	–
Mean followup time (year)	4.8	3.5	5.8	5.7	3.3	5.8	4.7
Death adjudicated N (rate/1000 p-y)							
All cause	71 (7.7)	132 (29.9)	24 (5.9	‡	62 (31.0)	63 (12.0)	352 (14.1)
MI death	1 (0.1)	7 (1.6)	0 (0)	‡	5 (2.5)	5 (1.0)	18 (0.6)
CHD death	6 (0.6)	33 (7.5)	5 (1.2)	‡	17 (8.5)	10 (1.9)	71 (2.5)
CVD death	6 (0.6)	49 (11.1)	7 (1.7)	‡	19 (9.5)	15 (2.9)	96 (3.4)
MI. adjudicated							
Num. w/o previous MI§	1779	1048	660	479	490	805	5261
Incident MI, N (rate/1000 p-y)	46 (5.4)	49 (13.3)	5 (1.3)	2 (0.7)	13 (8.0)	14 (3.0)	129 (5.2)
MI/re-vasculatization procedures, adjudicated							
Num w/o previous MI/re-vasc§	1730	–	–	–	–	799	–
Incident MI/rec-vascc. N (rate/1000 p-y)	96 (11.7	–	–	–	–	28 (6.1)	–
Stroke, adjudicated							
Num w/o previous stroke§	1866	1121	681	485	551	874	5578
Incident stroke. N (rate/1000 p-y)	22 (2.4)	53 (13.6)	10 (2.6)	0	7 (3.8)	12 (2.4)	104 (3.9)

*Based on 6,403 participants with known vital status/censoring date; date of death was imputed as the mid-point of the date on which death was reported and last patient contact

†FHS: adjudicated outcomes data for 301 participants in the Omni cohort have not yet been released to us by the parent study; NY: adjudicated outcomes data for 206 participants are not available - 84 unable to reach; 116 in the process of followup; 2 missing censoring dates; 4 status unknown

‡Unable to adjudicate cause of death until the death certificates are released by the NY State Health Department.

§Both the outcome datasets provided by the parent studies and the SHHS baseline health interviews indicate no previous event

7.2.2 Timeline for completion

Timeline for completion of outcome ascertainment and adjudication in years 11-14

Reliance on parent-study mechanisms for the ascertainment and adjudication of CVD outcomes has provided efficiency and cost savings to SHHS. A disadvantage of reliance on these parent-study data, however, is the time lag between CVD event occurrence and the final availability of adjudicated data, a lag that averages approximately 2.5 years for ARIC, CHS, FHS, and SHS. The timely completion of outcomes follow-up for the SHHS cohort requires that the SHHS investigators take over ascertainment and adjudication activities for the final period of SHHS follow-up prior to undertaking analyses to test primary hypotheses in year 14 of the renewal period. This will maximize the number of incident CVD events, improving statistical power to address primary hypotheses.

The SHHS Steering Committee has agreed on the following timeline for data collection and analysis in years 11-14.

April 1, 2006
CVD outcomes through this date will be included in final SHHS analyses.

May 31, 2007
Completion of ascertainment and adjudication of CVD outcomes through 4/1/06
Final CVD outcomes data transferred to SHHS Coordinating Center

August 31, 2008
Submission of manuscripts on primary SHHS hypotheses
End of grant year 14

To meet this timeline while maximizing the follow-up interval at sites (ARIC, CHS, FHS, SHS) with inherent lag times in the adjudication process, event adjudication for SHHS participants will either a) need to be performed by SHHS investigators starting in the spring of 2005, or b) need to be performed by parent study adjudication committees with an accelerated schedule for SHHS participants.

7.2.3 Plans for ascertainment and adjudication

Detailed plans for outcome ascertainment and adjudication in years 11-14

At some sites, parent-study event ascertainment will continue through 4/1/06 and will suffice to capture CVD events and diagnoses for SHHS participants participating in those parent studies. At other sites, SHHS investigators will need to take over event ascertainment in 2005 or 2006.

7. DATA COLLECTION

Outcome adjudication will continue at the New York and Tucson sites without change; i.e., a committee assembled by the SHHS PI will adjudicate outcomes specifically for SHHS. At the ARIC, CHS, and SHS sites, SHHS investigators will take over outcomes adjudication starting in the spring of 2005 to reduce the lag time between ascertainment and the availability to SHHS of adjudicated data. At FHS, the parent-study adjudication committee will continue to perform adjudication but will accelerate the adjudication process for SHHS subjects.

A summary of SHHS outcomes ascertainment and adjudication procedures for years 11-14 is shown in Table 7.3 below.

Table 7.3 Summary of outcomes ascertainment and adjudication

Sites	Ascertainment	Adjudication
ARIC	Will rely on ARIC system throughout	In final phase (starting spring 2005), will speed up medical record collection, and SHHS investigators will adjudicate.
CHS	CHS ascertainment calls will continue through 12/31/04, possibly 5/05. SHHS investigators will take over after that to cover period through 4/1/06.	Each CHS site will adjudicate its own events starting in spring 2005.
FHS	Will request FHS Exec Comm approval for ascertainment contact on 4/1/06	Will request that FHS M&M Committee accelerate adjudication of events ascertained on 4/1/06 contact
SHS	Will rely on SHS system throughout	Medical records will be duplicated at SHS field sites and sent to SHHS PI to adjudicate
NY	Contact cohort 9/1/04, 9/1/05, 4/1/06	Continue current adjudication process
Tucson	Continue yearly contacts	Continue current adjudication process

7.2.4 Ascertainment and adjudication by field site

7.2.4.1 Framingham

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.

7.2.4.2 Johns Hopkins

In the ARIC portion of the cohort, events are 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.

7.2.4.3 Minnesota

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

7.2.4.4 NYU/Cornell

Potential CHD events in the New York City cohorts will be ascertained every year by telephone, mail or clinic contact. Hospital and outpatient procedure records from any potential outcome event will be obtained and abstracted using the CHS forms. NYU 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.

7.2.4.5 Pittsburgh/Sacramento

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

7.2.4.6 Tucson

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 every year through an annual survey or by telephone call. Hospital and outpatient procedure records from any potential outcome event will be obtained and abstracted using procedures adapted from CHS. Subjects, or their legal representative, if they are deceased or not competent, will give consent to obtain copies of the medical records at the time of event ascertainment.

7.2.4.7 Strong Heart Study

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.

7.2.5 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 in Protocol 1), 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 New York and Tucson Investigative Centers' Adjudication Committees will adopt procedures based on the CHS abstraction forms and event criteria. 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.

7.2.5.1 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, and ECGs are 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 Centers' Adjudication Committees will adopt the procedures based on the CHS abstraction forms and event criteria.

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, 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.

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 procedures based on the CHS abstraction forms and event criteria.

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.

7.2.6 Congestive Heart Failure

7.2.6.1 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.

7.2.6.2 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. At the New York and Tucson sites, medical records for any potential episode of CHF ascertained during the follow-up questionnaire will be obtained and sent to their Cardiovascular Events Adjudication Committee.

