



Sleep AHEAD Study

Polysomnogram Reading Laboratory

Policies and Procedures

Polysomnogram Reading Laboratory

The policies and procedures that will be used by the Polysomnogram Reading Laboratory (PSGRL) in this clinical trial “Weight Loss and Sleep Apnea in SHOW Participants” (Sleep AHEAD) are taken directly from those detailed in the Polysomnogram Reading Center Manual of Operations developed for the Sleep Heart Health Study (1,2). The policies and procedures in the Sleep Heart Health Study were developed to obtain consistent (reliable), objective data in a large number of individuals studied with the same equipment in unattended settings for the purposes of developing a large and versatile research database (1,2). The Sleep Heart Health Study manual established the “gold standard” for the policies and procedures needed to perform sleep evaluations in multi-site clinical trials. Although the size of the current study is smaller than the Sleep Heart Health Study, the same challenges are faced in the proposed trial concerning the ability to uniformly collect data at different sites, transmit the data to a core laboratory, and analyze the data for the Data Coordinating Center. Large sections of the Sleep Heart Health Study manual have been reproduced in the current manual. Changes made from the Sleep Heart Health Study manual reflect differences in study design and implementation.

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1. Objectives of the PSG Reading Laboratory

- Standardize the performance of sleep studies among the Clinical Sites
- Provide timely review (for quality and medical alerts) and scoring of all records, generating reports needed for participant feedback and data files for Data Coordinating Center processing. Reports will provide the sleep outcome measures needed for the research project
- Participate in on-going quality assurance efforts to maintain high levels of technical performance of tests at the Clinical Sites and scoring accuracy in the PSG Reading Laboratory.

2. Structure and Resources of PSG Reading Laboratory

Samuel T. Kuna, M.D. will serve as the medical director and Beth Staley, RPSGT will be the Chief PSG Technologist of the PSG Reading Laboratory. They will hire and train the PSG technologist who will perform the scoring. Dr. Kuna will be ultimately responsible for achieving all of the objectives of the PSGRL. Two physicians with considerable experience in polysomnography (Allan I. Pack, M.D., Ph.D., and Richard Schwab, M.D.) will assist in the development of scoring procedures. They will participate in weekly staff meetings that discuss issues regarding scoring and quality control. The Chief PSG Technologist will:

- Assure high levels of accuracy and reproducibility of scoring procedures
- Review each sleep study the day it is received at the PSGRL
- Identify Medical Alerts
- Provide quality codes
- Monitor the scorer's performance
- Provide support for interpreting ambiguous studies
- Implement on-going procedures for assuring accuracy and reproducibility of scoring procedures

The PSGRL will be located at the Presbyterian Hospital Sleep Laboratory, the clinical research sleep laboratory for the Center for Neurobiology and Sleep Medicine at the University of Pennsylvania. The Chief PSG Technologist has an office in this facility and work areas are available for the scoring of the sleep evaluations. A dedicated personal computer is available for the analysis of the PSG files sent to the PSGRL from the Clinical Sites. A telephone, fax machine, and copy machine are also available for use by the PSGRL.

3. Training and Certification of technical personnel at PSG Reading Laboratory and Clinical Sites

Training and Certification of the Chief PSG Technologist at PSG Reading Laboratory: The Chief PSG Technologist is an experienced polysomnologist with > 5 years experience in scoring. This individual will be required to demonstrate a complete understanding of scoring rules and ability to articulate reasons for assigning epoch-by-epoch codes for sleep staging and respiratory events scoring. This will be judged by discussion with Dr. Kuna. Prior to data collection for the study participants, the Chief PSG Technologist will demonstrate a 5% level of agreement for RDI and sleep stages, and a 10% level of agreement for arousals (with-in scorer reliability) by scoring the same 20 records, at least one week apart.

Training and Certification of PSG Scorer at PSG Reading Laboratory: The PSG Scorer will be required to demonstrate a complete understanding of scoring rules and ability to articulate reasons for assigning epoch-by-epoch codes for sleep and respiratory scoring. This will be judged by review of several records with the Chief PSG Technologist or a physician-investigator (Drs. Kuna, Pack, Schwab). The scorer will be required to score at least 20 records, achieving a 10% level of agreement with the Chief PSG Technologist for respiratory events and sleep stages and a 15% level of agreement for arousals. The Chief PSG Technologist (or designee) will review the first 10 records on actual study participants scored by the PSG Scorer after training. After that the Chief PSG Technologist will check score a randomly chosen 10% of the PSG records using the above standards for agreement .

Training and Certification of Technicians Setting-up the Polysomnograms in the Participants' Homes: At least one technician from each site will be trained at a 2 day central training session held at the PSG Reading laboratory before the start of recruitment. The certification process will include written and practical examinations and successful performance of at least 3 practice hook-ups. Technicians trained at the PSGRL will be responsible for training other technicians at their local sites. Locally trained technicians will complete a written examination and practical evaluations, and successful performance of at least 3 practice studies. Certified technicians who performed 2 studies within a three month period that are failed studies or of poor quality will require recertification. In addition, the medical director of the PSGRL will visit each site prior to subject recruitment and at least once each year of the project to observe set-up, data transfer, and reinforce training.

Training and Certification of Polysomnographic Technologist at each Clinical Site: Each Clinical Site will designate a certified PSG Technologist who will be responsible for downloading and reviewing the home PSG recordings, assuring that all forms are complete, and transferring the data to the PSGRL and Data Coordinating Center. Ideally, the PSG Technologist at each Clinical Site will be the same individual who is training and supervising the technicians performing the home set-ups. In this case the Clinical Site's PSG technologist will attend the PSG training session held in Philadelphia and will be certified to perform the participant hook-ups and study assessment. In the event that PSG Technologist designated to review studies at a particular Clinical Site is not the same individual as the person who is supervising the technicians performing the home set-ups, the PSGRL medical director will certify the Clinical Site PSG technologist by visiting that Clinical Site prior to participant enrollment. Certification of PSG review will involve demonstrating the procedures for downloading the PSG data from Flashcard, viewing the studies to assess quality, and storing the data on CDs. In addition, the individual will be required to perform these procedures on sample files obtained from non-participants.

4. Procedures at PSG Reading Laboratory for Handling PSG Data

Within one working day of receipt of a PSG file from a Clinical Site, the Chief PSG Technologist at the PSGRL will review the study for quality of signals. The Chief PSG Technologist will complete the PSGRL Receipt Form, coding each channel of information according to the duration of artifact free signal that can be scored. The total duration of the study (from the lights off to the lights on) and the total duration of sleep will also be indicated. PSGs meeting the minimum criteria for acceptability will be assigned to the PSG scorer. All polysomnograms will be analyzed within 2 working days of receipt at the PSGRL with turn-around in 24 hours for those studies activating a Medical Alert (see below).

The minimally acceptable criteria for polysomnogram scoring include: record must contain at least 4 hr of scorable data with at least one scorable EEG, oximetry and a respiratory signal (either airflow, rib cage or abdomen) between recording on and off (Total Recording Time). Recorded time after final awakening will not contribute to this time. If data loss occurs at the beginning or end of the study, this period will be scored as Stage Wake and edited lights will be set "on" during this period. If data loss occurs at the beginning of the study, sleep latency will be noted as "unreliable". If periods of data loss occur after sleep onset and before final awakening, this period will be marked as Stage Wake. Two continuous blocks of data that can be scored, each at least 2 hr long, are required to consider study acceptable for scoring.

