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 renewal. The Centers are:

University of Arizona
Boston University
University of California at Davis/University of Pittsburgh
Johns Hopkins University
University of Minnesota
New York University/Cornell University
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/Pittsburgh site has two Field Sites, one in Sacramento, California, and one 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 CC is at the Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland. There are two central reading centers - the Sleep Reading Center at the Case Western Reserve University in Cleveland, Ohio, and the ECG Reading Center at Cornell University in New York City.

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. RECRUITMENT FOR FOLLOW-UP VISIT 2

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 will include all surviving members of the cohort who had a PSG at the baseline visit. In general, participants will be sent a letter, announcing the continuation of the study, and indicating that a staff member will 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 will take place at a study clinic, if the SHHS schedule coincides with a parent study exam; in other sites, participants will be recruited by telephone. It is expected that approximately 4,000 participants will undergo a second PSG. Recruitment attempts and outcome will be recorded on a contact form.

Exclusion criteria for the second PSG will be similar to the criteria that were used at the baseline examination, i.e., conditions that pose technical difficulties for polysomnography:

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

7. DATA COLLECTION

Data collection for variables not gathered from the parent cohorts will follow a priority list, as described below:

First priority: Conduct a home visit and obtain complete data from PSG-eligible cohort members including unattended PSG, other physical measurements, and questionnaire data.

Second priority: Conduct a home visit to obtain physical measurements and questionnaire data from cohort members who either refuse or are not eligible for a PSG.

Third priority: Obtain self-reported data via the Screening form (SC) and a mailed Sleep Habits and Lifestyle questionnaire (SH) from cohort members who refuse a home visit.

Fourth priority: Obtain limited self-reported data via the Screening form (SC) from cohort members who refuse any other data collection.

7.1 Consent procedures

Prior to any data collection at the home, a staff member will review the study procedures with the participant, and obtain a signed consent. Two separate consent forms will be used. One consent form will be used for participants willing to undergo a second PSG, and another for participants willing to participate in all other data collection, consisting of questionnaires and physical measurements. Prior

consent to participate in the SHHS, in conjunction with return of the Sleep Habits and Lifestyle questionnaire, should be sufficient to collect mail interview data related to sleep habits and lifestyle and telephone interview data related to cardiovascular events and procedures. Staff who are charged with acquiring informed consent from participants will be certified either according to procedures acceptable to their home institutions, or via the NIH intramural website course for researchers in the protection of human research subjects (http://ohsr.od.nih.gov/cbt/ as of 5 October 2000).

7.2 PSG Study

The second PSG study in the participant's home during SHHS Follow-up 2 will span Years 7-9 and will occur at the earliest 4 years 9 months after the Baseline with PSG-1. Preferably the PSG will be done at the latest by 5 years 3 months following the Baseline PSG, however, sleep studies done after that time will be accepted. The timing of the second PSG was determined to provide as large of a time interval between measurements as was feasible in order to maximize information on change. The montage and recording apparatus will be almost identical to that used in the first examination.

Recording Technique and Protocol

System and Montage. PSG data will be collected using the Compumedics P Series System (Abbotsville, AU, the same device used to obtain PSGs during the initial SHHS examination. This system consists of a Patient Interface Box (PIB "headbox") containing amplifiers and filters to which electrodes and sensors are connected. The PIB is attached by a cable to an 835 g data recorder containing a computer (PCMCIA card), a 15-hour rechargeable battery, and an oximeter. The PIB and loose electrode wires and sensor cables are supported by a cloth "bib" that is placed over the participants' nightclothes. The monitors used in SHHS PSG-2 will consist of the same data recorders as used for PSG-1, checked, cleaned, and upgraded with new parts as needed (per maintenance agreement with Compumedics). New PIBs will be used. These are similar to what was used for PSG-1, but are designed to be more durable and to have better cable connections.

To assure optimal ability to compare data longitudinally, the montage and hook-up procedures will be nearly identical to those used in the first grant period with the exception that the ECG will be recorded at a sampling rate of 250 Hz (rather than 125 Hz) to improve analysis of heart rate variability (HRV), identification of dysrhythmias, and detection of ischemia. We considered adding measurement of nasal pressure (via a nasal cannula) in addition to the thermistor. However, after lengthy deliberations, the Steering Committee decided that the potential the impact of this change on sleep quality and breathing events was not sufficiently understood to justify its inclusion in a longitudinal study. Instead, ancillary studies will be developed to explore the utility of nasal pressure recording to predict CVD in informative subsets of the SHHS cohort.

The following channels will be recorded: C_3/A_2 and C_4/A_1 EEG, right and left EOG, chin EMG, thoracic and abdominal displacement (RIP), airflow (nasal-oral thermocouples and nasal pressure), finger pulse oximetry, ECG, body position by a Hg gauge sensor, and ambient light.

Limitations of the Montage: Snoring will not be recorded because of difficulty in objectively defining and accurately measuring it. We carefully considered the costs and benefits of adding collection of leg

movements to our montage. We recognize that periodic leg movements may be common in the population, may contribute to arousals, and may be linked to other morbidities. However, the addition of these sensors was considered to present excessive subject burden, and possible danger (associated with tripping over wires) in this population who will undergo unattended monitoring. Furthermore, the additional sensors may alter the comparability of sleep quality and thus, limit the longitudinal comparisons.

Home PSG-2 Protocol

Procedures will follow those used for PSG-1. The home PSGs will be performed by two-person mixed-gender teams in visits that are likely to last between 1.5 to 2 hours. Sensors will be placed and equipment will be calibrated by technicians during the evening home visit. Sensors and electrodes are secured with combinations of tape, gauze and water-soluble pastes and electrical conducting gels. Signals will be visualized on the LCD and impedance values will be checked. Sensor positions are modified if poor signals are visualized or if impedance values are > 5 kohms (other than ECG, which impedance may be as high as 25 kohms). A Signal Verification Form (SV), similar to that used for PSG-1, will be completed by the technician, noting the impedance of each channel, the presence of any environmental conditions that might interfere with sleep monitoring, the need for alternative sensor placement sites, and whether resting oxygen saturation or resting heart rate, measured at the time of the home visit met "Medical Alert" criteria. The presence of a bedpartner will be noted.

During this visit, the participants will be instructed on what to do during the night and how to remove the equipment in the morning. A technician will return the next morning to pick up the equipment. The technician will disconnect the monitor if the participant has not already done so and collect the Morning Survey (MS) and the Night Medications (NM) forms which the participant should have completed. Later, the technician will download and review the data, assuring the adequacy of the study.

Data Storage and Transfer

Field Site: When the technicians return to the Field Site, they will download the sleep data onto the Field Site computer and will review the data, and problems with hook-up or data acquisition will be noted, ascertaining that there are no gross errors in the data (e.g., blank channels, extremely noisy channels). A PSG Evaluation form (SE) will be completed, indicating, for each study, the total duration of data and duration of artifact-free data for specific channels. The Signal Verification form (SV) and the PSG Evaluation form (SE) will be data entered to the Field Site computer datasystem, and a copy made of each form. The technician will then transfer the PSG data onto two zip cartridges, one to be kept at the Field Site and one to be sent to the SRC for processing (following a bi-weekly schedule of mailings). Paper copies of the SV and SE forms will accompany the zip cartridge to the SRC.

Sleep Reading Center: Shortly after receipt at the SRC, the Chief Polysomnologist will review studies and preliminary reports will be generated. After preliminary review, the raw PSG data will be moved to CDs. Each CD will be assigned to one scorer for full (manual) scoring. The magnetic cartridges are returned to the originating field site, and reused for subsequent data storage and

transfer. After scoring all studies on a CD, it (the raw and scored files) is replicated, with backup CDs sent to both the CC and the originating site.

Preliminary Study Review

Data received at the SRC will be reviewed for technical quality. Each data channel will be assigned a quality code grade according to the duration and quality of signals collected, and each study will be given an aggregate quality grade based on the overall interpretability and duration of artifact-free signals. The grading system and forms will be similar to those used for SHHS-1 with a few exceptions. First, additional categories are available for the scorer to note problems distinguishing apneas from hypopneas and central from obstructive events (this information, of potential use as a "filter" in data analysis, was previously inferred from the more cumbersome use of signal quality codes.) Secondly, the overall quality of each signal will be based on the percentage of sleep time that the signal was artifact-free (rather than the absolute duration of artifact free time.) This was decided to minimize ambiguity in signal grading caused by differences in signals in wake vs. sleep time, and improve the relevance of the grades to data used in analyses. However, the overall aggregate grades will be scored identically to the PSG-1.

Using computer-assisted scoring (with manual editing), a preliminary report will be generated that includes an estimate of the RDI, sleep length, and time in REM sleep. This report (containing quality assessment and preliminary PSG interpretation) will be e-mailed to the clinical site to provide rapid feedback regarding technical quality and feedback information for the participant. Studies with AHI estimates > 45 or with evidence of severe desaturation will be triaged for immediate full scoring to ascertain whether Medical Alert criteria are met.

Scoring of Polysomnograms

Following preliminary review by the Chief Polysomnologist, each study will be assigned to a scorer for manual scoring of sleep and breathing on an epoch by epoch basis, visualizing each epoch on a high resolution computer monitor, using Compumedics software that allows flexibility in choosing specific signals for visualization. Assignments will vary so that each scorer is presented equal numbers of studies from each site. Similar to the first phase of SHHS, full scoring will occur over a 2.6 year time period to allow for sufficient time to maintain high levels of scorer performance.

Identification of hypopneas and apneas will be done using algorithms identical to those used for PSG 1.(26) Events (apneas or hypopneas) are classified on the basis of the extent of the associated respiratory effort, associated arousal (occurring within 3 seconds of the termination of the event), and magnitude of associated desaturation (nadirs within 30 seconds of the termination of the event).

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

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

Obstructive events, the most common form in sleep apnea, are associated with chest and/or abdominal respiratory effort occurring in the face of an obstructed upper airway. Central events are associated with insufficient effort; an obstructed upper airway may or may not be a feature. This breathing pattern may be seen in heart failure and after strokes.
"Central" events will be noted if no displacement is noted on either the chest or abdominal inductance channels. Otherwise, events will be noted as "obstructive." Because of limitations in identifying central hypopneas without esophageal pressure measurements, no attempt is made to classify hypopneas as obstructive or central in nature.