7.2.6.3 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 crackles, 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. The New York and Tucson Investigative Centers Adjudication Committees will adopt procedures based on the CHS abstraction forms and event criteria.

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

7.2.7 Cerebrovascular Events

7.2.7.1 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.

7.2.7.2 Ascertainment

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

7.2.7.3 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 and Tucson centers will establish their own Cerebrovascular Events Adjudication Committees. For the carotid endarterectomy endpoint, documentation of this procedure during a hospitalization will be adequate to assign this endpoint without adjudication.

7.2.7.3.1 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, subarachnoid 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, subarachnoid hemorrhage
Hemorrhagic, indeterminaten	Any stroke, hemorrhagic stroke
Ischemic, lacunar	Any stroke non-hemorrhagic stroke
Ischemic, cardioembolic	Any stroke, hemorrhagic stroke
Ischemic, atherosclerotic	Any stroke non-hemorrhagic stroke
Ischemic, other (arterial dissection or arteritis)	Any stroke non-hemorrhagic stroke
Ischemic, unknown	Any stroke, hemorrhagic stroke

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

Framingham – 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
Hemorrhagic, subarachnoid	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".

New York/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 -- 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 procedures based on the CHS protocol. The Cerebrovascular Endpoints Committee, which includes a board certified neurologist, will then review the data and classify the event into one of SHHS categories.

A random sample of events reviewed by the Tucson and New York 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.

Strong Heart Study -- All CVD events, including cerebrovascular events, in Strong Heart Study are documented and reviewed with ongoing Morbidity and Mortality Surveillance. For cerebrovascular events, death certificates, and autopsy, physician and hospital records (ICD-9 discharge diagnoses 430—438) as well as information from Informant Interviews, are abstracted onto SHS forms. Death certificates are obtained and coded by a central nosologist, and deaths are reviewed by two members of the Mortality Review Committee. Hospitalized non-fatal stroke is determined by physician and laboratory findings, discharge diagnoses, and neurologic symptoms.

7.2.8 Hypertension

7.2.8.1 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.

7.2.8.2 Ascertainment

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

7.2.9 Mortality

7.2.9.1 Endpoints

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

7.2.9.2 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 New York Investigative Centers will use procedures adapted from CHS forms and protocol.

7.2.9.3 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. The New York and Tucson Investigative Centers' Adjudication Committees will adopt procedures based on the CHS abstraction forms and event criteria.

7.2.10 Transfer of Adjudicated Results from the Field Sites to the Coordinating Center

During the follow-up phase of the study, self-reported and adjudicated events will be reported to the CC periodically. Any self-reported symptoms or hospitalizations that have triggered parent study review and adjudication will be reported back to the CC. 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 Site 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 CC annually.

8. PROJECT MANAGEMENT

The CC has primary responsibility for study administration and data management. These responsibilities are outlined below.

8.1 Study Administration

The CC works with the Steering Committee and Project Office to administer the study, including the principal tasks of: 1) supporting the activities of the Investigative Centers and Field Sites; 2) monitoring overall study progress to ensure that goals are being met; and 3) carrying out data analysis and developing analytic approaches.

Many of these administrative activities fall under the rubric of communication, which is one of the CC's most important functions. These communications are summarized in Table 8.1 below. The CC is to be the primary conduit for communication between all participating sites, the Steering Committee, and the OSMB. Clear, frequent, and complete communications are vital to the successful operation of a collaborative study. In some instances communications will originate at the CC, and in other instances communications originating from another site will be sent to the CC 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. The SHHS website has an increasingly central role. Communications facilitated by the CC will be of several forms, including the following:

Routine communications: The CC will routinely distribute announcements regarding deadlines, upcoming meetings, decisions made by the Steering Committee, minutes from Steering Committee and OSMB meetings, and other study activities. Depending on the nature of a particular message, these communications may be sent to Investigative Center PIs, Field Site Directors, or Study Coordinators, the Steering Committee, or the OSMB. In general, copies of all communications will be sent to the Program Office.

Routine reports: During the follow-up data collection activities of this phase of the study, the CC will distribute reports to Investigative Center PIs and Field Site Directors and Study Coordinators and to the Project Office periodically. Comprehensive reports summarizing study progress will be prepared and distributed before each Steering Committee meeting and each OSMB meeting, approximately 1-2 times per year.

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

Documentation: The CC will also prepare and distribute study manuals and other policy documents as needed. These will be placed on the website.

Study Oversight: Another major function of the CC 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 Investigative Centers and Field Sites, the CC views itself as a collaborative supporter whose job is to provide the Field Sites the tools and support necessary to enable them to do their jobs efficiently.

Study oversight also includes quality assurance and control. The CC works with the appropriate Steering Committee Subcommittees to establish quality assurance policies (activities undertaken before data are collected to assure high quality). The CC will then take primary responsibility for monitoring that these policies are carried out. The CC 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 level.

Committee support: Each committee of the SHHS includes a member of the CC. This staffing assures that the CC will be fully aware of committee activities and able to facilitate communications among committees.

Table 8.1 Coordinating Center Communications

	Time frame	Sent to: IC/FS*	SC*	PO*	OSMB*
1. Routine communications: Deadlines, meetings, announcements, decisions	as needed**	X	X	X	X
2. Routine reports:					
Follow-up	2/yr	X	X	X	
Data quality	2/year	X	X	X	
Quality Control (performance)	2/year	X	X	X	
Steering Committee	2/year	X	X		
OSMB Report	1-2/year	X	X	X	X
3. Special reports: Problem identified Problem resolved Special progress report Statistical reports	as needed	X	X	X	X
4. Minutes from meetings		as needed	X		XX
5. Documentation Manuals Other policy/procedure documents	as needed	X	X	X	X

* IC = Investigative Center; FS = Field Site; SC = Steering Committee; PO = Program Office; OSMB = Observational Study 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 OSMB if the meeting being announced was the OSMB meeting.

8.2 Data Management

8.2.1 Data Management within the Coordinating Center

8.2.1.1 Outcomes Data Management

As outcomes data files are submitted to the Coordinating Center, they will be incorporated into the main database.

8.2.1.2 Backups and Data Security

Backups: Raw PSG data will be sent to the CC from the SRC on CDs. These will be archived permanently. Each CD will contain data from only one Field Site.

The database will be backed up monthly at the CC. The CC network is backed up every day. Some tapes are kept as permanent archives, others are rotated. An updated backup tape is taken off site weekly. Covariate information received from the parent studies will also be backed up onto tape and kept as a permanent archive.

Security: The CC is located in a secured building which allows no access by unauthorized individuals. The computer network is secured by use of passwords so that no unauthorized individuals (including unauthorized staff) have access to the SHHS database.

8.2.1.3 Database Management and Reporting

SAS 8.0 will be used for all database management functions at the CC. A set of programs for data checking and reporting will be written which will be run monthly by a data processor. SAS will be used to generate statistical reports.