Responsibilities of Chief Polysomnographic Technologist (or designee):

- Reads CD and prints receipt
- Requests any missing data from the Clinical Site via fax or e-mail
- Sends receipt to Clinical Site and Data Coordinating Center (via fax or e-mail)
- Fills out PSGRL Receipt Form within one working day of arrival, judging study quality
- Distributes completed PSGRL Receipt Form with CD to the scorer
- If Medical Alert activated, triages study to scorer for priority scoring
- If study is unacceptable due to the unreliability of signals, fills out Request for Repeat Study Form and PSGRL Receipt Form and faxes these forms to Clinical Site and Data Coordinating Center
- A copy is filed in PSGRL
- Verifies that all information is complete on QA form
- Verifies that data from the electronic forms and PSG results are on the database
- Transmits the appropriate electronic forms and PSG results to Clinical Site and Data Coordinating Center

If the scored polysomnogram study meets criteria for urgent Medical Alert, the PSGRL's physician-investigator reviews and initializes full report. The Clinic Coordinator at the Clinical Site will be contacted by telephone and the report is faxed to the Clinical Site. This transaction is documented in a Medical Alert Log.

Responsibilities of Primary Assigned Scorer:

- Completes Medical Alert priority within 24 hours and returns to Chief PSG Technologist
- Scores study and produces the Full Report
- Fills out PSG Scoring Form and Sleep Data Quality Assurance Form
- Backs up scored files
- Reviews PSG study for outliers and extreme values
- Reviews PSG study with physician investigator when:
 - Study scored sleep - wake only due to technical problems
 - "Alpha intrusion" or "abnormal awake EEG" are present
 - Any abnormal occurrences are noticed during scoring
- Sends CDs to the place of destination (Coordinating Center and Clinical Site)

Chief Polysomnographic Technologist final QA check

- Reviews all items completed on PSG Scoring forms and checks that all data has been electronically entered into the database
- Checks CDs for all necessary report/data files
- Verifies backup of scored files

5. PSGRL Receipt Form

To document the initial review of PSG files sent to the PSGRL from the Clinical Sites, the Chief PSG Technologist will fill out the PSGRL Receipt Form. This review determines whether the study is of acceptable quality to allow scoring and whether the recording may trigger a medical alert. Recordings that are technically acceptable are assigned to the PSG scorer. Recordings that are not technically acceptable will be documented on the PSGRL Receipt Form and Request for Repeat

Study Form. Recordings that trigger a medical alert will be assigned high priority for scoring. The following details the information collected on the PSGRL Receipt Form.

General Coding Instructions for PSGRL Receipt Form

Each box must be completed. If a piece of data is missing, the field should be left blank. It will be assumed that quality assessment was not or could not be done.

Question-by-Question Coding Specifications

Complete the following identification data:

Participant ID: a 9-digit field (use participant's Look AHEAD ID)
Date of Study (use month, day, year format; each a 2-digit field)
File ID: a 15-digit field (automatically entered from above two fields)
1st Tech ID: initials of technician applying sensors for PSG
2nd Tech ID: initials of technician filling out questionnaire form
Assessment time: Baseline, 1-year, 2-year
Arrival time: Time entering home to set up PSG
Departure time: Time leaving home following set-up

Date Received at RL: (use month, day, year format; each a 2-digit field)
Date Reviewed: (use month, day, year format; each a 2-digit field)
Reviewer's Initials: (up to 3 letters)

Items 1-12 check the quality of each signal, whether the study is acceptable for full scoring, and if the study should be a high priority.

Coding:

Permissible codes: 0 (=NO) 1 (=YES)

1. Problems with lights?
2. Problems with airflow?
3. Recording too short?
4. Problems with belts?
5. Problems with EMG?
6. Problems with oximetry?
7. Problems with EEG?
8. Equipment issue?
9. Problems with ECG?
10. Other problems?
11. Study passed?
12. If study passed, is it a high priority?

The final item requests a failure code assignment with responses of 1-12, each item specifying specific reasons why the study might not have passed for full scoring.

1. Oximetry
2. EEG
3. Short recording
4. No data on card
5. Start time setting
6. Participant
7. Multiple
8. Equipment – unknown
9. Cable disconnect
10. Respiratory
11. Corrupted file on CD – no backup at site
12. Not applicable – study passed review

Comments box: Make additional comments about review of study

6. Scoring Procedures for Polysomnograms

Overview of Scoring. The PSG will be assigned to a scorer for full scoring. Compumedics USA software will be used to process all the records. EEG offset will be checked and corrected if necessary. After correction, off-line analysis will be run in two passes. During the first pass, the study will be reviewed on an epoch-by-epoch (30 sec) basis and each epoch will be manually assigned a sleep stage, and EEG arousals will be marked according to the rules stated in **Section 17**. During second pass, the signal display will be compressed to 5 min/CRT screen and respiratory data (airflow/abdomen/rib cage/saturation) will be scored. Events will be marked manually according to the rules stated in **Section 17**. The light sensor signal for lights out will be used as the start of the polysomnogram recording and the patient's log will be used to obtain the time that he/she got out of bed in the morning. These measures will be used to calculate total recording time.

Sleep stages will be characterized by modified Rechtschaffen and Kales criteria (Rechtschaffen A, Kales A. A Manual of Standardized Terminology Techniques and Scoring System for Sleep Stages in Human Subjects. Washington, DC: US Government Printing Office, 1968.) and arousals by the ASDA criteria (The Atlas Task Force, EEG Arousals: Scoring Rules and Examples. Sleep 1992: 15:173-84). Arousals will be associated with events if they begin within 3 sec of the termination of the respiratory event.

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

"Central" events will be noted if no displacement is noted on either the chest or abdominal inductance channels. Otherwise, events will be noted as "obstructive." All hypopneas will be considered obstructive (because any effort, including that needed to

generate >25 displacement of the airflow signal, is considered obstructive).

Periodicity will be noted “manually” if marked waxing and waning of respiration occurs in a regular cyclic pattern. This requires at least 5 minutes of consecutive periods of crescendo-decrescendo breathing cycles (characteristic pattern – regardless of overlapping obstruction) of such a breathing pattern, lasting at least 10 consecutive minutes or 10 min of this pattern.

The desaturation associated with any respiratory event will be based on the nadir desaturation reached within a user defined amount of the time (usually 30 sec) of the end of the event. The magnitude of the desaturation for an event is the difference between the greatest saturation level observed during the event and this minimum. The scorer will manually check events to assure that the appropriate desaturation is identified.

After full scoring, presence of the following abnormal events will be noted:

- Abnormal awake EEG - when waking EEG contains waves in theta range. This should be distinguished from presence of theta waves as a result of excessive sleepiness, which will disappear after some period of sleep.
- Alpha intrusion - when alpha rhythm is present in more than 40% of Non-REM sleep.
- Abnormal eye movements – presence of the rhythmical lateral eye movements in Non-REM sleep.
- Periodicity - when airflow or inductance channels is increasing and decreasing at least 50% from the maximum in periodic (cyclic waxing and waning) manner, for a consecutive period of at least 10 min. Examples of this pattern will be printed and attached to the scoring form. This is independent from scoring apneas and hypopneas.
- Periodic large breaths - when very large breaths (one or two) occur periodically (mostly on the rib cage/abdomen channels) between runs of fairly normal breaths for a duration of at least 10 minutes.