Sleep stages are scored according to the guidelines developed by Recthschaffen and Kales. Arousals are identified according to American Sleep Disorders Association criteria, modified to accommodate situations in which EMG artifact obscures the EEG signal.

Detailed criteria for sleep staging, arousal detection, and marking of hypopneas and apneas, with example tracings and events, have been developed and documented in a SRC Manual of Operations. Analysis software links each apnea and hypopnea with data from the saturation and EEG channels, allowing each event to be characterized according to the degree of associated desaturation and arousal. This permits calculation of AHIs based on different hypopnea and apnea definitions. Software also provides summary measures of each apnea index and AHI in REM and NREM sleep and according to body position. Overall summary measures of desaturation, heart rate variation, arousal frequencies and sleep stages also are made. Qualitative sleep and breathing patterns not captured by summary measures of breathing or sleep are recorded on a data tracking form. Codes allow for the occurrence of alpha intrusion, periodic breathing, periodic hyperpneas, and abnormal eye movements. The form also provides an opportunity for the scorer to record their assessment of specific problems in signal appearance that might affect study reliability and that may not have been captured with the use of individual signal or overall study quality grades.

Quality Control

Quality control measures are directed at several levels to assure that all centers and personnel meet and maintain comparable and high levels of technical performance.

Training and Certification: At least one technician from each site will be trained and certified at a central location before the start of recruitment. Instruction will include: the background for SHHS, the basis for PSG, and specific procedures essential for protocol adherence. Sessions will be videotaped to provide a standardized reference for future training. Technicians will be trained to do the appropriate hook-ups (using easily recognizable body landmarks and reinforcing sensor placement with external fasteners or adhesives), trouble-shooting, and data review and transfer procedures. The certification process includes both written and practical examinations, and successful performance of at least five practice hook-ups. A Training Manual and a Manual of Operations details all procedures related to the performance of the PSG, equipment use, quality assurance procedures, and data management. Technicians who are trained centrally are able to train other technicians at their local sites. Locally trained technicians are certified after completing a written examination, performance evaluations, and successfully 1completing five practice studies. Technicians are required to perform a minimum of 4 satisfactory sleep studies per month to maintain certification. Central re-training will be considered depending on staff turnover and the results of quality monitoring.

Local Quality Assurance Procedures: Study data, including information on impedance values and hook-up procedures and the recorded PSG signals will be reviewed by the research team of each site soon after study retrieval. Problems with any channel will be noted and all efforts were made to resolve such problems before initiating another study. This may require involvement of the site's PSG Committee member, a senior on-site polysomnologist, or the SRC's Chief Polysomnologist. Each site will on a monthly basis receive study-specific data quality assessments made at the SRC and will be asked to resolve any problematic trends in data quality. The SRC Chief Polysomnologist also will lead monthly teleconferencing among technicians to facilitate dissemination of information regarding problem identification as well as developing solutions.

Central Review of Signals and Data Reporting: All studies are reviewed at the SRC and assigned quality codes, grading overall study quality and quality of each channel. Sites will be contacted by the Chief Polysomnologist if consecutive studies demonstrate poor quality. Signal and study quality codes, specific to each technician, each monitor, and each site, are summarized and reported on a monthly basis to all sites, the PSG Subcommittee, and the Steering Committee. These data are reviewed on a monthly basis by members of the Polysomnogram Subcommittee. Sites and individual technicians are expected to produce at least 85% of studies with a grade of "Good" or better. Those who do not reach this standard will be identified. Any downward trending of quality or deviation of specific technicians will require a written response from the Principal Investigator from that respective site. These data also are shared with members of the Steering Committee, the NIH program office, and an Observational Study Monitoring Board. Additionally, review of site specific quality grades will be discussed on a weekly basis by SRC staff, who will be asked to identify any trends in data quality that may suggest specific problems with specific equipment or technicians.

Training and Certification. Each scorer identified in this proposal has scored > 1000 SHHS PSGs. If these scorers are still available for the next study phase, they will undergo retraining and recertification. The latter will require demonstration of high levels of agreement with the Chief Polysomnologst, as indicated below. New scorers will undergo a 2 to 3 month training period and be asked to score a minimum of 100 practice PSGs using SHHS scoring rules (the number that appears to be minimal to achieve moderate or better reliability for arousal identification). Scorer certification requires the demonstration of a complete understanding of scoring rules and achievement of a 90% level of agreement with the Chief Polysomnologist for respiratory events and sleep stages and a 85% level of agreement for arousals for 10 or more independently scored practice records.

Local Quality Assurance Procedures. Weekly meetings of the SRC investigators and staff will be conducted to discuss scoring issues, to review problem studies, and to perform scoring reliability exercises. Disagreements between scorers in event or stage designation will be discussed with determination of a "consensus" designation. Levels of agreement among scorers and between each scorer and the consensus designation will be computed and tracked over time. Any scorer who systematically differs from the others over 3 consecutive weeks will be identified as potentially needing re-training.

Each scored record will be subjected to a computerized analysis that identifies the presence of any extreme values of summary data (e.g., >50% REM sleep) or potentially inconsistent relationships among the scored data (low arousal index and high RDI) prior to transfer to the CC. Studies so identified are reviewed by at least two scorers, with documentation of the problem. Other studies that are flagged for individual review were those in which the difference between the RDI determined by the preliminary analysis and final scoring > 5 and all studies that meet Medical Alert Criteria. Studies flagged by a scorer as being problematic

(e.g., difficulty distinguishing stages, uncertainty over respiratory events) are reviewed with the entire staff, and are documented in a computerized log.

Central Review of Scoring Quality: On a monthly basis, values of RDI (adjusted for age, weight, neck circumference, and gender), sleep stages, and arousal indices are computed for each scorer. These data will be reviewed by members of the PSG Subcommittee with reports to the Steering Committee and SRC regarding evidence of scorer drift over time, either within or between scorers.

A formal scoring reliability study, aimed to quantify within and between-scorer variability of the different measures of RDI (according to linked desaturation and arousals), arousal indices, and sleep stages will be designed, similar to what was done during the first study phase.

7.3. Non-PSG data collection

7.3.1. Parent Cohorts

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.

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	
Prevalent MI		medical history	
Prevalent Stroke		Family history of CVD	
Angina		Parental	
CHF		Sibling	
Self-reported hypertension	3 years	Occupation	
Self-reported diabetes	3 years	Psychosocial status	
Self-reported respiratory symptoms	3 months	Access to health care	
Self-reported hx of SDB	3 months		
Cigarette smoking status	3 months		
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	24^{th}, blood pressure
ECG	3 months prior to 2 months after F2		Carotid Ultrasound
			Holter
			MRI

7.3.2 Covariate Information

Once a participant has been contacted for Follow-up Visit 2, the goal is to conduct a home visit that includes a PSG. A participant who refuses, or is not eligible for, a PSG may be willing to participate in otherwise full data collection at a home visit. For PSG refusers who allow a home visit, a monitor will be kept in the technician's automobile, should the participant change his/her mind. If a home visit is refused the participant will be asked to allow a short telephone interview and to complete a lengthier mailed or telephone questionnaire. Usually the home visit will occur in the participant's home. However, under certain circumstances, such as overcrowding, or for safety reasons, data collection may take place in a location other than the participant's permanent residence, such as a motel or a clinic. A few days prior to the home visit, the participant is contacted to confirm the visit date, time, place, and traveling directions, and to determine if any recent event, such as illness or a family emergency, has occurred which would impact their typical sleep pattern and thus require rescheduling of the PSG study.

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

For home visits with PSG studies, one member of the team will set up the Compumedics monitor, while the other begins the data collection process. The sleep monitor is battery operated so the participant is not potentially in connection with any electrical outlets. Electrodes will be attached to the hair, face, and chest; a thermistor will be attached above the lip to monitor respiration; and an oximeter will be attached to one finger. In addition, a Morning Survey and a Night Medications log is left for the participant to complete in the morning after the monitoring is completed. At some sites the self-administered quality of life survey will also be left with the participant. The home visit with PSG study should take approximately 1.5 to 2 hours. For all home visits the participant's seated blood pressure, doppler Ankle-Arm blood pressure, and ECG are recorded. Weight, height, and neck circumference are obtained, and Health and Medication interviews are administered, and the Quality of Life survey may be self-administered. The previously mailed and self-administered Sleep Habits and Lifestyle questionnaire will be retrieved from the participant at this time.

For home visits with PSG studies, the next morning a technician returns to the participant's home at a pre-arranged time to collect the sleep monitor and the Morning Survey and Night Medications forms regarding the sleep monitoring experience and the use of alcohol, tobacco, or medications on the night of the PSG. The technician will thank the subject for participating and will indicate that a summary of the results of his/her PSG will be sent in about 12 weeks. This process will take approximately 10-15 minutes.

At the Field Site, the sleep technicians log in all data collected and evaluate the overall completeness and quality of the PSG by reviewing it on a personal computer. The PSG data are then sent to the SRC for processing and the paper forms submitted for local data entry. A few days following the home visit, the study

coordinator will personally call the participant to obtain feedback on the home visit and determine if there were any problems with the study personnel, paper form completion, or the sleep monitor. At sites where telephone calls are not feasible, an evaluation postcard will be left with the participant when the monitor is collected.

Table 7.2 lists all non-PSG data included in a full data collection at Follow-up Visit 2.