9. QUALITY ASSURANCE AND CONTROL

Quality control of adjudication procedures

At the initiation of SHHS, we compared the adjudications of medical records of suspected acute MI cases done by a committee of SHHS investigators with the adjudications of the parent studies. (See original protocol.) We observed a high degree of agreement between results from SHHS investigators and the parent-study adjudication committees. Thus, we anticipate that the outcomes adjudication performed by SHHS investigators in New York and Tucson will be consistent with those of parent-study committees at other sites.

As we transition in the spring of 2005 to having SHHS investigators adjudicate outcomes at most sites, we will undertake another comparison study to assure consistent adjudication across sites. We will photocopy medical records (names blacked out) that have been adjudicated at the Tucson SHHS site and have the adjudication committee at each SHHS site that is performing its own adjudications review these records and adjudicate them. Results will be compared across sites. Any between-site disagreements will be evaluated, and inconsistencies in adjudication procedures will be addressed.

In the SHHS, 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 Investigative Centers and Field Sites, the SRC, or the CC as needed to advise them of problems and to discuss corrective actions. The CC monitors database logs and correspondence regarding data problems, conducts quality control analyses, and generates reports.

Quality assurance includes the following activities:

1. Detailed protocol development and documentation, including study design and data collection activities.
2. Provision of training and training updates as the basis of continuing education involving the protocol.
3. Documentation of all changes in protocol.

For quality control purposes, SHHS data collection is monitored by using quantitative QC procedures such as statistical analysis of data.

10. DATA ANALYSIS

10.1 General Approach

The following is an outline of the general approach proposed. The overall analytic plan and approaches will continue to be developed by the Steering Committee in collaboration with CC personnel. Over the last year, a specific Working Group has been meeting to give consideration to issues around longitudinal data analysis and the SHHS data set. This Working Group will continue to function in order to provide a focus for methodologic discussion.

The SHHS data set includes repeated measures of a number of exposures (e.g., smoking and RDI) and outcome measures (e.g., blood pressure). Over the course of the data collection specifically within the SHHS funding, there have been three visits with participants, including the two PSGs and the interim, limited follow-up visit at Years 7-8. Additionally, for some cohorts, data were accrued prior to the first SHHS visit. Approaches to the analysis of such data, including handling the repeated measures and missing data have now been available for some years and implemented in widely used analytic software[91,92]. Thus, the approaches for analysis of SHHS longitudinal data will involve both standard techniques for analysis of cohort data as well as novel longitudinal techniques for handling the repeated measures nature of the data.

In order to address the primary specific aims of SHHS, the relationships between baseline measures of SDB and incident CHD, stroke, hypertension, and mortality will be investigated descriptively using standard techniques for the analysis of cohort data. For the analysis of incident CVD and mortality, incidence rates based on person-years will be compared according to the presence and degree of SDB. In order to address the relationship between baseline measures of SDB and incident CVD, CHD, stroke, hypertension and mortality will be investigated using Kaplan-Meier[93] survival curves and the log rank test[94]. For the analyses of incident CVD, participants with baseline CHD or stroke will be excluded. For overall mortality, stratified analyses by presence of baseline CVD will be done. Multivariable analyses to control for potential confounding variables will be performed using Poisson regression and Cox proportional hazards regression models[95]. In addition to controlling for confounding, these models will be used to assess suspected intermediate variables such as hypertension in an analysis of incident stroke. Information available from interim follow-up exams will be used as time-dependent covariates. For analyses incorporating repeated or multiple measures of covariates such as SDB, BP, BMI during SHHS follow-up, longitudinal data analytic methods that consider the autocorrelation structure of the data into consideration will be employed[96]. These methods include generalized estimating equations (GEE) and mixed effects models.

Among participants free of hypertension at Exam Cycle 1, the occurrence of incident hypertension will be studied based on BP measurements or hypertension therapy in the follow-up exams[3]. Multivariate analyses of the cumulative incidence of hypertension will be conducted using multiple logistic regression analyses. In addition, change in BP values will be studied in relation to baseline and follow-up RDI using linear regression models.

Similar analyses will be used to study the relation between baseline and follow-up SDB and QOL outcomes. For the analyses of the natural history of SDB, the change in RDI and other sleep parameters, and dependency on demographic, anthropometric, and other variables (e.g., CVD risk factors, co-morbidities) will be studied using stratified and multiple regression analyses.

The availability of 2 PSGs raises the question as to how to classify the RDI over the follow-up interval: by baseline, in a time-dependent fashion, or as the average of the 2 values, which may represent the most stable indicator. We have explored the change in RDI between the 2 PSGs, finding only a small change on average. However, for some participants the change was more substantial so that a time-dependent approach may be more appropriate for them. Similarly BMI can be updated across the follow-up interval. Additionally, the availability of the 2 PSGs will allow exploration of causal directions, e.g., does having an event, either MI or stroke affect RDI.

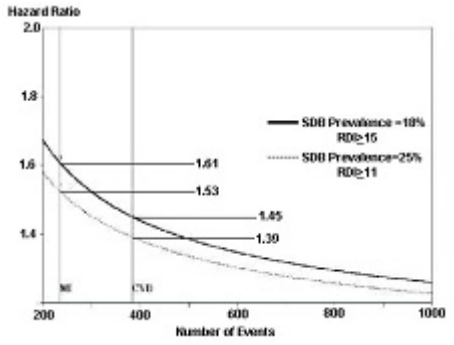
The SHHS represents a cohort of volunteers from previously established cohorts, raising the possibility that there may have been bias from greater representation of persons concerned about having SDB and possibly selection bias that would lead to inflation of risk estimates for the association of RDI with CVD risk. The potential for such bias will be explored by comparison of characteristics of the parent study participants and non-participants; for many of the latter, information will be available from the Sleep Habits Questionnaire. Similarly we will compare those having a second PSG with those not having a second study. For example, it appears that older age was a strong predictor of not having a second study.

10.2 Imputing SDB Prior to SHHS

Although SHHS began in 1994, its parent cohorts were started as much as 25 years previously (Appendix 5, Figure C.1.1). Thus, SHHS should be conceptualized as adding 2 assessments of sleep and SDB to existing cohort studies. This relationship to the parent cohorts provides the unique opportunity to explore novel analytic methods for using cross-sectional and longitudinal data to impute RDI severity or other measures prior to the start of SHHS. A similar approach was used to reconstruct the natural history of HIV infection from observations made over a limited window of the diseases course[97,94]. In the Progress Report, we describe initial efforts to predict the RDI, both cross-sectionally and longitudinally, using the two PSGs (Appendix 5, Section C.4.3).

If we proceed to use the prior information in the parent cohorts, the method of multiple imputation will be used to appropriately impute the missing RDI data for periods prior to the inception of the SHHS[98]. The main idea of multiple imputation is to predict the missing data from its conditional distribution given the observed data. Separate complete data sets (3-5) are created by independently simulating each missing observation from this conditional distribution, 3-5 repeated times.