Examples of this pattern will be printed and attached to the PSG Scoring Form. Before abnormal events are documented, they will be reviewed with the Chief PSG Technologist. Any study with abnormal occurrences or problems with scoring will be reviewed in the weekly QA meetings. Any technical problems or questions with regard to staging or marking of arousals will be noted and reviewed with a physician-investigator or the Chief PSG Technologist. A Final Report will be generated and scanned for the presence of outliers.

Outliers on PSG report

- % Stage (other than II) > 50%
- Sleep efficiency > 98% or < 20%
- HR < 20 or > 200
- Saturation < 40% or > 99%
- % REM > % NREM sleep
- Arousal index < 10% of RDI (unless no EEG data)
- Arousal index 4-fold > RDI

- RDI < 5 and desaturation index > 30
- Desaturation index (3%) 20% > RDI (3%)
- AH duration < 9 sec or > 125 sec

If any of these outliers are found, the scorer will trace the source and eliminate them, if indicated. The Final Report will be saved on disk.

The Final Report will also be reviewed for extreme values. If extreme values are identified, the study will be reviewed and the result of the review documented.

Extreme values on PSG report:

- 0 % of any sleep stage
- % Stage (other than Stage 2) > 50%
- RDI = 0 or > 160 events/hr
- Saturation < 40% or > 99%
- % REM > NREM
- Arousal index < 10% of RDI
- Arousal index 4-fold > RDI
- RDI < 5 and desaturation index > 15
- Central apnea index > 40 events/hr
- Apnea/hypopnea duration < 10 or > 150 sec
- Heart rate (beat by beat values) < 40 bpm or > 140 bpm

Scorers will review the record on the screen in two passes. During the first pass, sleep stages and arousals will be marked manually on an (30 sec) epoch-by-epoch basis. During the second pass, respiratory signals will be displayed (2-5 min of the record on the screen) and respiratory events will be manually marked.

7. PSG Outcome Measures

Polysomnographic Outcome Measures: After full scoring, analysis software will be used to link the various channels (multiplexing) to provide the following information regarding sleep staging:

- Total sleep time (TST)
- Sleep onset time
- Total recording time (TRT)
- Sleep efficiency, i.e., TST/TRT
- Stage 1 sleep, total time (mins) and % TST
- Stage 2 sleep, total time (min) and % of TST
- Stage 3-4 sleep, total time (min) and % of TST
- REM sleep, total time (min) and % of TST

The number of episodes of wakefulness, and the total duration of wakefulness while in bed, the time awake after sleep onset (WASO), and the latency to each sleep stage will also be calculated.

The primary polysomnographic outcome measure is the RDI (Respiratory Disturbance Index), defined as the mean number of respiratory events (apneas and hypopneas) per hour of the sleep. The outcome measures for sleep disordered breathing will include:

- Summary RDI values for all events

- Summary RDI values for events associated with desaturation levels > 2%, 3%, 4%, and 5%
- Summary RDI values for events associated with > 2%, 3%, 4%, and 5% desaturation levels and/or associated arousal
- Summary RDI values for events associated with arousal regardless of desaturation
- Percent of the sleep time in obstructive apnea/hypopnea events
- Percent of the sleep time in desaturation (<95%, <90%, <85%, <80%, <75%).
- Number of desaturations/hour of sleep (unlinked with respiratory events) of 2%, 3%, 4%, 5%.

8. Final Report Generation

The following are the templates for the PSG Reports that will be transmitted back to the Clinical Sites. Reports of slight different nature will be generated depending on whether the RDI is < 50 or ≥ 50 events/hr.

Template of PSG report to Clinical Site for RDI < 50

Sleep AHEAD Study
Pulmonary Sleep Evaluation Center
Montefiore University Hospital
3459 Fifth Avenue, Suite 639
Pittsburgh, PA 15213

Sleep Study Summary -- Test performed for Research Purposes

Participant Name: [full name]

Date of Study: [date of study]

Total Sleep Time: [sleep hours] hours and [sleep minutes] minutes

Total Time in REM: [total REM (in minutes)] minutes

Sleep Efficiency: asleep for [sleep efficiency] % of the time in bed

Respiratory Disturbance Index (apneas or hypopneas associated with 3% oxygen desaturation)
[RDI] per hour

Average Heart Rate: [average HR] bpm

% Sleep Time with Oxygen Saturation < 90%: [%oxygen < 90]

Template of PSG report to Clinical Site for RDI \geq 50

Sleep AHEAD Study
Pulmonary Sleep Evaluation Center
Montefiore University Hospital
3459 Fifth Avenue, Suite 639
Pittsburgh, PA 15213

Sleep Study Summary -- Test performed for Research Purposes

Participant Name: [full name]
Date of Study: [date of study]

Total Sleep Time: [total sleep period (hr:min)] hours
Total Time in REM: [total REM(in minutes)] minutes
Sleep Efficiency: asleep for [sleep efficiency] % of time in bed

Respiratory Disturbance Index (apneas or hypopneas associated with 3% oxygen desaturation)
[RDI] per hour

Average Heart Rate: [average HR] bpm
Minimum HR: [Minimum HR] bpm
Maximum HR: [Maximum HR] bpm

% Sleep Time with Oxygen Saturation < 90%: [SaO₂ % < 90]
% Sleep Time with Oxygen Saturation < 80%: [SaO₂ % < 80]
Minimum SaO₂: [minimum SaO₂] %

9. PSG Scoring Notes Form

This form is completed by the PSG scorer at the time the complete PSG scoring occurs.

Question-by-Question Coding Specifications for PSG Scoring Notes Form

Complete the following information:

Participant ID: a 9-digit field (use participant's Look AHEAD ID)
Date of Study (use month, day, year format; each a 2-digit field)
File ID: a 15-digit field (automatically entered from above two fields)
1st Tech ID: initials of technician applying sensors for PSG
2nd Tech ID: initials of technician filling out questionnaire form
Assessment time: Baseline, 1-year, 2-year
Arrival time: Time entering home to set up PSG
Departure time: Time leaving home following set-up

Acceptable codes for body of form:

Date Scored: MM/DD/YY

Scorer ID: enter initials of scorer

Items 1 through 5: Permissible codes: 0 (=NO) 1 (=YES)

1. Alpha Intrusion/Alpha Artifact?
2. Abnormal awake EEG?
3. Abnormal eye movements?
4. Periodicity?
5. Periodic large breaths?

Item 6 - Predominant ($\geq 75\%$) Channel for Scoring Respiratory: Permissible codes: 1, 2, 3, 4, 5, 6, 7

1. Nasal pressure
2. Chest
3. Abdomen
4. Combination of chest and abdomen
5. Combination of nasal cannula and chest
6. Combination of nasal cannula and abdomen
7. Combination of all 3 channels

Item 7 - Sleep Latency:

Coding: Permissible codes: 0 (=Unreliable); 1 (=Reliable)

Item 8 - Staging Notes: Was study scored with minimal ($< 10\%$) staging or arousal problems?

Coding: Permissible codes: 0 (=NO) 1 (=YES)

Item 9 – If > 10% problems encountered with staging or arousals, select those that identify how the study was scored:

- a. REM/NREM unreliable
- b. Scored Wake, Non-REM, REM only
- c. Arousal unreliable
- d. Scored Sleep-Wake only
- e. REM arousals (only) unreliable
- f. Wake-Sleep unreliable

Coding: Permissible codes: 0 (=NO) 1 (=YES)

Item 10 – Restricted Analysis: Was entire record scored?