Table 7.2 - Non-PSG Data Collected at Follow-up Visit 2

Data collection form	Status compared to baseline	Completed by/when	Content
Contact form	Revised	Interviewer/recruitment	Final disposition of recruitment for Follow-up Visit 2; level of participation
Health Interview	Revised and standardized across sites	Study personnel/home visit	Prevalent respiratory disease, aspirin use previous 2 weeks, previous night rest, naps and stress on day of PSG, Restless Legs syndrome questions
ECG	New	Study personnel/home visit and morning after	Quality assurance and tracking for ECG
Physical Measurements	Revised and expanded BP form	Study personnel/home visit	Height, weight, neck circumference, seated BP, ankle-arm index doppler BP
Medications	Revised	Study personnel/home visit	Rx and non Rx medications taken in the last two weeks, and whether on day of home visit
Night Medications	New form: previously collected on Morning Survey	Participant/ morning after PSG *(only participants who have PSG)*	Medications taken between the time the technician departed and the end of the PSG
Sleep Habits and Lifestyle Questionnaire	Revised Sleep Habits Questionnaire	Participant/mailed prior to home visit, collected at home visit	Sleep habits, snoring, apnea, sleepiness, tobacco, caffeine and alcohol use
Quality of Life survey	Unchanged	Participant *(at all but Strong Heart Field Sites)*	SF-36
Morning Survey	Revised	Participant with PSG/morning after PSG	Sleep quality, medications, alcohol caffeine and tobacco use, nasal status, and presence of bedpartner on night of PSG and as usual
Alerts and Adverse Events	Revised Adverse Events form	Study personnel/at home visit *(for all participants)*	Immediate and urgent medical alerts, other problems on night of PSG
Alerts and Adverse Events Action	Revised Adverse Events form	Study personnel/at home visit, and when action taken *(for participants who had an alert or AE)*	Action taken for medical alerts and adverse events, including referral and physician notification

8. MEDICAL ALERTS

8.1 General

Certain findings made at the time of the home visit or during analysis of the PSG may require medical intervention. Medically relevant data are collected in SHHS, including the PSG, the blood pressure and the ECG. Although the PSG performed as part of the SHHS is not considered a diagnostic study, the SHHS

investigators have an obligation to refer some participants to their local physicians, if a value is identified that should have immediate clinical attention.

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

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

8.2 Non-ECG Medical Alerts

Findings constituting an immediate alert at the time of the PSG setup are as follows, unless the parent study specifies different criteria:

Awake blood pressure:	Systolic ≥ 180, or Diastolic ≥ 110
Awake heart rate:	> 150 beats/minute for longer than 2 minutes at rest < 30 beats/minute for longer than 2 minutes at rest

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

The blood pressure alert values are lower than those used at the SHHS Baseline visit (200 systolic or 120 diastolic), however, in the interim, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure published its sixth report (25), and established that a systolic pressure of 180 or a diastolic pressure of 110 requires either immediate referral, or referral within one week depending upon the clinical situation. Therefore, these values will be handled as immediate alert values, regardless of whether the participant is or is not taking anti-hypertensive medications, in Follow-up Visit 2.

Urgent alerts arise when abnormalities are detected at the time of hook-up, or on review of the PSG, that require medical attention, but not on an emergency basis. Notification of the participant and his/her physician will be sent by mail within 10 days.

Findings constituting urgent alerts are as follows, unless the parent study specifies different criteria:

Awake blood pressure:	Systolic > 170 or Diastolic > 100
Sleeping heart rate:	> 150 beats per minute for longer than 2 minutes < 30 beats per minute for longer than 2 minutes

Baseline awake oxygen saturation <85% (but ≥ 80%)
Oxygen saturation < 75% for more than 10% of total sleep time
Apnea-Hypopnea Index ≥ 50 events/hour

Data received at the SRC will be reviewed initially for technical quality and for evidence of marked

abnormalities in breathing, heart rate, and oxygen saturation that might require timely participant notification according to criteria for "Urgent Medical Alerts." Medical alert criteria were developed in the initial funding period by the PSG Subcommittee, with review by an external Data and Safety Monitoring Board. Studies with an AHI ≥ 50; oxygen saturation < 75% for > 10% total sleep time; and more than 2 continuous minutes in which heart rate is < 30 or > 150 BPM will be triaged for immediate full scoring. If the findings of the preliminary review are confirmed, a SRC physician will review the study, and prepare a Medical Alert Notification form that will be faxed or e-mailed to the study coordinator at the respective clinical site. This information will be reviewed by a physician at the clinical site (often a study P.I.) who determines the appropriate actions. These participants, and their physicians, will receive letters.

8.3 ECG Medical Alerts

An electrocardiogram will be obtained with suppression of the computer reading in the field. Each Field Site will elaborate a protocol for interpretation of alerts that will use prior ECG data, if available, and follow parent study protocols, if applicable. If there is no parent study protocol, a local protocol will be generated. Local/Parent protocols are as below, and sample letters to participants and physicians for ECG medical alerts are included in Appendix 5.

8.3.1 Framingham

An electrocardiogram (ECG) will be obtained by a technician during the sleep home visit. Participants in the Framingham site are already enrolled the Framingham Heart Study (FHS) and therefore an ECG is taken when they come in for their clinic visit. Those participants who have been seen in the clinic or are scheduled to be seen in the FHS clinic within three months of the SHHS home visit will not undergo an electrocardiogram during the home visit. The technicians will not be printing the results of the electrocardiogram in the participant's home and will not be required to interpret the ECGs.

On the day after the sleep home visit, the study coordinator will present to the study physician the ECG from the night before and a copy of the ECG from the participant's previous exam in the FHS clinic for comparison and reading. If any marked changes are observed, both the participant and his/her primary care physician will be informed immediately by the study physician. The decision on whether observed ECG changes warrant contacting the participant and his/her primary care physician will be made by the study physician. After a contact is made, the study physician should complete a phone encounter sheet to document his/her actions.

If there is no need for notification of an outside physician, the ECGs should be returned to the participant's chart.

8.3.2 Johns Hopkins

On the day of the home PSG, the field center technician will pull the participant's parent study records (from the ARIC or CHS files, kept in the field center). The latest ECG obtained by the parent study will be identified and a photocopy will be made. This copy will be kept in a dedicated folder in the PSG field center.

The morning after the home PSG, the Study Coordinator will prepare a hard copy of the current home visit ECG. This copy, along with the latest ECG from the parent study on file, will be faxed to Dr. Philip Smith, at the Johns Hopkins University, Bayview Medical Center for interpretation. Dr. Smith will compare the old and new ECGs, and will determine whether immediate or urgent referral is indicated. This physician will notify the Study Coordinator of these results by telephone within 24 hours.

Participants needing an immediate referral will be called directly by Dr. Smith or by the principal investigator (Dr. Nieto) and advised to contact their physician or a hospital immediately.

Other urgent referrals are made for abnormalities or conditions that require medical attention but not on an emergency basis. Notification of the participant and/or his physician will be sent by letter within 10 days.

Electrocardiogram findings of a routine nature will be contained in the letter which provides information about the PSG study and other routine or "of participant interest" data.

8.3.3 Minnesota

The Minnesota SHHS Follow-Up 2 will be operating from two locations: The Division of Epidemiology at the University of Minnesota School of Public Health and the Sleep Laboratory of Hennepin County Medical Center. Sleep technicians from The Sleep Lab will conduct the ECGs. Each morning, the Coordinator at the Sleep Lab will fax a copy of the ECGs from the previous might to the Coordinator at the Division for review. (Originals of the ECGs will be sent to The Division of Epidemiology with the daily delivery of completed data collection forms.)

Fax'd ECGs will be reviewed by the PI and compared to any previous tracing from the parent study (ARIC). In the event of an immediate alert, the PI will call the participant and the participant's physician, if acceptable to the participant. Non-urgent ECG findings will be reported in the Results Letter that will be mailed 10 to 12 weeks after the in-home PSG. If requested by the participant, a copy of the ECG will also be mailed to the subject's physician along with a cover letter explaining how the abnormality was detected. The physician will be informed in this letter that the subject has been given these results and told to discuss the findings with his/her physician.

8.3.4 NYU/Cornell

The ECG technician is not expected to interpret the ECG, but will need to be familiar with the significance of the interpretative statements printed on the hard copy of the ECG analysis. Situations may warrant referrals because of the possibility of acute cardiac injury (myocardial infarction) or certain arrhythmic events or cardiac conduction problems which may call for therapeutic action.

Because computerized ECG analysis programs may be overly sensitive, many of the interpretive statements are not considered to warrant referral.

The following conditions are considered as Alerts:

1. Heart rate <[45] beats per minute or >[110] beats per minute
2. Ventricular tachycardia
3. Acute myocardial infarction
4. Atrial fibrillation or flutter
5. Complete AV block

The following conditions are considered as Abnormalities:

Ventricular preexcitation or WPW ECG pattern
Left Bundle Branch Blcok
Any statement which includes a reference to acute injury, ischemia or pericarditis

If the ECG Interpreter determines that the ECG is normal, a copy of the ECG will be faxed to the Research Coordinator ("RC") for entry into a database and storage in files.

If the ECG Interpreter determines that the ECG statement indicates an Alert, he shall contact the Study Physician by telephone immediately. If the Study Physician agreed that the ECG indicates an Alert, immediate notification of both the participant and his/her physician or health care provider will be made by telephone as quickly as possible.

For ECG readings indicating Abnormalities, referrals will be made, but not on an emergency basis, a by a telephone call or letter sent to the participant and his/her physician within 10 days of the ECG.

In the case of any of any Alerts or Abnormalities detected by the ECG technician, the technician will casually inquire if the subject has recently had any chest pain or discomfort. If the response is a positive, it is particularly important that the study physician be notified as soon as possible. A negative answer does not mean that the Abnormality may be ignored, as cardiovascular and cerebrovascular events may be asymptomatic. In all cases of technician-detected Alerts or Abnormalities, the technician shall notify the RC by telephone and shall fax a copy of the ECG to the RC, who will alert the study physician as soon as possible and deliver to him a copy of the ECG in question. Upon review of the ECG, the study physician will decide if any further action will be required.

8.3.5 Pittsburgh/Sacramento

The technician is not expected to be able to interpret ECGs. However, the technician will need to be familiar with the interpretative statements printed on the ECG hard copy by the 12SL ECG analysis program of the MACPC. These alert conditions include situations which may warrant referral because of the possibility of acute (NEW) cardiac injury (myocardial infarction) and certain arrhythmic events or cardiac conduction problems which may call for therapeutic actions.

The 12SL ECG program should be considered a screening device which tends to be overly sensitive. Most of the interpretative statements such as “non-specific repolarization abnormalities” or even “myocardial infarction-age undetermined” are not considered as acute events needing referral.

The following conditions are suggested as possible alerts.

d) Heart rate $\leq$ 45 beats per min, or $\geq$ 110/min.
e) Ventricular tachycardia
f) Acute MI
g) Ventricular preexcitation or Wolf-Parkinson-White (WPW) ECG pattern
h) Atrial fibrillation or flutter
i) Complete A-V block
j) Left Bundle Branch Block
k) Any statement which includes a reference to acute injury or ischemia or pericarditis.