Figure D.4.3: Minimum Detectable Hazard Ratios



Each of the complete data sets can then be used to estimate the relative risk of interest, leading to 3 separate estimates and 3 separate standard errors.

The overall estimate is simply the average of the 3; its standard error combines uncertainty within each of the 3 analyses as measured by the 3 standard errors as well as differences among the 3 analyses as measured by differences among the 3 separate estimates. This second component takes appropriate account of the fact that data were imputed and not observed. The conditional distribution of the missing data given the observed data is estimated from the set of observations without missing data using the appropriate regression methods. To obtain a simulated value for a missing observation, we combine the predicted value of the missing observation given the other observed values for that individual with a random error, so that the imputed values reflect both the systematic and random components of missing data.

10.3 CVD and Mortality Risk Assessment-Precision and Power

As of May 2003, the observed event rates (per 1,000 person-years) in SHHS participants were 5.1 and 9.9 for AMI and incident CVD events respectively. Total numbers are shown in Appendix 5 Table C.4.1-6. Preliminary analyses reported in Section C.4.1 suggest that SDB adversely affects CVD risk and overall mortality. However, there are insufficient numbers of events to calculate stable estimates of risk as demonstrated by wide confidence intervals. Hence, a longer follow-up period than the current mean 4 year adjudicated follow-up interval is required in order to capture an adequate number of events. If the current event rate is extrapolated over 4.25 years of additional follow-up to August 2007, we project that the number of deaths in the cohort will increase from 488 to 1000 (104%). Furthermore, we project that the number of incident myocardial infarctions will increase from 106 to 234 (125%) and the number of total incident CVD events will increase from 187 to 384 (127%).

As shown in the Figure D.4.3, by lengthening the duration of follow-up, we will have at least 80% power assuming a SDB prevalence rate in the SHHS population of 25% to detect a hazard ratio for total incident CVD events as low as 1.39 and for incident myocardial infarction as low as 1.53. Slightly higher minimum hazard ratios would be detectable if a slightly lower SDB prevalence rate is used. Depending on the definition of SDB employed, the prevalence rates used in these projections are currently observed in our cohort[99]. Given the relatively high prevalence of SDB in the general population[13], even a hazard ratio of 1.39 would have important public health implications.

An alternative approach is to calculate the available precision afforded by this sample size in estimating the difference in event rates between groups defined by SDB. Given the observed number at risk and the projected event rates, the difference in proportion with AMI events can be estimated to within $\pm$1.5%. Similarly, the difference in proportion with incident CVD events can be estimated to within $\pm$2.0%. Thus, with additional follow-up of the cohort, it highly likely that SHHS will be able to complete its primary mission of determining whether SDB operates as an independent risk factor for the development of new CVD and mortality.

11. DATA SHARING

11.1 Data Sharing Plan

One component of the proposed research plan is the establishment of a data sharing infrastructure that will allow interested and qualified investigators who are not members of the SHHS research group to access PSG and associated clinical data. In addition, SHHS currently and will continue to encourage collaboration with other investigators. The mechanisms in place for initiating collaboration with SHHS are outlined on the SHHS website, http://www.jhucct.com/shhs/. Briefly, prospective collaborating investigators are encouraged to contact a SHHS investigator to discuss their proposed research. If after these discussions, the project appears appropriate and feasible, and additional data collection is required, a formal application for an ancillary study is submitted to the SHHS Steering Committee. If the project involves only analysis of data already collected by SHHS or one of its parent cohorts, a manuscript proposal is prepared according to the SHHS Manual of Operations, http://www.jhucct.com/shhs/manual/procedures/. Some projects may involve transfer of data from the SHHS CC to a non-SHHS investigator. In such cases, the investigator will be required to sign a data-sharing agreement that provides for (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

11.2 Rationale

We plan to develop the large, unique PSG and covariate database generated from the SHHS 1,2, and 3 exams into a national research resource readily available to the scientific community. This will be accomplished by providing detailed documentation of the data, developing tools to facilitate identification of records for specialized analyses, and developing archival and access tools available through universally available web-based systems. There are 2 main groups of potential users. First are physiologists/engineers interested in developing advanced signal processing algorithms for efficient scoring of PSG records, or for identifying novel “hidden’ features that predict outcomes. Participants at a recent NIH Workshop on Sleep Informatics noted that databases like SHHS have the potential to contribute to the development of improved processing and analysis algorithms because they use digital time series-type data, and include information collected and scored using standardized, well-documented and highly reliable approaches from subjects representing diverse demographic backgrounds and physiologic variation. The second group is epidemiologists/clinicians interested in linking the physiological signals and/or scored data to risk factors and outcomes to develop improved estimates of population-based risks from sleep-related exposures. Databases for these purposes will generally require linking the scored (annotations and/or summary) files with data on relevant clinical covariates, such as demographics, medications, co-morbidity, and prospectively determined outcomes.

11. DATA SHARING

A primary collaboration with Physionet (Research Resource for Complex Physiologic Signals), a NIH-funded National Center for Research Resources program, will be established. This will permit a 2-level approach to data access, capitalizing on Physionet's expertise in developing open source software for displaying and accessing biomedical data via web interfaces to assure that a large sample of PSGs rapidly will be made publicly available. In addition, the SHHS SRC will supplement the primary posting by Physionet with development of a full archive of ***all*** SHHS data (physiological signals and covariate data) on a SHHS Reading Center Server (SRCS) accessible via a web interface. The SRC also will develop software tools to allow the full SHHS dataset to be interrogated, with creation and dissemination of new data subsets for the analytic purposes collaborating investigators.

11.3 Procedures for Establishing a Reference Set of PSGs Accessible Via Physionet

Procedures are being created for establishing a reference set of 1000 PSGs accessible via physionet. 1000 representative PSGs will be selected to assure a wide range of sleep physiology and demographic representation. This data set will be restricted to studies with quality grades of "very good or better" (comprising » 80% of total studies). All such studies with an RDI $\geq$ 30 as well as all studies performed on ethnic minorities, and a random sample of the remaining high quality records will be selected from age (</$\geq$ 65 years), gender, and site-specific stratum. The digitized Compumedics records will be converted at the SRC to European Data Format (EDF) using Nexusã, a PSG database system currently residing on the SRCS. The Nexus conversion process will also create SQL tables of the associated "event files" (containing summaries of all scored "annotations"). Digitized records also will be converted to Waveform Form Database formats (WFDB) using existing open-source software created by PhysioNet. These files, including covariate data on sex, age, and BMI, will be transferred to Physionet, which through its 3 core and interrelated components (PhysioBank, a data resource; PhysioToolkit, an analytic/software resource; and PhysioNet, a dissemination /communications resource) will provide web-based, unrestricted access to the raw physiological signals, scored annotations, summary scored data (staging, arousals, respiratory events), associated quality control codes, and demographic data (see Appendix 2 and www.physionet.org/physiobank/database/shhspsgdb/ for an example of a SHHS record and associated files posted). PhysioNet has agreed to post the files containing sleep staging, arousals, and respiratory event annotations, demographic data, and both the EDF and WFDB files containing the digitized PSGs. Physionet open-source software provides tools for creating, viewing, editing, and analyzing signal and annotation files in any of the many formats supported by a WFDB formats library. Their experience with other biomedical datasets and web development, and large server based at MIT, will assure an efficient, cost-effective means for rapidly making available a standard reference dataset of PSGs that are universally accessible.