Coding: Permissible codes: 0 (=NO) 1 (=YES)

Item 11 – If total sleep period is not captured, indicate reasons for not scoring entire record

- a. Scoring started after sleep onset
- b. Scoring ended before lights on/awake
- c. Intervening period bad EEG
- d. Intervening period bad Resp/Oximetry

Coding: Permissible codes: 0 (=NO), 1 (=YES), 2 (=N/A)

Item 12 – Were extreme values found on Outlier Check?

Coding: Permissible codes: 0 (=NO) 1 (=YES)

Item 13 – Do extreme values remain after review

Coding: Permissible codes: 0 (=NO) 1 (=YES)

10. Protocol for Repeating Unsuccessful Polysomnograms

Not all polysomnograms that are scheduled will be successfully completed. Failures can occur due to the collection of the data at the Clinical Site or transfer of the data to the PSGRL. When a study fails, attempts will be made to repeat the study. Tracking repeat studies requires communication between the Clinical Site, PSGRL, and Data Coordinating Center. The protocol for tracking and processing repeat sleep studies is described below.

Study is initiated but the data are found to be inadequate at Clinical Site review: In this situation, the study is performed but the data is lost due to technician error or hardware/software problems. The problem with the sleep data is noted on the Sleep Data Retrieval form, which is sent to the Data Coordinating Center. The Clinical Site tracks whether the study is rescheduled. If another hook-up is completed, it will be considered a repeat study. The Data Coordinating Center will send a list to the PSGRL once a month, listing all failed studies that month that did not result in

a data file being sent to the PSGRL, so that if these studies are repeated, the PSGRL will know that they are repeat studies.

Study is initiated, data are found to be inadequate at the PSG Reading Laboratory: In this situation, the hook-up is completed, the sleep data are reviewed by the Clinical Site, and the data are then forwarded to the PSGRL. Upon review, the PSGRL determines that the study does not meet minimum acceptable criteria (e.g., PSG does not contain 4 hours of scorable data). Through completion of the PSGRL Receipt Form and the Request for Repeat Study Form, the PSGRL requests the Clinical Site to repeat the study, and notifies the Data Coordinating Center. The Clinical Site will have one week to respond to the request and let the PSGRL and Data Coordinating Center know whether or not the study will be repeated.

Study is not repeated: If the study will not be repeated, the PSGRL does not score the data. However, the raw data are sent to the Data Coordinating Center and are archived onto CD ROM so that they may be retrieved at a future time, should this be deemed necessary. If possible, some preliminary results are sent to the participant by the PSGRL.

Study is repeated: If the study will be repeated, the Clinical Site schedules and tracks this. The Data Coordinating Center also tracks anticipated repeat studies, and sends a list to the Clinical Site of any expected repeat studies that have not been received within one month of the repeat study request being received at the Data Coordinating Center.

When the repeat study is performed, the Clinical Site handles the sleep data just as it would for a first study. When the PSGRL receives the sleep data, they are handled just like a first study, except that the PSG Data Retrieval Form notes that it is a repeat study.

If the second study is successful, the sleep data from the first (failed) study are deleted from the PSGRL computer system. However, the sleep data from the first study are not deleted until the second study has been completed and reviewed at the PSGRL. The raw data from the second study and the scored file are forwarded to the Data Coordinating Center, where they are handled in the same way as first studies.

If the second study is also a failed study, the raw data from one of the studies (the one with the “best” data in the judgment of the PSGRL) is archived at the Data Coordinating Center, but no scored file exists. No further attempts are made to complete the study. All efforts should be made to repeat the sleep study as soon as possible, in order to maintain the best possible relationship with the participant.

Sleep AHEAD Study

Repeat PSG Study Request

DATE: _____
(MM/DD/YY)

TO: _____
(SITE COORDINATOR)

FAX: _____

STUDY ID: ____ was received at the Reading Laboratory on
____/____/____. As the preliminary report attached indicates, this study has insufficient data
for reliable scoring due to _____

Indicate below with a check whether or not this study can be repeated:

_____ Study will be repeated

_____ Study cannot be repeated

Signature

Date (MM/DD/YY)

Fax your reply to the Reading Laboratory and Coordinating Center within one week of receipt.

Reading Laboratory's Fax: 215-243-4632

Coordinating Center's Fax: xxx-xxx-xxxx

cc: Coordinating Center

11. Transmission of PSG Data from PSGRL to Coordinating Center

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

In addition, the Reading Laboratory will send the Coordinating Center CD-R's each week containing studies that have been read so that they can be permanently archived at the Coordinating Center. The Reading Laboratory and Clinical Sites will also send the Coordinating Center data files every other week containing participant results files. The participant results files will be read into the Coordinating Center database, with programs checking for the following potential problems:

- Data files that arrive for participants for whom we have no other home visit data
- Data files that cannot be read into the database due to incorrect format, file corruption, etc.
- Data values that are extreme in value or fail internal consistency checks

In addition, a program will check for any participants for whom the Coordinating Center has not received a participant results file within 14 working days of the home visit. If any of these problems are noted, lists will be generated that will be sent to the Reading Laboratory or the Clinical Site, as appropriate, for resolution.

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

12. Backups and Data Security

Raw PSG data and home visit data will be sent to the Coordinating Center from the PSGRL on CDs on an every other week basis. A backup CD will be kept in the PSGRL. Each CD will contain data from only one site. The Coordinating Center will make back-up CDs of the data received from the PSG Reading Laboratory. None of the information available to the PSGRL will be identifiable with a participant's name. All data files and reports are coded based on the participant's 15-digit ID number. The first nine digits are the Look AHEAD ID which includes site designation the tenth through fifteenth digits are the date of the data collection.

13. Medical Alert Generation – see Sections 20 and 21 of Policies and Procedures for Polysomnogram Recordings at Clinical Sites

14. Quality Assurance/Control of Procedures at Clinical Sites and PSG Reading Laboratory

Quality control measures, implemented at several levels, will assure that all centers and personnel meet and maintain comparable and high levels of technical performance. The following quality assurance/control measures cover activities at the Clinical Sites as well as the PSGRL.

Quality control of sleep studies will occur:

1. By assuring that study personnel meet certification criteria
2. By clear documentation of home hook-up procedures and their review (by an individual uninvolved in the hook-up, e.g., the Study Coordinator) soon after each study (based on Sleep Data Retrieval Form).
3. By review of each study prior to its transfer to the PSGRL, with early identification of problems with equipment or sensor placement (based on Signal Verification Form; Section 6.9.2). A Sleep Study Resource will be identified for each Field Center who will be charged with the responsibility of ascertaining the sleep studies meet QA standards and who will provide “troubleshooting” support. The Clinical Site Study Coordinator will fill this role provided that he/she is a certified PSG technologist and has been certified for PSG set-ups in the Sleep AHEAD study. Otherwise, each individual site will be responsible for identifying this individual.
4. By review of all studies at the PSGRL, with grading of the quality of each signal, and overall study interpretability (based on Sleep Data Quality Assessment).
5. By ongoing review of participant reports regarding the quality of interactions with study personnel and overall comfort ratings for sleep studies and hook-ups (based on Morning Survey).

The Coordinating Center will process all data collected as above. Monthly reports (specific to Clinical Site and technician) will be distributed to all PIs.