In the case of any of these alert statements, the technician will notify the study physician-investigator who will decide if any further action will be required. The technician will casually inquire if the participant has recently had chest pain or discomfort. If the answer is yes, it is particularly important that the study physician is notified. A negative answer does not mean that the alert can be ignored since heart attacks are often asymptomatic (silent). These “asymptomatic alerts” are most of the time not in the same category of possible urgency as alerts associated with recent chest pain or discomfort or fainting attacks.

Immediate referrals are potential medical emergencies, which may require immediate notification of both the participant and his/her primary physician or other available health care provider. These are findings made at the time of the PSG setup in the participant’s home. The technician performing the setup is in general

neither trained nor licensed to perform clinical diagnostic assessments, all findings requiring immediate referral will be referred by the technician to the SHHS physician-investigator. This physician, based on information obtained from the technician and/or the participant, will determine whether immediate referral is indicated. Participants receiving immediate referrals are those who would be advised to go directly from home to their physician or to a hospital. Notification of the participant will be performed by the SHHS physician-investigator and should occur prior to the technician's departure from the home. Notification of the participant's physician or other medical health care provider (such as a hospital emergency department physician), will occur as deemed necessary by the SHHS physician-investigator. A follow-up letter documenting the information discussed by telephone will be sent to the participant's physician.
The SHHS physician-investigator will document the time/date of contact, the problem identified, and the action taken or recommended to the participant. Within 48 hours the clinic coordinator will contact the participant by telephone and ascertain and document what follow-up was taken.

Urgent referrals are made for abnormalities detected either at the time of hook-up, review in the clinic by the SHHS physician-investigator or ECGRC. The ECG reading may require medical attention but not on an emergency basis. Within 10 days of an urgent referral, a notification letter will be sent to the participant and his/her physician.

8.3.6 Tucson

An electrocardiogram (ECG) will be performed on all consenting participants at the Tucson SHHS site. All ECGs will be done in the participant's home on the night of PSG data collection. ECGs will be completed by a certified technician in accordance with the SHHS Manual of Procedures for ECG.

During the ECG, a paper tracing will be generated *without* computer assisted scoring. Within 3 days of the date of ECG, the printed tracing will be given to a Tucson PI or Co-PI for interpretation. The investigator will also be given tracings of past ECGs for comparison, as available. The investigator will review the ECG within 48 hours, and then do one of the following:

1. If ECG is normal or has no significant changes:

    a. Complete the ECG Interpretation form.
    b. Return original tracings and ECG Interpretation form to the Study Coordinator.

2. If ECG is abnormal or has significant changes, either of which mandate RAPID participant notification as defined in the SHHS manual of operations, the investigator will:

    a. Notify the Study Coordinator immediately to get the participant's contact information. The coordinator will provide this information to the investigator as soon as possible.
    b. Contact the subject and discuss findings; recommend follow up with primary care physician or other specialist as appropriate within 24 hours.
    c. Document ECG findings and a synopsis of the discussion with the participant on the ECG Interpretation form.
    d. If the participant requests that a copy of the ECG be sent to his/her physician, document this on the ECG Interpretation form, and get physician information.
    e. Return original tracings and ECG Interpretation form to the Study Coordinator.

3. If ECG is abnormal or has significant changes that require participant notification, but do not require RAPID contact as defined in the SHHS manual of operations, the investigator will:

a. Document ECG findings on the ECG Interpretation form; include a synopsis of the problem.
b. Return original tracings and ECG Interpretation form to Study Coordinator.

c. The study coordinator will generate a letter to the subject within 72 hours. The letter will be signed by an SHHS investigator.

The Tucson Study Coordinator will maintain entries in the SHHS tracking database to insure that every subject who has a home ECG completed also has an ECG review done within 1 week, including all of the steps above. Additionally, the Study Coordinator will maintain a written log of each subject who receives a Rapid or non-Rapid notification for ECG abnormalities. The Study Coordinator will review this process with the Primary Investigator periodically to insure any problems or concerns pertaining to ECG review are resolved.

8.3.7 Strong Heart Study

It is the intention of the Strong Heart Study Center of the Sleep Heart Health Study (SHS/SHHS) that individuals who participate in the physical examination will be provided both with education and encouragement concerning a healthy life style aimed at preventing cardiovascular disease and that participants receive assistance in securing medical care for any significant medical conditions uncovered during the course of the SHHS exam. SHS principal investigators, field coordinators, nurse-researchers, and technical staff work together with the Indian Health Service (IHS) to ensure that information collected during SHS participant examinations is maximized for the benefit of the participants. This may mean referring SHS participants to a physician or health care facility because of concern arising from measurements collected during the examination.

The three SHS/SHHS field centers are unique with respect to participant characteristics, distance from field center coordinators, the PI, and access to physicians and health care facilities. However, all field centers follow the same criteria for medical referrals following collection of SHS ECG data. SHS/SHHS examination teams at each of the three field centers will include at least one nurse who can provide emergency care to the best of his/her ability as appropriate for emergencies that arise during the home visit. In such cases, guidelines are in place for "emergency referrals," those referrals designed to respond to evidence of a life-threatening illness. Guidelines for non-emergency referrals are also in place, and all are summarized below.

1) Referral procedure:

All participants in SHS/SHHS will receive appropriate educational materials concerning a heart healthy lifestyle. In addition, the examining personnel, when possible, will endeavor to educate the participants during the exam concerning the importance of risk factor reduction and modifications that the individual might make to improve his/her risk for cardiovascular disease.

After results from the ECG are returned from the ECGRC, a form will be generated by each Field Center which will be available to the Indian Health Service for insertion into the participant's medical record. This will contain results of the electrocardiogram, and other measures collected in the Sleep Heart Health Study which might be of benefit for their future medical care.

In order to insure that the patient receives appropriate referral and treatment for significant medical conditions uncovered during the course of the examination, consistent referral levels have been established as described below which will be applied at each center.

2) General Referral and Review Guidelines for SHS Participant Follow-up

The Strong Heart Study refers participants using established guidelines for referral. Uniform criteria for referral of participants are implemented at all centers. Emergency, immediate, urgent, and routine referrals are made. Methods for referring participants who have no physician are established with the participant. All referrals are documented on a separate log and copies of the referrals are kept in the Strong Heart Study folders. The SHS nursing staff, in consultation with on-call physician back-up when necessary, determines the acuteness of the findings, as well as whether or not the condition is being followed by a physician. Referrals are made using preliminary equipment-based ECG interpretations and familiarity with the participant's SHS medical record, including previous ECGs. SHS staff will bring the previous ECG to the home visit. This will allow immediate comparison in the event of a major abnormality. If the participant is aware of and being followed medically for a condition, judgement is exercised about whether to refer. The standard IHS referral form is used to provide appropriate clinical information to the health care professional who will evaluate the participant. A copy of this referral will be retained with the research forms to document the referral that was made. SHS staff follow-up the next day or week to be certain that care was received.

a) Emergency Referral

The participant is immediately escorted to a physician, an IHS facility or an emergency squad or ambulance is summoned to the participant's home. Any finding or symptom suggestive of a life-threatening illness, including evidence of acute MI, unstable angina, or pulmonary edema. In such situations study personnel will provide emergency care to the best of their ability. The rationale for referral is described to participant and local IHS referral forms are used. The PI and/or on-call physician are notified immediately.

b) Immediate Referral Statement to Participant

The participant is urged to see his/her physician within one day. The SHS staff notifies the participant's physician or nearest IHS facility and makes appropriate arrangements for SHS participants to be seen the next day. The participant is provided with an IHS referral form to take to his/her physician and transportation is provided or arranged if needed.

Angina in last day: "Your chest pains may be important"
Neurologic symptoms in past week: "Your symptoms may be important"
Other severe symptoms or findings: "Your symptoms may be important"

c) Urgent Referral Statement to Participant

The participant is urged to see his/her physician within one week and SHS staff makes an appointment for needed follow-up whenever possible. An IHS referral form is filled out and transportation is arranged if needed.

Angina during past 24 hours: "Your chest pains may be important"
Suspected congestive heart failure: "Your symptoms may be important"
Other acute, but less severe symptoms: "Your symptoms may be important"
Inappropriate medication usage: "Taking medication incorrectly may be dangerous"

d) Routine Referral

The participant is asked to see his/her physician within one month, or at first convenient appointment, and appointments for the patients are made by community health representatives or clinic staff. An IHS referral form is filled out and transportation is arranged if needed.

Old MI: "Your chest pain may be important"
Previously unrecognized stroke: "Your symptoms may be important"

e) Referral after Results Are Available

Routine report: copies of routine results are sent to each participant with an interpretation of results. If the participants have new findings that they have not previously been advised, an IHS referral form should be filled out and SHS staff should assist participant in making an appointment and arranging transportation for follow-up.

3) ECG Referral:

a) ECG Findings Requiring Review by a physician before SHS staff leave participant's home ("We would like to review these findings with a physician." Call will be made to appropriate medical staff previously identified by each Field Center.) Before leaving participant's home, a physician will consulted, and if necessary, the participant will be transported to a physician, IHS facility or an ambulance or emergency squad will be called. For ECGs that are performed in IHS clinics, IHS medical staff will be consulted.

- Acute pattern abnormalities (MI, ischemia)
- Rhythm disturbances
- 2nd or 3rd degree block, ventricular tachycardia,
- any type of ectopic beat > 6/minute
- couplets bigeminy, R on T
- multifocal premature ventricular contractions
- atrial fib/flutter with ventricular rate < 60/min or > 110/min
- sinus bradycardia < 40/min, sinus tachycardia > 110/min, PR interval > 0.26 sec
- Any other ECG findings, alone or in conjunction with symptoms suggestive of a life-threatening illness

b) ECG Findings to be reviewed the next day; if possible

- QT Prolongation (confirm medications)

c) ECGs where Routine Referral is usually appropriate

- New left bundle branch block
- New right bundle branch block
- Wolff Parkinson White
- Left Ventricular Hypertrophy

d) Examples of Usually Benign ECGs (always obtain old comparison ECG when available)

- Left Axis Deviation/Left Anterior Hemi (Fascicular) Block
- Atrial Abnormalities, Intra-ventricular Conduction Delay
- Unusual P Wave Axis, Wandering Atrial Pacemaker
- S1 S2 S3 Pattern, Old Right Bundle Branch Block
- Incomplete Right Bundle Branch Block
- ST Elevation compared with Early Re-polarization
- First Degree AV Block

Copies of each ECG obtained as part of the SHS/SHHS will be forwarded to either the local clinical director or other identified local clinical personnel, if the participant consents to having results sent to the local IHS facility.