11.4 Procedures for Establishing the SRCS Web-Accessible Database

Although PhysioNet provides a large collection of open-source software, they do not currently have a full set of tools for searching/extracting specific features of the digitized records or the resources to provide support for linking the physiological signal data to the varied and complex SHHS covariate data. Thus, SHHS will provide specialized tools and additional support for assuring appropriate access and interpretation of the covariate data and the full set of 9736 SHHS PSGs. Each PSG is associated with 8 files that contain information on the various scored annotations (e.g., arousals, respiratory events, etc.) that could serve as "objects" for varied analyses. Reports of each scored record each contain >700 summary PSG indices. Covariate data include BP, waist and hip measurements, sleep symptoms, medications and co-morbidities from each SHHS exam. Specialized SHHS input and detailed documentation is required to assure these data formats, structure, and content are understood by outside investigators, and data are used appropriately. Analyses may require access to specialized software tools to search all PSG records and covariate databases to identify specific clinical characteristics or signal features relevant for varied hypotheses, extracting such features (e.g., all epochs with arousals), and then concatenate data subsets into analytic files.

To meet these needs, the engineering team at the SRC will develop a Web application that will provide convenient and restricted access to the large and complex SHHS data stored in the SRC Nexus System. Existing Nexus software provides some search and link functions (e.g., records can be searched according to parameters that specify ranges of summary PSG statistics contained within SQL tables, such as the RDI, sleep stage distributions). These algorithms will be further extended to allow studies to be searched by items in SHHS non-PSG data tables. Some examples that will serve as indices as search options include: age, sex, race/ethnicity, and data regarding hypertension and CVD disease. Additional information available for subsets of SHHS include cerebral MRI data, glucose and insulin levels and echocardiographic findings. Finally, new tools will be developed to directly search the raw PSG signals to identify studies defined by characteristics as spectral power of the EEG, heart rate variability, and clustering patterns of O_2 saturation. Users will be able to construct their own queries on the data set, view the resulting data sets and download the raw PSG data. The final structure will be modified according to a needs assessment conducted during the first few months of the study (see timeline, Section 11.5). The hardware system overview is diagrammed in Appendix 4.

The development of the SRCS Web application includes meeting the following requirements:

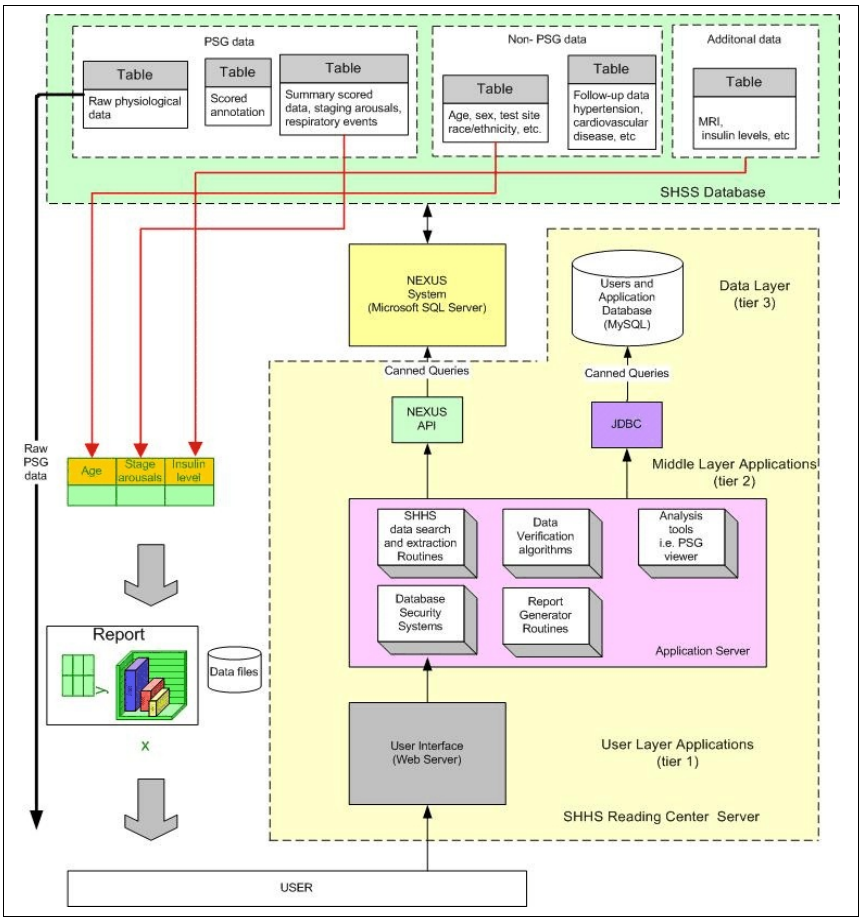
- Secure and controlled access to the 6441 and 3295 PSGs obtained during the SHHS-1 and SHHS-3 cycles, respectively including the raw physiological signals, scored annotations, summary scored data (staging arousals, respiratory events, etc.) and detailed SHHS covariate;
- A user interface that allows convenient construction of complex search criteria of the SHHS data, viewing of the results of the queries and retrieval of the raw PSG data corresponding to the results;
- Tools for sorting data, cross-linking various data sets, extracting subsets of records, verifying the integrity of the data, and concatenating the results of the queries into specific analytic data files;

- Providing documentation of current status of the data and any changes, SHHS procedures and activities;
- Protection against user modification of the database;

- HIPAA compliance to ensure security and privacy.

Design of the SRCS Web application

The design of the SRCS Web application is a 3 tier system as shown in Figure D.5.3 The first tier consists of Web server applications that provide a user interface. This provides information on the SHHS data such as the study procedures and offers a convenient way to specify search criteria in both PSG and non-PSG data tables. It also notifies the user of changes in the SHHS database. After the application retrieves results from the database, the user is able to view the results of the query and to download the raw PSG data corresponding to those reports. The data entered into the first tier application is passed through simple error checking routines and passed down to the application server in the second tier.



The second tier contains the bulk of the application logic and all database connectivity. In order to enhance the security of the database, the data security systems are additionally integrated at the SHHS Web application, the routines in the second tier verify the user information and allow access only to users approved by SHHS. A Web application database in the third tier stores the account information of the registered users. The application server accesses this database through Java Database Connectivity (JDBC). JDBC is an application programming interface (API) that gives access to any tabular data source from the Java programming language. The security system also audits the user activities to monitor overall concurrent user activity and pinpoint malicious activity.