<u>Quality Assurance Tracking Measures</u>	
<i>Parameter</i>	<i>Source of Information</i>
<u>Tracking Measures for Clinical Sites</u>	
Number of studies performed/site	PSGRL Receipt Form
Number of failed studies identified at site/site	Sleep Data Retrieval Form
Number of failed studies identified at PSGRL/site	PSGRL Receipt Form
Number of repeat studies/site	Sleep Data Retrieval Form
Breakdown of reasons for failure	Sleep Data Retrieval Form
Number of awake Immediate Medical Alerts/site	PSGRL Receipt Form
Number of awake Urgent Medical Alerts/site	Medical Alert Form
Number of studies performed by a particular tech	Medical Alert Form
Time in days from PSG recording to Receipt at PSGRL	Signal Verification Form
Mean impedance values/site	PSGRL Receipt Form
Grades for quality of each channel/site	Signal Verification Form
Overall grade for study quality/site	Sleep Data QA Form
Duration of each home visit	Sleep Data QA Form
	Morning Survey and Signal Verification Form

Tracking Measures for PSGRL

Time in days from PSG receipt and report generation	PSGRL QA Form
Number of Urgent Medical Alerts from PSG results/site	PSGRL QA Form
Intra-scorer comparisons on randomly recycled studies	PSG database
Inter-scorer comparisons on first 20 studies	PSG database
Mean RDI	PSG database
Mean RDI/site	PSG database
Percentage of sleep stages/site(Stg 1, 2, 3-4 NREM, REM)	PSG database
Mean arousal index	PSG database
Mean arousal index/site	PSG database

Local Quality Assurance

A Sleep Study Resource will be identified who will:

1. Review the first 5 “practice” studies and first 10 “cohort” studies performed by each technician performing home studies. If more than 2 of these 10 studies have problems determined to be related to sensor placement, additional batches of 10 (successive) studies will be reviewed until 80% (should it be more?) of records are determined to be technically adequate (define).
2. Be available to reinforce the technical skills of any new personnel or any personnel identified by the Reading Center as exceeding the minimum standards for study acceptability.
3. Be available for ongoing review and trouble-shooting of technically problematic record (“flat lines,” “increase artifact,” etc.).

Tracking of sleep study results by the Chief Polysomnographic Technologist: The Chief PSG Technologist will be responsible for filling out the Sleep Data-Quality Assessment Forms (see below). Prior to sending any scored record to the Data Coordinating Center, the data will be reviewed for outliers and extreme values (see above). In addition, the Chief PSG Technologist will be responsible for the PSGRL’s review of the quality of data collection at the Clinical Sites. All studies will be reviewed at the PSGRL and assigned quality codes, grading overall study quality and quality of each signal. Signal and study quality codes specific to each technician, each monitor, and each site will be summarized and reported on a monthly basis. Sites and individual technicians will be required to produce at least 85% of studies with a grade of “good” or better as assessed on the Sleep Data Quality Assurance Form. Those who do not reach this standard will be identified. Downward trending of quality or deviation of specific technicians will require a written response from the PI from that respective Clinical Site specifying how the problem will be corrected.

Quality assurance meetings in the PSG Reading Laboratory: The weekly meetings will be attended by the medical director of the PSG Reading Laboratory, the Chief Technologist, the PSG scorer. Dr. Allan Pack, and Dr. Richard Schwab will attend every other week. Every other week, each scorer will score the same 50 epochs from selected studies. Most studies for quality assurance (QA) scoring will be chosen randomly; however, scorers will also identify problematic studies that may show useful training/teaching points during QA exercises. Scoring of such designated studies will be

recorded on an epoch-by-epoch basis. Differences in any epoch or event assignment between scorers will be discussed during the weekly QA meeting. When a group consensus cannot be reached, the epoch or event will be designated "indeterminate". Data will be entered into a database and summarized quarterly for internal QA tracking.

On the weeks when no QA study is scored, 1 hr of paired scoring (one scorer scoring, one watching) will be done. Noted differences will be discussed during the QA meeting. The entire PSGRL staff will review studies that pose difficulties in scoring or present interesting problems during weekly meetings. Minutes from these meetings and printed copies of problem epochs will be maintained.

Repeat analysis of PSG studies: Every month, one randomly selected, previously read polysomnogram from each Clinical Site will be assigned a new "dummy" identification number by the Data Coordinating Center and forwarded back to the PSGRL for repeat analysis. Studies will be integrated into the normal workflow to minimize their likelihood of being identified as a special study. Studies will be also forwarded to the same scorer at defined time periods to define intra-reader reliability. The Data Coordinating Center will determine intra-scorer differences in the summary data for RDI, sleep stages, and arousal indices. The Data Coordinating Center will monitor intra-scorer reliability to determine the threshold (10% level of agreement on RDI and sleep stages, 15% level of agreement on scoring of arousals)for requiring remediation, including retraining or removing a reader. The Director of the PSGRL will review random records, interview scorers and review tracking procedures, to ensure the accuracy and completeness of all scoring procedures.

Tracking of results from scorers and sites by Data Coordinating Center: The overall means for RDI, sleep stage percentage, and arousal indexes will be calculated by the Data Coordinating Center for each scorer over discrete time periods (monthly to quarterly) and reported to the PSGRL. Intra-scorer variation will be examined. The means of the same values will be calculated for each Clinical Site over the same time periods. The PSGRL staff will review these statistics and identify any explanations for differences. If differences can not be explained by real differences in the studies assigned to any given scorer in any given time period, the scorers will score together, concentrating on the areas where differences were noted. Differences detected in scoring will be discussed at weekly QA meetings.

15. Sleep Data - Quality Assessment Form

The Sleep Data - Quality Assessment Form is completed by the PSGRL for each PSG study processed. It grades the quality of each channel (based on the duration of each signal with sufficient amplitude and free of artifact) and overall grade for study interpretability. In addition, medical alerts are checked and the preliminary RDI (respiratory distress index) is recorded.

General Coding Instructions for Sleep Data - Quality Assessment Form

Each box must be completed. If a piece of data is missing, the field should be left blank. It will be assumed that quality assessment was not or could not be done.

Question-by-Question Coding Specifications

Complete the following identification data:

Participant ID: a 9-digit field (use participant's Look AHEAD ID)
Date of Study (use month, day, year format; each a 2-digit field)
File ID: a 15-digit field (automatically entered from above two fields)
1st Tech ID: initials of technician applying sensors for PSG
2nd Tech ID: initials of technician filling out questionnaire form
Assessment time: Baseline, 1-year, 2-year
Arrival time: Time entering home to set up PSG
Departure time: Time leaving home following set-up

Section-Specific Instructions

1. Is this a repeat study?

Coding: Permissible codes: No (0) or YES (1).

2. What is the RDI (event/hr)?

Coding: up to a 3-digit field (0-999)

3. What is the total sleep time (minutes)?

Coding: up to a 3-digit field (0-999)

4. What is the total recording time (minutes)?

Coding: up to a 3-digit field (0-999)

5. Lights: Mark the box indicating whether lights were calibrated appropriately

Coding: Permissible codes: No (0) or YES (1).

6. Medical Alerts

As the study is reviewed the following medical alerts should be checked for.

Heart Rate > 140 for at least 2 minutes.

Heart Rate < 40 bpm for ≥ 2 minutes

Oxygen saturation < 80% for > 10% total sleep time (TST)

RDI ≥ 50 events/hr

Evidence of seizure activity on EEG

Evidence of ventricular tachycardia or high grade AV block (type 2 or 3) for at least 10 consecutive beats

Coding: Permissible codes: 0 (=NO) 1 (=YES) 2 (=N/A)

A "YES" response on any one of the above indicates a medical alert occurred, NO indicates a medical alert did not occur, and N/A indicates that there is insufficient data to determine medical alerts (i.e., heart rate, oxygen saturation, or RDI).