9. PARTICIPANT FEEDBACK

Participants will be sent a report summarizing the findings of their sleep studies and providing results of the PSG, based on the final reading for the test obtained at Follow-up Visit 2. The preliminary reading from the baseline visit was previously given. A copy of the report will also be sent to the participant's primary medical care provider. Included will be information regarding total sleep time, sleep latency, AHI, REM, and average heart rate during sleep. Additionally, some Investigative Centers may choose to include information on blood pressure and weight. Participants with an AHI $\geq$ 50 will be sent a different letter than those with lower AHI levels, recommending that they discuss the report with their personal physician. In addition, all participants will be told that they should contact their personal physicians if they have symptoms or experience daytime sleepiness.

After many deliberations, the PSG Subcommittee and Steering Committee developed an approach for informing participants of study findings. This required sensitivity to IRB issues, recognition regarding the uncertainty of what level of SDB poses a health risk, interest in being informative but not alarming, and acknowledgment that the study is observational and not interventional in nature. Example letters are found in the SHHS Manual of Operations. The approach to date appears to have worked well, with participants satisfied with the type of feedback received. For the vast majority of participants, it appears that the letters did not prompt medical or surgical intervention.

10. OUTCOMES DATA COLLECTION

10.1 Coronary Heart Disease events

10.1.1 Endpoints

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

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

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

a. HAMI
b. coronary surgical intervention

10.1.2 Ascertainment

Cardiovascular events will be ascertained at least every two years. Each investigative center will identify potential outcome events and obtain the relevant hospitalization, outpatient procedure, and physician records. Protocols vary for the different parent study cohorts, and are summarized below.

10.1.2.1 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.

10.1.2.2 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.

10.1.2.3 Minnesota

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

10.1.2.4 NYU/Cornell

Potential CHD events in the New York City cohorts will be ascertained every two years by telephone or clinic contact after PSG or at the end of Grant Year 3 (whichever is earlier). 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.

10.1.2.5 Pittsburgh/Sacramento

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

10.1.2.6 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.

10.1.2.7 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.

10.1.3 Adjudication

Each parent study will adjudicate potential cardiovascular events which occur among its participants. Based on the quality assurance procedures of the parent studies and the results of the HAMI Comparability Study (summarized 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.

10.1.3.2 Cohort-specific protocols for cardiovascular event adjudication.

HAMI -- All parent studies rely on a combination of chest pain, ECG tracings and myocardial enzyme profiles to define MI. For the SHHS both incident and recurrent HAMI will be adjudicated at all sites. At

ARIC sites, abstracted data including the Minnesota codes for serial ECGs will be entered into a computer algorithm; the result will then be reviewed by the Events Committee. CHS centers also will abstract the hospital record and Minnesota code the ECGs, but no computer algorithm will be used. Both CHS and ARIC code HAMI events as definite or probable (counted as MI in analyses), or suspect or no MI. FHS reviews will not use abstracted data (only a copy of the medical records), and ECGs will not be Minnesota coded; however, the ECG from the FHS clinic visits before and after the potential event will be considered. At FHS, HAMI is classified as definite (the only cases used in analysis), maybe and no MI. At Strong Heart, medical records are abstracted, 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, angina pectoris or cardiovascular death; however, documentation of a CABG or PTCA during the hospitalization will be adequate to assign this outcome for the SHHS without specific adjudication.

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

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.

10.2 Congestive Heart Failure

10.2.1 Endpoints

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

10.2.2 Ascertainment

Ascertainment for potential CHF events will occur using the same forms during the same interviews as ascertainment of potential cardiovascular events at FHS and CHS. 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.

10.2.3 Adjudication

Incident CHF will be adjudicated by the Events committees. CHS criteria for CHF include decreased systolic cardiac function, a report of cardiomegaly and pulmonary edema on chest X-ray, or an appropriate response to pharmacologic treatment for CHF. Framingham criteria include a combination of clinical signs and symptoms such as 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.

10.3 Cerebrovascular Events

10.3.1 Endpoints

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

10.3.2 Ascertainment

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

10.3.3 Adjudication

Stroke is broadly defined as a constellation of neurologic symptoms with a sudden onset which lasts at least 24 hours or until death. The SHHS will use the parent study adjudication results for stroke (assuming that a planned comparability study reveals a high degree of agreement between sites). The NYU 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.

10.3.3.1 Site-specific protocols for cerebrovascular adjudication

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

reviewed by the Events Committee. ARIC classifications for stroke will correspond to the following SHHS endpoints:

ARIC Endpoint	SHHS Endpoint
Subarachnoid Hemorrhage	Any stroke, hemorrhagic stroke, subarachnoid hemorrhage
Brain hemorrhage	Any stroke, hemorrhagic stroke, subarachnoid hemorrhage
Thrombotic brain infarction	Any stroke, non-hemorrhagic stroke
Non-carotid embolic brain infarction	Any 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.

10.4 Hypertension

10.4.1 Endpoints

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

10.4.2 Ascertainment

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

10.5 Mortality

10.5.1 Endpoints

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

10.5.2 Ascertainment

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

10.5.3 Adjudication

All investigative centers will adjudicate all ascertained deaths using the forms and protocols established by each parent study. Events which meet the criteria for a cardiovascular or cerebrovascular outcome which also result in death will be coded as death due to cardiovascular or cerebrovascular disease. The New York and Tucson Investigative Centers' Adjudication Committees will adopt procedures based on the CHS abstraction forms and event criteria.

10.6 Quality of Life

10.6.1 Endpoints

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

10.6.2 Ascertainment

At some Field Sites the SF-36 Quality of Life instrument will be re-measured in SHHS participants in the appropriate window for the PSG-2 and Home Visit for Follow-up Visit 2.

10.7 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.

11. PROJECT MANAGEMENT

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

11.1 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 11.1 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 the study, the CC will distribute reports to Investigative Center PIs and Field Site Directors and Study Coordinators and to the Project Office monthly summarizing recruitment progress to date, and data completeness and quality. At a frequency appropriate to activities, the CC will distribute Quality Control reports to Investigative Center PIs and Field Site Directors and Study Coordinators and to the Project Office. These reports will summarize Field Site and technician performance and identify any potential problems. Outlying data values will also be returned to the Field Site to be checked. 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 Quality Control Committee and the SRC to establish quality assurance policies (activities undertaken before data are collected to assure high quality), including requirements for technician certification and observation, and equipment maintenance. The 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 and technician 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 11.1 Coordinating Center Communications

		Sent to:			
	Time frame	IC/FS*	SC*	PO*	OSMB*
1. Routine communications: Deadlines, meetings, announcements, decisions	as needed**	X	X	X	X
2. Routine reports:					
Recruitment	monthly	X	X	X	X
Data completeness	monthly	X	X	X	
Data quality	2-3/year	X	X	X	
Quality Control (performance)	2-3/year	X	X	X	
Steering Committee	2-3/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	X	X	
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.

11.2 Data Management

11.2.1 Data Management within the Coordinating Center

11.2.1.1 Field Site Data

Each month a set of data files will be transmitted from each Field Site to the CC via zip disk. These raw files will be copied onto backup disks before any processing occurs. Next the files will be read into the database. A set of routine programs will be run to check the data for completeness. Reports generated by these programs will be sent to the Field Sites/ Investigative Centers, Steering Committee, and Program Office monthly. Recruitment status reports will be sent monthly. Data quality will be assessed and reported 2-3 times per year.

11.2.1.2 Sleep Reading Center Data

The PSG data collected during Follow-up 2, will be sent from the Field Sites to the SRC for reading, entry into a database, and archiving. The SRC will supply the CC with a fully edited data for the analytic database. Monthly, the SRC will send the CC a list of all studies received. The CC will match this list against the data received from the Field Sites, to ascertain that all studies arrived as they should. If any problems are noted, lists will be generated and sent to the SRC and the Field Sites asking them to resolve the discrepancies. This will include both expected studies that did not arrive at the SRC and unexpected studies that did arrive.

11.2.1.3 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.

11.2.1.4 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.

11.2.2 Data Management at the Field Sites

The CC will provide software to the Field Sites for data entry and management. Double-data entry will be required on all data entered at the Field Sites to reduce keying errors. Once a month, data will be transferred from the Field Sites to the CC using zip disks. The CC will return receipts to the Field Sites to verify successful data transfer. The Field Site software will include components for tracking data sent to the CC and the SRC.

At the end of each day, data entered that day will be backed up onto removable disk using backup utilities supplied by the CC.

11.2.3 Data Management at the Sleep Reading Center

Data will be transferred from the Field Sites to the SRC using zip disks. The disks will be logged in at the SRC and receipts returned to the Field Sites.

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

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

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

Computer analysis linking the data from multiple channels will provide the predictor variables described in the Data Analysis section below.

12. QUALITY ASSURANCE AND CONTROL

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. The SRC assigns a quality grade to the PSG data, and will assign “quality grade” reports for each field center and technician, and provides reports to the CC for merging with other QA/QC report components.

Quality assurance includes the following activities:

1. Detailed protocol development and documentation, including study design and data collection activities.
2. Establishment of certification, recertification, and maintenance of certification requirements for technicians in order to ascertain and maintain an individual’s expertise in executing study protocol and procedures.
3. Provision of training and training updates as the basis of continuing education involving the protocol.
4. Documentation of all changes in protocol or equipment.

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

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

2. Early feedback and communication are used in monitoring and correcting problems such as data entry and data transmission errors. All data entry requires double-entry of values. The CC provides 2-3 times per year reviews of the data to detect outliers or unreasonable data. Questionable data are returned to the Field Sites to be verified or corrected. Study data are used to monitor performance of staff and Field Sites.
3. Equipment will be calibrated and checked for accuracy and proper functioning on a monthly basis.