11. DATA SHARING

The data search and extraction routines process the data received from the Web server, generate the transactions and send them to a NEXUS API. The API is an application programming interface between the SHHS database and the NEXUS system. Once the NEXUS API receives the transactions from the application server, it translates them to the protocol of the NEXUS system. The transitions from the second tier are then sent to the NEXUS system in the third tier or the data layer.

The transaction from the second tier is processed in the NEXUS system. The results from the queries are passed back to the second tier. The data verification algorithms examine the results in order to check the integrity of the data. The report generator then concatenates the resulting data into a specific analytic data file and produces the report. After the application retrieves results from the SHHS database, the user is able to view the reports generated from the results of the query and to download the raw PSG data corresponding to those reports. The analysis tools provide a means for the user to view a graphical representation of the results specified in the report as well as the associated raw PSG data through an appropriate viewer. These data and the report are then passed back up to the user interface in the first tier.

Implementation of the SRCS Web application

The development team (Co-I's: Loparo, Phattanasri, see PI: Redline application) will implement the Web server and the application server of the SRCS Web application using the Java platform. This platform enables software developers to create applications that run on either the server or the client. On the server side, Java Server Page (JSP) technology is an extension of the Java Servlet technology and can be used to extend the capabilities of a Web server with minimal overhead, maintenance, and support. JSP also has powerful tools for managing and controlling the databases. On the client side, Java applets can be used to develop client side applications allowing for very elaborate user interface programming. By using this advantage, the team can add useful analysis tools such as feature extraction or data mining tools to the SRCS Web application with minimal server load. Furthermore, this technology is platform-independent. Therefore, the developed applications and tools can be implemented in any server platform without changing the code. This is done by using the Java Virtual Machine (VM). The Java development tools are available free of charge from Sun Microsystems, Inc. The database server of the NEXUS system is a Microsoft SQL 2000. Microsoft has already provided JDBC drivers for Microsoft SQL 2000 server since early 2002. The engineering team will develop a NEXUS API by using the JDBC driver. For the application database, the team will use MySQL as a database server. MySQL is a powerful open source database server that supports JDBC. The Web server, the application server and the application database will run from the SRSC.

11.5 Timeline

- 09/04-10/04: Solicit community input on needs. (Write/email user groups and NIH funded investigators in the sleep or signal processing fields; post information on Physionet and SHHS web sites soliciting suggestions)
- 9/04-12/04: Migrate the 9736 PSGs (currently on »300 CDs, each record with 8 subfiles) to the SRCS. Convert studies to EDF and WFDB files and SQL tables.
- 12/04-2/05: Identify 1000 PSGs for unrestricted access and transfer these files for posting on Physionet.
- 8//04-8/06: Develop SRCS web applications.
- 2/05-4/05: Cross-link all PSG files to covariate data files.
- 4/05-6/05: Initial public posting of SRCS web site. Solicit community feedback.
- 6/05-8/08: Modify web applications per community feedback. Develop/refine software tools to expedite searching, extraction, and concatenation.
- 09/04-8/08: Develop detailed documentation for all variables and study methods, including a potentially universally relevant data dictionary that defines key elements common to sleep epidemiology studies. Develop and disseminate detailed procedures for accessing SHHS data and collaborating with the SHHS investigators.

11.6 Accessing the detailed data

To facilitate external collaborations, the SRC will transfer appropriate data sets to outside investigators who identify specific hypotheses that cannot be addressed by the Physionet SHHS archive. Data access will require submitting a form that contains a data request and collaboration and confidentiality agreements (available through the SHHS web site). Requests will be reviewed within 4 weeks by the SHHS Publications and Presentations Subcommittee. They will recommend approval or modifications to the Steering Committee who will grant final approval. Appropriate SHHS collaborators will be identified to help external investigators best understand the structure of the data and the context of each analysis in regard to other SHHS projects (i.e., assuring that each group is informed of relevant progress/obstacles faced by others). It is anticipated that most of these projects will be funded by grants awarded to external collaborators. A format for maximizing input while encouraging creativity and maintaining the study's integrity will be developed including user-friendly application procedures, web-updates summarizing ongoing analytic activities, and web-based tools. Data will be made available either by specific password access to the SRCS, or by delivery of CDs with the requested datasets.

11.7 Assuring confidentiality

All accessible data will be de-identified. Because SHHS personal ID numbers include a site code, all such IDs will be recoded without reference to site to minimize any chance that a PSG record for a person of a given age, sex, and BMI can be tracked to a specific community. To be compliant with HIPAA, specific ages for any individual with an age > 90 will not be provided (i.e., will be coded as >90).

11.8 Data Dictionary

A comprehensive data dictionary will be available both on the SRC and PhysioBank web sites that will describe how all data were collected, will specify the algorithms used for scoring all events and epoch assignments, and will describe all quality codes assigned to each study and each signal. An electronic atlas, as developed for SHHS, will also be updated to provide visual examples of the scoring algorithms.

11.9 Future Extensions of the PSG Data Sharing Systems

The SHHS SRC is also the Reading Center for other large-scale NIH funded cohort studies that have incorporated PSGs. These include the MrOS Sleep Study (a prospective study of 3000 older men), the SOF Study (of 500 older women), the Honolulu Asian American Aging Study of Sleep Apnea (n=700), the Harvard PPG pollution–apnea study (n=250), the Pickering Neighborhood Studies (n=300), the Cleveland Family Study (n=700 with PSGs similar to SHHS), and the Cleveland Children's Health and Sleep Study (n=250). These studies all have use(d) comparable technology to SHHS, with studies scored in a nearly identical manner. Although the proposed efforts by SHHS will pioneer the establishment of a fully accessible web based PSG data system, such efforts should easily translate to these other studies, facilitating cross-study collaborations. Such collaborations may facilitate conducting subanalyses of carefully defined groups, in whom frequency in any given study may be low (e.g., individuals with high RDI and no sleepiness or no hypertension), as well as allow full exploration of population (gender, ethnicity, age) differences in disease expression. Additionally, since the SHHS SRC had established many of the procedures used by other, newer Reading Centers (e.g., Look Ahead, University of Pennsylvania; TuCASA, University of Arizona), data approaches should be easily extended to include those studies as well.

12. PROJECT GOVERNANCE

The SHHS consists of several key components: the eight Investigative Centers, the CC, the SRC, and the NHLBI Project Office. 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 the University of Arizona, Boston University, University of California-Davis, University of Pittsburgh, Johns Hopkins University, University of Minnesota, New York University, and at Medstar for the Strong Heart Study. 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 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 4 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 high-quality data and adherence to the protocol, 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 the Operations Subcommittee as necessary.

12.1.2 Coordinating Center (CC)

The CC, at the Johns Hopkins Bloomberg School of Public Health, is responsible for statistical planning and accumulation of quality data from the Field Sites, training of the Field Site personnel in non-PSG functions and data collection, data management and transmission, and the management of technical aspects of CC activities.