7. Date Entered: Complete with the date the data were entered, in month, day, year format; each a 2-digit field.

8. Quality Assessment of Channels

The following signals will be recorded: EEG (C3A2), EEG (C4A1), R-EOG, L-EOG, Submental EMG, Rib cage movement, Abdominal movement, nasal pressure, oxygen saturation, body position, ECG.

For each channel score the following:

- Hours of scorable signal: 00-18 (2-digit field)
- Quality Code: A single-digit value. Select appropriate code based on the hours of signal mostly free from artifact, and enter the corresponding numeric value:
≥6 hours = 4; ≥ 4 but less than 6 = 3; ≥2 but less than 4 = 2; <2 = 1.

9. Overall Study Quality

Coding: Permissible codes: 1-7, where 1=G=Unsatisfactory to 7=A=Outstanding.

7 – Outstanding. All channels good for > 5 hours and entire sleep time

6 – Excellent. At least one EEG channel, one EOG channel, EMG, oximetry, all respiratory channels usable for > 5 hours and > 75% of the sleep time.

5 - Very good. At least one EEG channel, oximetry, airflow and either chest or abdomen usable for > 5 hours and > 50% of the sleep time.

4 - Good. At least one respiratory channel (airflow or either band), oximetry and one EEG usable for > 5 hours and > 50% of the sleep time

3 – Fair. At least one respiratory channel, oximetry and one EEG usable for > 4 hours or study scored sleep-wake only (because of the EEG artifact).

2 – Poor. Respiratory channels (airflow and bands), oximetry signals, or EEG channels contain less than 4 hours of data, but interpretable data on any other channel.

1 – Unsatisfactory. No usable data. Less than 2 hours on all channels

16. Guidelines for Scoring Problem Studies

A scoring form will be developed that will allow the scorer to document any problems encountered during the PSG analysis.

Excessive noise on EEG channels: When the level of the noise is such that the scorer feels that > 2 hours of the record will include unreliable staging and arousal data, then the entire study will be scored "sleep - wake" only. As such, the entire portion of the sleep time is marked as a Stage 2 and no arousals are scored. Also when the level of the artifact makes arousal detection impossible, regardless of the ability to score sleep stages, the sleep study will be scored "sleep - wake" only. Any study scored "sleep - wake" only will be given grade Fair regardless of the hours of scorable signal. Note: studies with identified alpha intrusion will be fully scored and notations made that arousal

scoring is unreliable.

Respiratory artifact on EEG: When the level of the artifact makes distinction between Stage 2 and Stage 3 unreliable, but allows scoring of arousals, the study will be fully scored and notations made that the study was "scored wake, Non-REM, REM only".

EMG signal missing or bad during the entire study or during Stage REM portion of the study: The study will be fully scored. Rules for scoring stage REM and arousals in stage REM when EMG is bad or missing are in Section 17. Note: Sometimes problems with atonia during Stage REM are present. Prolonged bursts of elevated EMG often are observed during eye movements. Rules for scoring stage REM in such cases are found in Section 17. Problems in detecting arousals in REM, distinguishing NREM and REM sleep will be noted on a scoring form.

Both EOG signals missing: Distinction of REM from NREM sleep is impossible. Study will be scored sleep - wake only.

Airflow signal bad or missing: All respiratory events will be marked as a hypopnea (none as apnea). The one exception is when both inductance channels (thoracic and abdomen) are flat for > 10 s. Then the event will be marked as a central apnea.

Thoracic or/and abdominal channel bad or missing: Events will be noted only as "obstructive" (no central designations).

Variation in signal amplitude on airflow, thoracic and abdominal channels in the different time: Scoring will be done from the channel which correlates the best with the changes in the oxygen saturation. If there are no changes in O₂ saturation, scoring will be done from the channel that shows the clearest amplitude variation.

If staging or scoring respiratory events are impossible during the beginning or end of the study, this period will be scored as Stage Wake and edited lights will be set as "On" during this period (sleep latency will be unreliable if this occurs in the beginning of the study). If periods of data loss occur in the middle of the study:

- On the O₂ saturation signal - period will be marked as a O₂ saturation artifact
- On airflow and both inductance channels - no respiratory events will be scored during this period
- On both EEGs - period will be scored as a Stage Wake

17. Scoring Rules for Polysomnograms

Rules for assigning epoch-specific sleep score: The polygraph record is divided into consecutive segments of equal size (30 s., each termed an "epoch"). This epoch duration is maintained for the duration of the recording. Portions of two epochs may not be combined to create a new epoch. Each epoch has assigned a single score. The score is the same as the sleep stage present in an epoch. When more than one stage is present in an epoch, the score is the same as a stage occupying the greatest portion of the epoch. When two stages of sleep are evenly distributed on the epoch, epoch will be scored as a preceding stage.

Sleep onset: Sleep onset on the polysomnograms is defined by three consecutive epochs of stage 1 or one epoch of any other sleep stage.

EEG arousal: Scoring arousals is based on "A Preliminary Report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association" Sleep, vol. 15, 1992 (11). By definition, an EEG arousal is an abrupt shift in EEG frequency, which may include alpha, theta waves and/or frequencies greater than 16 Hz, but not sleep spindles, lasting at least 3 sec after at least 10 continuous seconds of sleep. Artifacts, K complexes and delta waves are included in meeting the 3 sec duration criteria only when they occur within the EEG frequency shift (change in frequency must be visible before them). Parts of the EEG totally obscured by the EMG are considered arousal if they last more than 3 sec. Alpha activity of less than 3 sec duration in NREM sleep at a rate greater than one burst per 10 sec is not scored as an EEG arousal. Three seconds of alpha sleep is not scored as an arousal unless a 10 sec episode of alpha free sleep precedes this. The scoring of EEG arousals is independent from the scoring of sleep stages, i.e., an arousal can be scored in an epoch of recording, which would be classified as wake by Rechtschaffen and Kales criteria (10). An arousal can proceed to the wake stage (by Rechtschaffen and Kales criteria) or can be followed by a return to sleep.

In stage REM, EEG frequency shift must be accompanied by a simultaneous increase in amplitude of the chin EMG (lasting over 0.5 sec). An arousal starts when a definite change in background EEG is visualized. The increase in the chin EMG can occur anytime during the arousal (can be at the end) and is not a marker for the beginning of the arousal. A long period of alpha activity before EMG change is considered an arousal if it represents a change in the background pattern.

Rules for assigning score when arousal is present in the epoch: The following rules were established to maximize the amount of sleep and thus the number of respiratory events:

Brief arousals (e.g. arousals < 15s long) do not change sleep stage and the epoch is scored according to sleep stage on the remaining parts of the epoch. If an arousal or an area of increased EMG causing artifact in the EEG channels is followed by stage Wake, then the arousal is considered part of the record scored as a stage Wake. If this part is > 15 sec long, then the epoch is scored as a stage Wake. In cases where frequent, repetitive respiratory events associated with arousals occur, the duration of each arousal may be shortened to minimize the time in the epoch that is scored as Stage Wake (i.e., to enable the epoch to be considered a sleep epoch, and thus allow the respiratory events in this epoch contribute to the overall RDI). It is recognized that this approach may falsely lower the duration of arousals in such study and may increase the amount of sleep time. This procedure avoids reporting falsely low RDI values.