The following quality control data are sent to the SHHS CC on a regular basis:
1. Field Sites send: contact/recruitment data and study data (monthly); calibration logs and quality control supervisor check lists (monthly); responses to QA/QC reports as needed.
2. SRC sends: status of data upon arrival and study data (monthly); technician performance (monthly); internal QA/QC report (quarterly); site visit reports and responses to QA/QC reports as needed.

The CC produces and distributes the following QA/QC reports:
1. Field Site recruitment status and data completeness reports (monthly).
2. Data integrity reports (2-3/year)
3. ECGRC performance reports (2-3/year)
4. Field Site Technician QC Reports (2-3/year)
5. Summary reports of all QA/QC activities that have occurred (as needed).

13. DATA ANALYSIS AND LIMITATIONS

13.1 Data Analysis

13.1.1 Procedures for Data Analysis

The SHHS operates with a central CC, a SRC, an ECGRC, seven Investigative Centers, and thirteen Field Sites. Capacity for data analysis lies not only within the CC but within the Reading and Field Sites. This protocol describes a model for both central analysis and distributed analysis that will draw on the capabilities at all centers, while ensuring the validity of analyses through central verification.

As of November, 1999, a full data set has been collected from the SHHS Baseline and Follow-up 1 visit along with the A– variables from the parent studies. Data items already collected include the PSG, the SHHS sleep habits questionnaire, medications, and other data collected during the home visit. After data checking and editing of Baseline and Follow-up Visit 1 data have been performed, the CC will create an edited, complete set of these data for distribution to the reading and investigative centers. Distribution is intended to encourage data utilization and to provide an opportunity for independent analyses at these centers.

13.1.2 Baseline Data Analysis

The CC in collaboration with the study investigators will plan and execute a thorough statistical analysis of the Baseline data. These analyses will take two forms. First will be a series of analyses to describe the sample in terms of the baseline variables collected. The descriptive analyses will be primarily composed of simple tabulations for discrete variables, and the calculation of a variety of summary statistics for the continuous variables such as means, medians, variances, maxima and minima, etc., and graphical displays such as frequency distributions or density estimates. Extensive data checking will be a crucial component of these early analytic activities. In addition, standard, study-wide definitions for many of the

key analysis variables will be developed. Early assessment of the comparability of variables among the different parent study populations will result in the identification of important differences in some variables that will be addressed by adjustment through data analysis.

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

Multivariate analyses will be emphasized so that the complex relationships between groups of exposure variables, confounding variables, and outcomes of interest may be thoroughly examined.

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

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

13.1.3 Accumulated Follow-up Results

As will be done in the analysis of the baseline data, extensive descriptive displays of the results of Follow-up 1 and endpoint data will be provided. These will take the form of tables, plots, and descriptive statistics. The primary goal at this stage will be analyses that address the primary study hypotheses. A preliminary assessment will be made of the power to test these hypotheses based on the number of events that have accumulated by the end of follow-up. The statistical methods available to appropriately model relationships between events and the length of time until events and various risk factors with adjustment for potential confounders are multiple logistic regression and the Cox proportional hazards model, respectively. Estimates of relative risks and confidence intervals associated with the important risk factors will also be obtained. The major challenge in the application of these methods in this study is the potential heterogeneity of the covariate data collected from different parent studies. Random effects models and other statistical techniques will be used to identify and adjust for these various sources of variability.

Similar statistical methods will likely be used to address the secondary hypotheses. However, determination of the appropriate statistical methods will depend on the study design selected to address a particular hypothesis. Substudies done in selected cohorts may be used for collecting information pertaining to one or more of the secondary hypotheses. When data are available from Follow-up 2 longitudinal data analysis techniques will be employed in addition to survival analysis techniques.

13.1.4 Analytic Approaches Associated with Measurement of Exposure Variables

SDB has direct physiological consequences that are potentially involved in the pathogenesis of cardiovascular disease, including negative intrathoracic pressure swings, hypoxemia, arousal, and changes in sleep architecture. For assessment of the CVD risk associated with SDB (Aim 1), the primary measure of exposure to SDB will be the AHI, defined as the total number of apneas plus hypopneas per hour of sleep. The AHI is the most commonly used metric for quantifying SDB, although the operational definitions of apnea and hypopnea differ among sleep laboratories, with resultant differences in the magnitude of the RDI. While respiratory events can be identified solely on the basis of reductions in thermocouple or respiratory band signals, associated physiologic measures such as a fall in SaO_2 or EEG evidence of arousal are often included in the definition in order to reduce the frequency of artifactual event detection. For the primary analysis, the AHI will be calculated using apneas and hypopneas, which are associated with a 4% fall in SaO_2. The AHI calculated in this way is highly correlated with AHI calculated using different thresholds of fall in SaO_2 (Aim 2), and is most consistent with reports in the literature from other epidemiologic studies, including the Wisconsin Sleep Cohort Study (13) and the community-based studies of Kripke, Ancoli-Israel and colleagues. Regardless, in SHHS we will be able to: 1) quantify the magnitude of any change in the AHI or blood pressure between the first and second PSG; 2) use repeated measures analysis to estimate more precisely the value of these variables over a six-year period.

While the RDI is commonly used to quantify SDB severity, the PSG measures which best predict risk of CVD have not been characterized. To assess alternative measures of SDB as predictors of CVD risk, assuming that a significant association is found between AHI and CVD disease in Aim 1, we will compare various measures obtained from PSG to determine which are most strongly associated with CVD risk (Aim 2). The measures to be evaluated include measures of sleep architecture (percent time in Stage 1, Stage 2, Stage 3/4, and REM sleep), sleep fragmentation (sleep arousal index, transitions to Stage 1 or wakefulness, and sleep maintenance efficiency), oxygen saturation (percent time with SaO_2 below specified thresholds), alternative measures of RDI obtained by varying the definition of apnea and hypopnea (requiring or independent of EEG arousal, requiring or independent of falls in SaO_2 of varying magnitude from 2-5%), and percent of sleep time spent in apnea or hypopnea.

The following is a summary of variables available by computer analysis with linking the data from multiple channels:

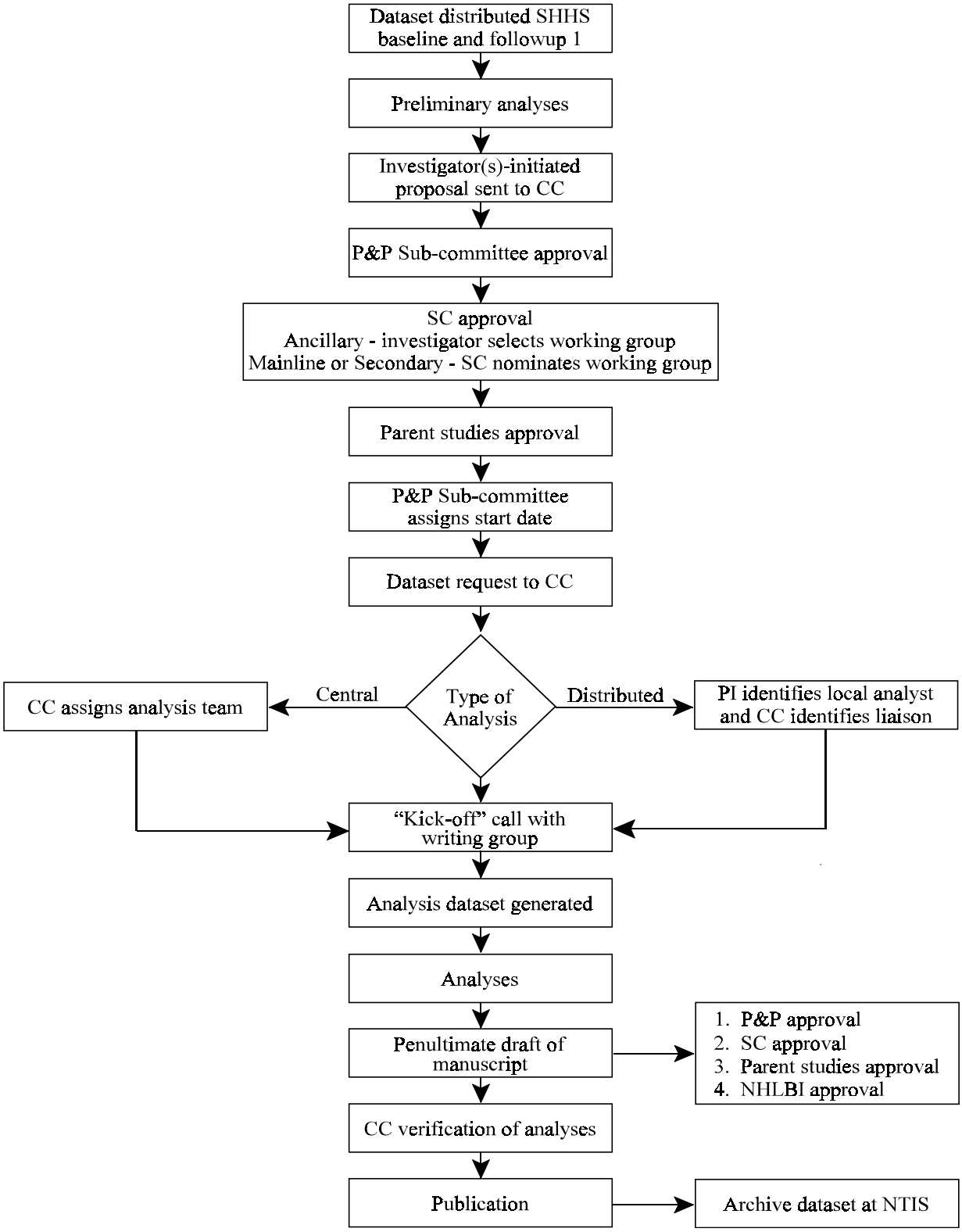
Summary RDI values, based on requiring > 2%, 3%, 4%, and 5% desaturation levels, occurring within 30 seconds of the termination of the event; based on an associated arousal, occurring within 3 seconds of the termination of the respiratory event; and based on all combinations of arousal and the five levels of desaturation.
Percent sleep time in apnea (obstructive or central).
Percent sleep time in hypopnea.
Percent sleep time in desaturation (<95%, <90%, <85%, <80%, <75%).
Percent time in each sleep stage.
Arousal index.
Number/hour stage 1 shifts.
Number/hour wake shifts.
Sleep efficiency.
Maximum, minimum and mean heart rate noted with each event and over the entire recording period.