The CC participates in and coordinates the development of the study protocol and the Manual of Operations. It also coordinates 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. CC investigators design, produce, and test forms to be used in the study, and develop, test, and implement the data entry system. The CC is also responsible for arrangements for the Steering Committee meetings and minutes from these meetings.

Quality and quantity of data from the Field Sites is monitored and reported by the CC to the centers and to the Steering Committee. The CC prepares confidential reports for the Observational Study Monitoring Board (OSMB), as well as interim and final analyses and other specific statistical analyses and reports. The CC supports manuscript preparation through data analysis, statistical consultation, editorial tasks and coordination of meetings.

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

12.1.3 Sleep Reading Center (SRC)

In this phase of the study, the SRC at Case Western Reserve University serves as a centralized laboratory to provide standardized interpretation and quality assessments of all sleep studies obtained as a part of this study. It will assist the CC in establishing all procedures related to obtaining sleep data that best meet study objectives and in implementing these procedures. The SRC is responsible for: developing a PSG data sharing infrastructure as described in section 11.0, assisting in data analysis, and development of ancillary and nested studies. The Director of the SRC is 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 Officer. The NHLBI Project Officer 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 Officer 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 OSMB. The NHLBI Project Officer may, consistent with the publication policy to be adopted by the Steering Committee, have lead responsibilities in the preparation of some publications. The NHLBI Project Officer has voting membership on the Steering Committee and, as appropriate, its subcommittees.

12.2 Committees

A complete list of SHHS committees and an organizational chart are included in Appendix 3.

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 Steering Committee meets on an as-needed basis, depending on data collection and analysis activities. It meets both in-person and by telephone conference call.

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 OSMB.

Voting members of the Steering Committee include the P.I. from each Investigative Center (or the designated alternate); the P.I. from the CC (or the designated alternate); the director of the SRC, and the NHLBI Project Officer. Other, non-voting attendees at Steering Committee meetings may include other NHLBI staff; other CC staff; other investigative center participants; other expert consultants invited to committee meetings 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 memberships of the subcommittees for Years 11-14 of the study are listed in Appendix 3.

Publications and Presentations Subcommittee:

The Publications and Presentations (P&P) Subcommittee is charged with reviewing and maintaining publication and presentation policies. A Principal Investigator (P.I.), elected by the Steering Committee, serves as the Chairperson (which may be a rotating position). The major responsibilities of the committee are to develop and maintain policies and execute procedures for the approval and review process 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. The P&P Subcommittee serves in an advisory capacity to the Steering Committee, which has final authority for approval or disapproval of all recommendations of the P&P Subcommittee.

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.

Data Dissemination

The Data Dissemination Subcommittee is charged with developing the large, unique PSG and covarite database from SHHS 1, 2, and 3 exams into a national research resource readily available to the scientific community.

12.3 Observational Study Monitoring Board

The Observational Study Monitoring Board (OSMB) 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 OSMB 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 OSMB 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 CC and/or other SHHS Investigators, as determined by the Steering Committee will attend OSMB meetings to present data. The NHLBI Project Officer will serve as executive secretary of the OSMB. If necessary, the chairperson of the Steering Committee will be contacted (by mail or phone) to answer questions.

The OSMB will meet twice a year to ensure participant safety and/or study integrity. The OSMB will monitor data quality, including protocol adherence, and identify emerging operational issues. The OSMB 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 OSMB will be strictly confidential.

The OSMB 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 CC. 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 OSMB 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 OSMB 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 OSMB.

13. PUBLICATION AND PRESENTATION POLICIES AND PROCEDURES

The Publications and Presentations (P&P) Subcommittee has been appointed by the Steering Committee to develop and maintain policies and procedures for the review and conduct of abstracts, presentations and publications relating to the SHHS.

13.1 Publication and Presentations Subcommittee

The responsibilities of the P&P Subcommittee are to stimulate scientific presentations and manuscripts from SHHS investigators and to assure that:

1. abstracts, presentations and publications are scientifically accurate and objective
2. all investigators have the opportunity to participate in the preparation of SHHS publications
3. data analyses and manuscript preparation/submission are completed in a timely fashion, and
4. appropriate review is conducted by the SHHS Steering Committee, NHLBI and parent studies

13.2 Study documents related to Publications and Presentations

Procedures have been established for the following:

1. Submission of a formal proposal for an abstract or manuscript
2. Composition and responsibilities of writing groups for an abstract or manuscript
3. Time schedule for manuscript preparation after approval
4. Schedule for the review procedures for proposals, abstracts, presentation materials and manuscripts by the P&P Subcommittee, Steering Committee, NHLBI and parent studies.

13. PUBLICATION AND PRESENTATION POLICIES AND PROCEDURES

13.3 Study documents related to Publications and Presentations

The following study-related materials are maintained by the CC:

1. Checklist/tracking form of steps in manuscript proposal and development
2. Manuscript proposals and descriptions of all approved papers
3. Correspondence regarding review and approval of abstracts and manuscripts, including Steering Committee nominations for writing groups
4. Presentation materials
5. Reprints of manuscripts
6. Lay summaries of manuscripts
7. Manuscript matrix listing manuscript number, abbreviated titles, writing group, important dates and status of all active manuscripts.
8. Current listing of SHHS publications.

APPENDICES

APPENDIX 1: References

1) Hoffstein, V., C.K. Chan, and A.S. Slutsky. Sleep apnea and systemic hypertension: A causal association review. Am. J. Med 91:190-196; 1991.

2) Koskenvuo, M, J. Kaprio, T. Telakivi, M. Partinen, K. Heikkila and S. Sarna. Snoring as a risk factor for ischemic heart disease and stroke in men. Brit Med J. 294:16-19; 1987.

3) Partinen, M. and H. Palomaki. Snoring and cerebral infarction. Lancet ii:1325-26; 1985.

4) Williams, A.J., D. Houston, S. Finberg, C. Lam, J. Kinney and S. Santiago. Sleep apnea and essential hypertension. Am J. Cardiol. 55:1019-1022; 1985.

5) Fletcher E.C., R. DeBenke, M. Lovoi, and A. Gorin. Undiagnosed sleep apnea in patients with essential hypertension. Ann. Intern. Med. 103:190-5; 1985.

6) Young, T., M. Palta, J. Dempsey, J. Skatrud, S. Weber, and S. Badr. The occurrence of sleep disordered breathing among middle-aged adults. N. Engl J. Med. 328:1230-5; 1993.

7) Hung, J., E. Whitford, R. Parsons, and D. Hillman. Association of sleep apnea with myocardial infarction in men. Lancet 336:261-64; 1990.

8) He J., M. Kryger, F. Zorick, W. Conway, and T. Roth. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. Chest 94:9-14; 1988.

9) Redline, S. Hans, M., Prackarkon, N., et. al. Differences in age distribution and risk factors for sleep disordered breathing in Blacks and Whites. AJRCCM 149 (S): 576; 1994.