In unequivocal stage 3-4 NREM sleep, when fast frequency waves are riding on the top of the delta waves, and there are no frequencies characteristic of Stage Wake, an arousal is not scored if there is any reason to suspect that the fast frequencies are result of artifact (e.g. suddenly increasing EMG bleeding into EEG). When the fast frequencies are not the result of artifact, an arousal is scored. Stage 3-4 NREM is scored when delta waves persist despite the faster frequencies riding on top, independent of the length of the arousal.

Note for Stage 3-4 NREM Sleep: When an arousal includes bursts of delta waves, these waves are

not used for meeting Stage 3-4 NREM sleep criteria (e.g. Stage 3-4 NREM sleep is scored only if there is > 20 % of the epoch covered by delta waves outside of the arousal).

Episodic events in sleep:

Sleep spindles: clearly visible, rhythmic bursts of activity 12-14 Hz, duration at least 0.5 s. (one should be able to count 6 or 7 distinctive waves within a half-second period). Sleep spindle activity occurs in adults with a frequency of about three to eight bursts per minute. Spindle rate appears to be a fairly stable individual characteristic. In older persons, sleep spindles tend to lose their classic morphology and have a slightly slower frequency, lower amplitude, and shorter duration.

K-complex: EEG wave forms having a well-outlined negative sharp wave, immediately followed by a positive component. Total duration of the K complex should exceed 0.5 s. Waves of 12-14 Hz (sleep spindles) may or may not constitute part of K complex. K complexes can occur as a response to sudden stimuli. K complexes may be reflected on the EOG channels. When in doubt about whether a particular polyphasic wave is a "true" K complex, record is scanned for clear Stage II sleep. Questionable K complexes are only designated as K complexes if their morphology closely matches those seen in unequivocal Stage II sleep. Also the EOG channel is checked, as the K complex is often reflected there.

Hypersynchrony: bursts of high voltage delta (< 4 Hz) or theta (4 - 7 Hz) waves lasting 2-3 s. (in children 20-30s). Hypersynchrony is not considered an arousal. May need to be distinguished from epileptic activity.

SERDA (Subclinical Epileptiform Rhythmic Discharges of Adults) is a normal variant, rhythm in theta range (5 - 7 Hz), seen in light sleep, and usually in older adults. It is temporal and in our montage cannot be distinguished from normal drowsy rhythms (5 - 7 Hz in frontal-central region).

Seizures: This is manifest by an abrupt change in background EEG. Two patterns are commonly seen: 1) High voltage, rhythmic activity in the 2-6 Hz range, or 2) Diffuse sustained beta activity. A seizure is often accompanied by prominent muscle artifact. A seizure is usually followed by low to moderate voltage irregular slowing. On the 10 second screen, characteristic "spike and wave" pattern may be seen. Once a pattern identifying possible seizure is identified, a physician investigator will be immediately asked to review the study.

Rules for assigning sleep stages: EEG waves frequencies are divided into following ranges:

- beta > 13 Hz
- alpha between 8-13 Hz
- theta between 4-7 Hz
- delta < 2 Hz
- spindle between 12-14 Hz

Alpha wave is any wave that has frequency in alpha range. Alpha rhythm (also known as posterior

rhythm, background) has the following characteristics:

1. Is seen in the relaxed waking state with the eyes closed.
2. Attenuates with eyes open, anxiety or mental activity such as mental calculations
3. Slows then disappears in sleep. The slowing may be so brief as to be unnoticed.

The alpha rhythm is usually in the alpha range, but can be outside that range in a variety of normal (i.e. children) or abnormal conditions.

Stage Wake: Stage Wake, when eyes are open is defined by the low voltage, mixed frequency EEG in the alpha and beta ranges. When eyes are closed, wake is defined by the presence of the alpha rhythm. There is usually (but not necessarily), a relatively high tonic EMG. Waking shows frequent eye movements and eye blinks. Some subjects may have virtually continuous alpha activity, others may show little or no alpha activity in the waking record.

Stage 1 sleep: Stage 1 sleep occurs most often in transition from wakefulness to other sleep stages. Stage 1 is defined by a background of relatively low voltage, mixed frequency EEG activity with noticeable activity in the 2-7 Hz range. Faster frequencies are mostly lower voltage (amplitude) this activity. High voltage (50-75 m V) 2-7 Hz activity tends to occur in irregularly spaced bursts mostly during the later portions of the stage. There are slow eye movements, each of several seconds duration, usually most prominent during early portions of the stage. No rapid eye movements or blinks are present. During the latter portion of the stage, vertex sharp waves, occasionally as high as 200 mV, are often seen in conjunction with high amplitude 2-7 Hz activity. The amount of alpha activity combined with low voltage activity comprises less than half of the epoch. Finally, the tonic EMG level may be lower than observed during relaxed wakefulness. There cannot be any clearly defined K complexes or sleep spindles. Traces of low voltage activity at 12-14 Hz may begin to appear as the transition to Stage 2 approaches, but this activity is not defined as a sleep spindles until the rhythmic bursts are clearly visible for at least 0.5 sec.

Stage 2 sleep: Stage 2 is defined by a background similar to Stage 1 sleep with the presence of K complexes and/or sleep spindles. It is impossible to define the difference between Stage 1 and Stage 2 sleep on the basis of background activity alone. Bursts of other polymorphic high voltage slow waves that do not have the precise morphology of a K complex are also frequently seen. Delta waves: high amplitude (> 75 m V), slow (< 2 Hz - duration 0.5 s. and longer) activity are occupying no more than 19% of the epoch. At the beginning of the Stage 2, slow eye movements may infrequently, and only briefly, persist after the appearance of sleep spindles and K complexes. Relatively long periods may intervene between K complexes and/or sleep spindles without a background change in the EEG. Regardless of the presence of an arousal, if there is no more than 3 minutes of the low voltage, mixed frequency EEG between sleep spindles and/or K complexes, this portion of the record is scored Stage 2. Otherwise this portion of the record is scored Stage 1.

Stage 3 and 4 NREM sleep: No attempt is made to distinguish Stage 3 from Stage 4 which are combined into a single category. Stage 3-4 NREM sleep is scored when 20% or more of the epoch consists of delta waves which are < 2 Hz (duration 0.5 s. and longer) and have an amplitude greater than 75 μ V (difference between the most negative and the most positive points of wave). The 20% refers specifically to the time occupied by the high amplitude, slow waves, and does not include intervening waves of higher frequency and lower amplitude. In practice to fulfill criteria for Delta Sleep one should be able to find at least 5-6 high voltage delta waves in the epoch.

Sleep spindles and K complexes may or may not be present in Stage 3-4 NREM sleep. Eye movements do not occur in Stage 3-4 NREM sleep, although the EOG will register the high voltage slow wave activity. The EMG is tonally active, although the tracing may achieve very low levels, indistinguishable from that of REM sleep. An attempt should be made to distinguish between spontaneous K complexes and delta waves, although this distinction is not always easy. When a K complex distinction is in doubt, the complex in question should be made with the K complex in unambiguous Stage II.