13.1.5 Protocol for Data Analysis

For any analysis that is intended to become the basis of a manuscript, a proposal must be submitted to the CC for review by the P&P subcommittee. The proposal and analysis steps are represented in the Figure below.

The proposed type and site of analysis is to be provided on the submitted proposal. Secondary papers are those dealing with non-primary hypotheses or with data collected at more than one, but not all, Investigative Centers. Mainline papers are those dealing with primary hypotheses. Mainline and secondary papers use data from either the full set of SHHS sites, or a significant proportion thereof. Ancillary papers are those using data collected at only one Investigative Center.

In considering the matrix of potential paper types (mainline, secondary, or ancillary) by analysis site, i.e., Central (CC) or distributed (Field Site or a central reading center), most analyses would fit into one of three categories: 1) mainline or secondary paper analyzed at the CC; 2) mainline or secondary paper analyzed at a reading center or an Investigative Center; and 3) ancillary paper analyzed at a reading center or an Investigative Center. CC members may act as primary authors. With regard to distributed analyses, any involving the full SHHS data and comprising other mainline or secondary studies would involve verification of analyses by the CC. For ancillary papers, an analysis plan would be included as part of the submission to the P&P Subcommittee, but the level of verification required by the CC would be determined on a case by case basis by the P&P Subcommittee and the CC. The P&P Subcommittee would need to approve the analysis plan, as provided.


Dataset distributed SHHS baseline and followup 1
Preliminary analyses
Investigator(s)-initiated proposal sent to CC
P&P Sub-committee approval
SC approval
Ancillary - investigator selects working group
Mainline or Secondary - SC nominates working group
Parent studies approval
P&P Sub-committee assigns start date
Dataset request to CC
Type of Analysis
Central
Distributed
CC assigns analysis team
PI identifies local analyst and CC identifies liaison
"Kick-off" call with writing group
Analysis dataset generated
Analyses
Penultimate draft of manuscript
1. P&P approval
2. SC approval
3. Parent studies approval
4. NHLBI approval
CC verification of analyses
Publication
Archive dataset at NTIS

13.1.6 CC Analysis Procedures

Each proposal approved by the P&P Subcommittee that involves analysis by the CC will be reviewed initially at the CC. The reviewing group will include the CC's leadership as well as the main analyst to be involved in the project. At that meeting, data items to be used will be reviewed and the structure of the analysis plan developed. When the analysis plan has been approved at the CC, a conference call will be convened for members of the writing group. This group will have been identified by the P&P Subcommittee. Participants in the "kick-off" conference call will include the writing group, the main analyst, and a designated representative of the CC's internal analysis committee. During the kick-off call, the analytic approach will be reviewed, timelines set, and responsibilities designated for manuscript development.

13.1.7 Verification of Data Analyses

Analyses carried out by the a reading center or an Investigative Center will be verified centrally. The center will provide the CC with a listing of the variables used in the analysis and the analysis code. Important counts, and a sample of analyses included in text, tables, and figures will be verified.

13.2 Limitations

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

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

Combining information from parent studies with major differences in their populations, sampling designs, protocols and procedures is one of the major challenges of SHHS. Efforts have been made to identify potentially important risk factors and confounding variables and to obtain the maximum level of comparability across the various parent studies. Information on a subset of the important variables will be collected on all participants using standard, study-wide procedures, while other variables may have to be adjusted statistically. Analyses based on statistically adjusted variables will have to be viewed cautiously. In addition, additional variables not measured in some participants may be responsible for major differences in the samples and cannot be adjusted for in the analyses. Only a study design based on randomization procedures can protect against these unknown effects.

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

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

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

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

14. PROJECT GOVERNANCE

The SHHS consists of several key components: the seven Investigative Centers, the CC, the SRC, the ECGRC, and the NHLBI Project Office. Operational mechanisms include several subcommittees, procedural guidelines, and budgetary and fiscal management policies.

14.1 Components

14.1.1. 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 5 year project period.

A study coordinator is supported at each of the participating Investigative Centers, who functions under the supervision of the P.I. The coordinator certifies personnel, establishes procedures to ensure 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 CC; and participates in the Operations Subcommittee as necessary.

14.1.2. Coordinating Center

The CC, at the Johns Hopkins University School of Hygiene and 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.

14.1.3 Sleep Reading Center

The SRC at Case Western Reserve University serves as a centralized laboratory to provide standardized scoring and interpretation and quality assessments of all sleep studies obtained as a part of this study. It will assist the 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: assisting in protocol development; developing performance standards for sleep studies; developing a Manual of Operations for unattended and laboratory-based sleep studies; coordinating the purchase and maintenance agreements for sleep equipment; developing and maintaining software for sleep data processing; training sleep technicians centrally; providing technical support services to the Field Sites; ascertaining and reporting on the quality of sleep studies; providing centralized sleep scoring of unattended and laboratory-based sleep studies; interpreting sleep studies and providing sleep reports to the Field Sites; assisting in data analysis, and development of ancillary and nested studies. The Director of the SRC is a voting member of the Steering Committee.

14.1.4 ECG Reading Center

The ECGRC at Cornell University serves as a centralized unit to receive modem-transmitted ECGs, interpret them and produce reports to the Field Sites and an analysis database for transmission to the CC. It is responsible for assisting in the development of a protocol for ECG performance and reading, developing standards for, and reporting on quality of ECGs so that performance can be determined by Field Site and technician. It will produce a Manual of Operations for activities at the ECGRC. It will maintain software consistent for interpretation of ECGs originating at the Field Sites. The ECGRC will also assist with technical questions regarding the ECG.

14.1.5 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.

14.2 Committees

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

14.2.1 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.

14.2.2 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 are listed in Appendix 5.

Publications and Presentations Subcommittee:

The Publications and Presentations (P&P) Subcommittee is charged with reviewing and maintaining publication and presentation policies. A 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.

Polysomnography Subcommittee

The purview of this committee is selection of study equipment, determination of variables to be measured, definitions, and development of the protocol. Feasibility studies will be conducted at the SRC and possibly at some or all of the sites. This subcommittee will also be responsible for quality control of the sleep studies.

Protocol Subcommittee

This subcommittee is responsible for developing materials for non-PSG data collection and for communication with participants. These materials include questionnaires and documentation (such as coding guides) as well as consent forms, recruitment and retention materials, participant assessment forms, and PSG results reports for participants and their physicians. This subcommittee also will develop protocols and data collection instruments for physical measurements, such as height, weight, BP, ankle arm index, and ECG.

Quality Control Subcommittee

The Quality Control Subcommittee has been charged with coordinating and directing all non-PSG SHHS quality assurance and control activities. Working with the specialty subcommittees and the CC, the Quality Control Subcommittee determines the areas of emphasis for each routine quality control report in response to priorities for quality assurance developed by the Steering Committee. The subcommittee also reviews all reports with specific attention to deviations from protocol, recurrent problems and trends, and shifts in data over time.

The Quality Control Subcommittee prepares recommendations to the Steering Committee concerning quality assurance and control and contacts Field Sites, the ECGRC, or CC, as needed to advise them of

problems and to discuss mechanisms for correction. The Quality Control Subcommittee will meet at least 3 times per year during data collection years, and then periodically thereafter.

Operations Subcommittee

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

14.3 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.

14.4 Scientific Advisory Committee

This committee was established at the time of renewal of SHHS for Years 6-10 at the recommendation of the Initial Review Group (IRG). The function of the Scientific Advisory Committee is to make recommendations to the SHHS investigators in the following areas:

1. hypotheses that can be tested within the observational study paradigm of SHHS;

2. alternative interpretations of study data;
3. areas in which collaboration with non-SHHS investigators would further the goals of the SHHS;
4. advice regarding technical issues related to the SHHS data acquisition protocols;
5. development of protocols or ancillary studies which would address the pathogenesis of cardiovascular disease associated with sleep-disordered breathing

The Scientific Advisory Committee was constituted in the spring of 2000.

15. 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.

15.1 Publications 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.

15.2 Policies and Procedures

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.

15.3 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

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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

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

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

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

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:	F. Javier Nieto, M.D., Ph.D.	Baltimore
	George T. O'Connor, M.D., M.S.	Boston
	David M. Rapoport, M.D.	New York City
	Helaine Resnick, PhD	Washington, D.C.
	John A. Robbins, M.D., M.H.S.	Sacramento
	Eyal Shahar, M.D., M.P.H.	Minneapolis
Sleep Reading Center:	Susan Redline, M.D., M.P.H.	Cleveland
Coordinating Center:	Jonathan M. Samet, M.D.	Baltimore
NHLBI Project Scientist:	Michael Twery, Ph.D.	Bethesda

SUBCOMMITTEES

Polysomnography / Quality Control Subcommittee
Chairman: Susan Redline
Members: Daniel Gottlieb, Conrad Iber, Vishesh Kapur, Naresh Punjabi, David Rapoport, Mark Sanders, Philip Smith, Stuart Quan

Morbidity and Mortality Subcommittee
Chairman: George O'Connor
Members: Tauqeer Ali, Russell Dodge, Nancy Min, Anne Newman, F. Javier Nieto, Thomas Pickering, Eyal Shahar

Protocol Subcommittee
Chairman: Eyal Shahar
Members: Adele Gilpin, Daniel Gottlieb, Michael Lebowitz, Anne Newman, F. Javier Nieto, Jonathan Samet, Joyce Walsleben

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

Quality Control Subcommittee
Chairman: F. Javier Nieto
Members: Paul Enright, Joel Hill, Conrad Iber, Michael Twery, Joyce Walsleben, Terry Young

NHLBI APPOINTED COMMITTEES

Observational Study Monitoring Board (OSMB)

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

Scientific Advisory Committee (SAC)

Jerome Dempsey, Ph.D.	Madison
Jan Hedner, M.D., Ph.D.	Gothenburg, Sweden
Russell Tracey, Ph.D.	Colchester, VT
David White, M.D.	Boston

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,

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

POLICY

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

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

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

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

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

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

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

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

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

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

PROCESS

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

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

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

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

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

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

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

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

DISCLOSURE STATEMENT FOR INVESTIGATORS OF THE SLEEP HEART HEALTH STUDY

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

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

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

APPENDIX 5: Sample participant and physician letters for medical alerts

See the following pages

DATE

DR. NAME, .
DR. ADDRESS.
Tucson, AZ ZIP

Dear Dr. NAME: Your patient, NAME is a participant in the Sleep Heart Health Study at the University of Arizona Respiratory Sciences Center. Sponsored by the National Heart, Lung and Blood Institute and the National Sleep Center, the purpose of this study is to determine the cardiovascular consequences of sleep apnea. As a part of this study, participants undergo an electrocardiogram in their home. Your patient, Mr. Name, had an ECG performed on DATE OF ECG. Mr. Name has requested that a summary of these results, which are enclosed with this letter, be sent to you.