10) Block, A.J., J. Wynne, P. Boysen, S. Lendsey, C. Martin, and B. Canton. Menopause, medroxy-progesterone, and breathing during sleep. Am. J. Med. 70:506-510; 1981.

11) Hla, K., T. Young, T. Bidwell, et. al., Sleep Apnea and Hypertension: A Population Study. Ann Intern Med. 120:382-388; 1994.

12) Kostis, J.B., and R. Rosen. Central nervous system effects of beta-adrenergic blocking drugs: the role of ancillary properties. Circ., 75:204-212; 1987.

13) Ancoli-Isreal, S. Epidemiology of sleep disorders. Clinics in Geriatric Medicine. 5:347-362; 1989.

14) Kales, A., R. Cadieux, E. Bixler, et. al. Severe obstructive sleep apnea I. Onset, clinical course and characteristics. J. Chronic Dis. 38:419-425; 1985.

15) Schmidt-Nowara, W., D.B. Coultas, C. Wiggins, B. Skipper, and J. Samet. Snoring in a Hispanic-American population. Arch Int Med 150:597-601; 1990.

APPENDIX 1: References

16) D'Alessandro, R., Magelli, C., Gamberini, G. Snoring every night as a risk factor for myocardial infarction: a case-control study. Brit Med J 1990;300:1557-8.

17) Spriggs, D., French, J.M., Murdy, J.M., et al. Historical risk factors for stroke: A case control study. Age Aging 1990; 19:280-287.

18) Palomaki, H. Snoring and the risk of brain infarction. Stroke 1991; 22:1021-1025.

19) Lund-Johansen, P., White, W. Central hemodynamics and 24 hour blood pressure in obstructive sleep apnea syndrome: effects of corrective surgery. Amer J Med 1990; 88:678-682.

20) Guilleminault, C., Dement, W.C. Sleep apnea syndromes and related disorders. Williams, R.L., Katacan, I., eds. Sleep Disorders: Diagnosis and Treatment. New York: Wiley; 1978.

21) Partinen, M., Guilleminault, C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. Chest 1990;97:27-32.

22) Kales, A., Cadieux, R.J., Shaw, L.C., VelaBueno, A., Bixler, E.O., Schneck, D.W. Sleep apnea in a hypertensive population. Lancet 1984; 2:1005-8.

23) Rechtshaffer, A., Kales, A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Washington DC: US Government Printing Office, 1968.

24) Atlas Task Force. EEG arousals: Scoring rules and examples. Sleep 1992;15:173-184.

25) The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; Arch Int Med 1997; 157(21):2413-2446.

26) Redline, S., Kapur, V.K., Sanders, M.H., Quan, S.F., Gottlieb, D.J., Rapoport, D.M., Bonekat, W.H., Smith, P.L., Kiley, J.P., Iber, C. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment; Am J Respir Crit Care Med 2000; 161:369-74.

APPENDIX 2: 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	X	---
Death	X	X	---	X	X	X
CHF	X	X	X	---	X	---
Pulmonary Disease	---	---	---	---	---	X
Coronary Artery Bypass	X	---	---	X	X	---
Coronary Angioplasty	X	---	---	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	
SES						
Education	X	X	---	X	X	X
Occupation	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 circumference	---	X	---	---	X	---
Bioelectrical impedance	—	X	X	---	---	
BLOOD PRESSURE						
BP measured	X	X	X	X	X	X

Potential Risk Factors Collected by Parent Cohorts (cont'd)

Key: X = collected --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
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						
Past/Current/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	
ALCOHOL INTAKE						
History	X	X	---	X	X	X
Habits & Type	X	X	X	X	X	X
SUBCLINICAL CVD						
ECG, 12-lead	X	X			X	
B-mode Ultrasound					X	
Carotid	X	X	X	Some	X	---
Popliteal	X	---	---	---	X	---

Potential Risk Factors Collected by Parent Cohorts (cont'd)

Key: X = collected --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
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						
Total cholesterol	X	X	X	X	X	X
Triglycerides	X	X	X	X	X	---
HDL	X	X	X	X	X	---

Potential Risk Factors Collected by Parent Cohorts (cont'd)

Key: X = collected --- = not collected

Component	ARIC	CHS	Framingham	New York	Strong Heart	Tucson
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

Potential Risk Factors Collected by Parent Cohorts (cont'd)

Key: X = collected --- = not collected

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	---	—	---	---	---	---
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	---	---	—	---	---	---
Get too much sleep	---	---	—	---	---	X
Wake up too early and not being able to get back	---	---	—	---	---	X
Falling asleep during the day	---	—	—	—	---	X
Nightmares	---	—	—	—	—	—

APPENDIX 3: SHHS Committee Organization

SHHS COMMITTEE ORGANIZATION

STEERING COMMITTEE

Chairperson:	Stuart F. Quan, M.D.	Tucson
Investigative Centers:	Naresh Punjabi, M.D., Ph.D.	Baltimore
	George T. O'Connor, M.D., M.S.	Boston
	David M. Rapoport, M.D.	New York City
	Helaine Resnick, Ph.D.	Washington, D.C.
	John A. Robbins, M.D., M.H.S.	Sacramento
	Eyal Shahar, M.D., M.P.H.	Minneapolis
	Anne Newman, M.D., M.P.H.	Pittsburgh
Sleep Reading Center:	Susan Redline, M.D., M.P.H.	Cleveland
Coordinating Center:	Jonathan M. Samet, M.D., M.S.	Baltimore
NHLBI Project Scientist:	Michael Twery, Ph.D.	Bethesda

SUBCOMMITTEES

Morbidity and Mortality Subcommittee

Chairman:	George O'Connor
Members:	Tauqeer Ali, Russell Dodge, James Goodwin, Anne Newman, Eyal Shahar

Publications and Presentations Subcommittee

Chairman:	John Robbins
Members:	Marie Diener-West, George O'Connor, David Rapoport, Susan Redline, Michael Twery

Data Dissemination Subcommittee

Chairman:	Susan Redline
Members:	Kenneth Loparo, Naresh Punjabi, David Rapoport , Jonathan Samet, Susan Surovec, Michael Twery

NHLBI APPOINTED COMMITTEES

Observational Study Monitoring Board (OSMB)

Chairperson:	John V. Weil, M.D.	Denver
Board Members:	Julie E. Buring, Sc.D.	Boston
	Vernon M. Chinchilli, Ph.D.	Hershey
	Stephen Loring, M.D,	Boston
	Otelio S. Randall, M.D.	Washington, D. C.
	Wolfgang W. Schmidt-Nowara, M.D.	Albuquerque
	Phyllis Zee, Ph.D.	Chicago

APPENDIX 4: Policy on conflict of interest 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:

1) 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,

2) 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:

APPENDIX 4: Policy on Conflict of Interest

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.

APPENDIX 4: Policy on Conflict of Interest

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 Relation _____

_____

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: _____

6/7/95