Mr. Name may be contacting you to discuss this ECG. However, these results were obtained as part of a research protocol and should be interpreted in the context of your patient's current clinical symptoms and condition. The enclosed copy of the ECG is provided for your information. If you require additional information or you wish to discuss this ECG further, please do not hesitate to call me at (520) 626-6115.

I appreciate the opportunity to have your patient, Mr. Name, participate in the Sleep Heart Health Study.

Sincerely,

Stuart F. Quan, M.D.
Professor of Medicine & Anesthesiology
Director, Sleep Disorders Center

DATE

NAME, .
ADDRESS.
Tucson, AZ ZIP

Dear NAME:

Thank you for your continued participation in the Sleep Heart Health Study and to have had another recording of your sleep at night. We have recently reviewed some of the results of your study and have noted the following finding which we believe you should discuss with your physician in the near future:

Your electrocardiogram (ECG) showed signs of an abnormality or change from a previous ECG obtained as part of this study.

If you wish for a copy of your ECG tracing be sent to your physician, please let us know and we will do so. If you do not have a personal physician, your local medical society may be of assistance.

If you require additional information or you wish to discuss this ECG further, please do not hesitate to call me at (520) 626-6115. Thank you again for your participation in the Sleep Heart Health Study.

Sincerely,

Stuart F. Quan, M.D.
Professor of Medicine & Anesthesiology
Director, Sleep Disorders Center

APPENDIX 6: Consent statements

(1) For participants consenting to home visit with PSG

(2) For participants consenting to home visit without PSG

See the following pages

COMMITTEE ON HUMAN RESEARCH CONSENT FORM

The Johns Hopkins University
School of Hygiene and Public Health

Title of Research Project:
CHR#:H.34.99.0518.A

SLEEP HEART HEALTH STUDY
Prototype Consent Form for participants undergoing a PSG study

Explanation of research project:

You are invited to continue your participation in the Sleep Heart Health Study (SHHS). The SHHS research study began in 1994. It is funded by the National Institutes of Health. The main goal of this study is to learn more about how breathing patterns during sleep might affect a person's risk of developing heart disease or stroke. Another goal is to understand how sleep patterns change as people age. You are being asked to participate because you were one of 6,440 people nationwide who have already had the first sleep study. We expect it to take about two years to complete all of the second sleep studies and other measurements. After that, it may take an additional five or more years to gather information on future heart disease. As in your last visit, your participation will last only for the time of your home visit.

Procedures:

If you agree to participate, you will have another sleep study at your home. It will also involve:

- A short interview about your health
- Measurements of your height, weight, and neck circumference
- Measurements of your blood pressure in the arms and legs
- An electrocardiogram (EKG)
- Recording the medications you have taken recently
- Filling out questionnaires about your sleep and other health-related issues

For the sleep study, the technicians will connect you to a sleep monitor. This involves attaching several sensors (wires) to your skin using adhesive disks, similar to EKG recording. The wires will be connected to a monitor that will record your heart function, breathing, eye movements, oxygen level, and brain activity. One sensor will be taped below your nose to record your breathing while you sleep. Another small sensor, taped to one of your fingertips, will measure your oxygen level throughout the night. You will need to remove any fingernail polish you may be wearing on that finger. To record your brain function two small disks will be attached to your scalp and several small disks to your forehead and chin. All of the wires will be tucked into pockets on a vest, which you will wear until the next morning. When you go to bed you will attach a cable from the vest to a small recording box. The box will be placed next to your bed.

You will be able to move about carrying the device with you, or to disconnect yourself completely from all wires. When you wake up in the morning, you will disconnect yourself. The technicians will return in the morning at an agreed upon time to collect the equipment. Information about your sleep and other measurements will be mailed to you 10-12 weeks after the study.

Occasionally (less than 5% of the time), because of equipment failure or electrodes coming off, or the like, a sleep study either gives poor quality information or no information at all. If that were to happen, you would be asked to have another sleep study along with answering the morning questionnaire and the

medications questionnaires. You would not be asked to sign another consent form, but it would be your decision whether to have another sleep study or not.

Risks/discomforts:

The study procedures are safe. Some people report some trouble sleeping during the night of the study. There could be some discomfort where electrode leads are placed on your chest and head. When the sensors are removed it may cause some temporary pain, may remove some hair, and may leave a small area of red skin which is painless and goes away within a few days. If such irritation occurs, remove the paste with warm water, and if the irritation persists over the next day, please seek medical attention. There are no other foreseeable risks.

Benefits:

The benefits to you are that you will have a review of your current sleep patterns and other measurements. Irregular heart rhythms or other factors that may be important to your health may be identified. These results will be available to you. The study does not provide medical care and is not intended to interfere with your relationship with your doctor. The results of your study will be sent to your doctor if you wish. This home sleep study and its results will be provided free of charge.

By participating in this study, you will be contributing to medical knowledge about sleep patterns, their relation to heart disease, and factors which could be important in treating people in the future.

Confidentiality:

The confidentiality of the information you give will be protected as much as is legally possible. Only the selected personnel who come to your home and those who manage the data will know your name. All papers containing data are kept secure in locked file cabinets. Offices are locked when personnel are absent. The database at the central data management unit will identify you only by number and a five character, randomly selected, letter code. Study information may be made available to other scientists for approved research purposes, but no identifying information will be released. Study records may be kept indefinitely for analysis and follow-up.

Compensation for illness or injury:

The [Name of Institution] and the Federal Government do not have a program to provide compensation to you if you experience injury or other bad effects which are not the fault of the investigators.

Voluntary participation

You can decide not to be in the study, or to stop being in the study at any time. It will not affect your medical care at this facility, or cause a loss of any benefits to which you would otherwise be entitled.

Questions about the research study

If you want to talk to anyone, now or in the future, about this research study, you should call the Principal Investigator [NAME] at [telephone #], or call the [TITLE OF OFFICE FOR RESEARCH SUBJECTS], at [telephone #, FAX #]. They will answer your questions and/or help you to find medical care if you are hurt during the study. The researchers will tell you about any new significant findings that they think will affect your willingness to continue participation.

A copy of this consent form will be given to you. Your signature below means that you have freely agreed to participate in this research study.

_____
Participant Signature

_____
Participant Printed Name

_____
Witness

_____
Date and time

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

Void One Year From Above Date
CHR No. _____

COMMITTEE ON HUMAN RESEARCH CONSENT FORM

The Johns Hopkins University
School of Hygiene and Public Health

Title of Research Project: **CHR#H.34.99.05.18.A**

SLEEP HEART HEALTH STUDY
Prototype Consent Form for participants not undergoing a PSG study

Explanation of research project:

You are invited to continue your participation in the Sleep Heart Health Study (SHHS). The SHHS research study began in 1994. It is funded by the National Institutes of Health. The main goal of this study is to learn more about how breathing patterns during sleep might affect a person's risk of developing heart disease or stroke. Another goal is to understand how sleep patterns change as people age. You are being asked to participate because you were one of 6,440 people nationwide who have already had the first sleep study. We expect it to take about two years to complete all of the second sleep studies and other measurements. After that, it may take an additional five or more years to gather information on future heart disease. As in your last visit, your participation will last only for the time of your home visit.

Procedures:

If you agree to participate, you will have a home visit. It will also involve:

- A short interview about your health
- Measurements of your height, weight, and neck circumference
- Measurements of your blood pressure in the arms and legs
- An electrocardiogram (EKG)
- Recording the medications you have taken recently
- Filling out questionnaires about your sleep and other health-related issues

Information about your measurements will be mailed to you 10-12 weeks after the study.

Risks/discomforts:

The study procedures are safe. There are no foreseeable risks.

Benefits:

The benefits to you are that you will have a review of your EKG, blood pressure, and other measurements. Irregular heart rhythms or other factors that may be important to your health may be identified. These results will be available to you. The study does not provide medical care and is not intended to interfere with your relationship with your doctor. These results will be sent to your doctor if you wish. This home visit and its results will be provided free of charge. By participating in this study, you will be contributing to medical knowledge about sleep patterns, their relation to heart disease, and factors which could be important in treating people in the future.

Confidentiality:

The confidentiality of the information you give will be protected as much as is legally possible. Only the selected personnel who come to your home and those who manage the data will know your name. All papers containing data are kept secure in locked file cabinets. Offices are locked when personnel are absent. The database at the central data management unit will identify you only by number and a five character, randomly selected, letter code. Study information may be made available to other scientists for

approved research purposes, but no identifying information will be released. Study records may be kept indefinitely for analysis and follow-up.

Compensation for illness or injury:

The [Name of Institution] and the Federal Government do not have a program to provide compensation to you if you experience injury or other bad effects which are not the fault of the investigators.

Voluntary participation

You can decide not to be in the study, or to stop being in the study at any time. It will not affect your medical care at this facility, or cause a loss of any benefits to which you would otherwise be entitled.

Questions about the research study

If you want to talk to anyone, now or in the future, about this research study, you should call the Principal Investigator [NAME] at [telephone #], or call the [TITLE OF OFFICE FOR RESEARCH SUBJECTS], at [telephone #, FAX #]. They will answer your questions and/or help you to find medical care if you are hurt during the study. The researchers will tell you about any new significant findings that they think will affect your willingness to continue participation.

A copy of this consent form will be given to you. Your signature below means that you have freely agreed to participate in this research study.

_____
Participant Signature

_____
Participant Printed Name

_____
Witness

_____
Date and time

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

Void One Year From Above Date
CHR No. _____