Stage REM sleep: Stage REM is defined by a background of relatively low voltage, mixed frequency EEG with accompanying episodes of REMs (Rapid Eye Movements). The EEG pattern resembles Stage 1, except that vertex sharp waves are not readily noticeable. Bursts of characteristic of Stage REM "sawtooth" waves may appear. Alpha activity is usually more prominent than in Stage 1 and its frequency is 1-2 Hz slower than the alpha rhythm in wakefulness. No sleep spindles and K complexes are present. The EMG reaches its lowest levels (it can not be higher than the level during the preceding stage). Periods of the relatively low voltage, mixed frequency EEG and EMG at Stage REM level but without eye movements may follow unambiguous stage REM. This period is scored as a Stage REM. Earlier Stage REM episodes contain fewer REMs than later episodes.

Start of Stage REM: At the start of Stage REM, K complexes, sleep spindles and delta waves end, characteristic sawtooth waves can appear, and the EMG drops to the level seen after eye movements begin. The fall in EMG may not coincide with the EEG changes. If the EMG drops before last the sleep spindle, K complex or delta wave, Stage REM is scored from the last sleep spindle, K complex or delta wave. Otherwise, Stage REM is scored from the point where EMG drops. The period of the record before the EMG drop is scored according to the rules for NREM sleep. When one epoch or more of Stage Wake changes into low voltage, mixed EEG before REMs or sawtooth waves starts, Stage 1 is scored until the EMG drops to REM level and Stage REM afterwards.

Periods of elevated EMG during Stage REM sleep: When EMG is elevated above REM level, then this portion of the record is scored as a NREM sleep.

When Stage Wake (> 15sec) interrupts Stage REM (i.e., REM, WAKE, REM): If the EEG background of the epochs between the intervening waking epoch and the appearance of REMs (eye movements) is ambiguous (i.e. the EEG background is compatible with either REM or Non-REM sleep), then score as Stage 1 if the EMG is elevated. Score as Stage REM when EMG is at the Stage REM level. However, if a sleep spindle or K-complex appears prior to the appearance of REMs, then the waking epochs are considered the end of the Stage REM.

End of Stage REM: Stage REM is scored until a clear evidence of sleep stage change is visualized: transition to stage Wake or resumption of K complexes or sleep spindles without presence of eye movements or sawtooth waves between them. If sleep spindles are seen in stage REM, then spindle activity in NREM sleep should be reviewed.

Note: Presence of sleep spindles in stage REM should be treated with caution. Benzodiazepine or barbiturate ingestion may induce excessive beta activity in both REM and NREM sleep. This beta activity can mimic sleep spindles. Their frequencies often are faster than those seen with the true sleep spindles. Medication effects can persist for an unknown period of the time after ingestion.

Indicators of Medication Effects:

- Excessive beta range activity (> 15 Hz, often spindle-like) in well-defined REM sleep
- Excessively long spindles (spindles longer than one sec)
- More than 5 spindles per epoch seen throughout the record
- Excessive activity in the beta range seen in the record, especially during wakefulness

None of these rules are absolute indicators of drug induced activity. Drug induced activity is more likely to have one or more of these characteristics.

When K complexes or unquestionable sleep spindles are seen in the Stage REM: When K complexes or unquestionable sleep spindles are present in stage REM, then an interval between two K complexes or sleep spindles is scored as Stage II only if there are no REMs (eye movements) or saw tooth waves in this interval and it is less than 3 min long. Otherwise the interval is scored as Stage REM. Note: Sleep deprivation may increase the occurrence of sleep spindles in Stage REM.

General guidelines for scoring Stage REM when there are problems with REM related atonia: Identification of the Stage REM is difficult when there are prolonged bursts of elevated EMG seen during eye movements. The portion of the record with unquestionable Stage REM should be reviewed to provide a visual reference of the characteristic Stage REM pattern. Stage REM is scored when EEG pattern changes to the pattern characteristic for Stage REM regardless of the level of the EMG. Distinguishing between Stage 1 and Stage REM is unreliable and noted as such on the PSG scoring notes form.

Scoring Stage REM when EMG is difficult to interpret: When EEG during Stage REM is clearly different from EEG during Stage Wake then Stage REM is scored from the last K complex, sleep spindle or delta wave.

Scoring Respiratory Events:

Obstructive apnea/hypopnea event will defined as an event of 10 seconds or longer with either of the following: 1) a > 50% decrease from baseline in the amplitude of a valid measure of breathing during sleep, or 2) a clear amplitude reduction of a validated measure of breathing during sleep that does not reach the former criterion but is associated with either an oxygen desaturation of > 3% or an arousal (3). Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the 3 largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern). Apneas will be called “central” when there is no associated chest wall movement. A mixed apnea will be scored as being “obstructive”.

The Compumedics system provides automated scoring of respiratory events according to these rules. However, such scoring is thoroughly reviewed and edited as appropriate by a trained technologist. RDI will be calculated for the entire sleep time and for different body positions separately (supine, lateral position). O₂ saturation will be plotted across time of night. These data will be used to plot the cumulative time at different levels of O₂ saturation, as described by Slutsky and Strohl (12). From this plot we will extract the following variables: mean O₂ across the night, O₂ nadir, and % of

time with O₂ saturation less than 90%.

Duration criteria: The beginning of an apnea/hypopnea is marked at the end of the last "normal" breath; the end as at the beginning of the first normal or breaking breath.

Redline et al. (13) recently used 10 different definitions of apneas and hypopneas to determine the RDIs on overnight unattended 12-channel polysomnography in 5,046 participants in the Sleep Heart Health Study. The magnitude of the median RDI varied 10-fold using the different criteria. While currently recommended techniques will be used in the proposed study to analyze the polysomnograms (3), we recognize that variability in respiratory event identification can lead to large differences in RDI, a measure that will be used to determine the presence or absence of disease and assess its severity (14). It is currently not known which RDI derivation(s) best predicts different health outcomes associated with OSA. Therefore, in addition to the analysis of respiratory events detailed above, analyses will also be performed using a variety of different RDI derivations: respiratory events with or without associated oxygen desaturation and with or without associated arousal. Cut-offs for oxygen desaturation of $\leq 2, 3, 4,$ or 5% will be assessed.

Dealing with ambiguous respiratory events: If changes in amplitude are $< 50\%$, but a > 10 sec period of a clearly discernible reduction in the amplitude of respiratory signals from baseline is observed, then score events when they occur as part of a series of events (that do meet the 50% reduction criteria) or if they are associated with an arousal or oxygen desaturation of at least 3%.

Apneas/hypopneas following large breaths or movements are not scored, unless they are part of the cycle (there are other respiratory events before and following). Such isolated events may be "sighs" or artifact. When such an event is noted after a movement/large breath and appears to "trigger" a series of events, first respiratory event is not scored (unless apneas/hypopneas were scored before the movement/large breath).

Determining whether to score one long event or two short events (i.e., after an initial decrease in amplitude of a breathing signal, there is some increase, but not to baseline, and then a fall again): oxygen saturation channel is checked. If the event is punctuated by a clear decrease in oxygen saturation followed by a rise or a stabilization, and then a decrease again, two events are marked; otherwise if the event is characterized by one steady progressive fall in desaturation, than one event is scored.

Periods of hyperventilation followed by long periods of hypoventilation: If periods of hypoventilation have clearly visible beginnings and endings (i.e., are "discrete") and are associated with at least 3% desaturation, score as hypopneas regardless of their length (they can last up to a few min). (Note: This is commonly observed in REM.)

References

1. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. *Sleep* 1998; 21:759-767.
2. Sleep Heart Health Study manual. <http://140.142.220.3/SHHS/manual/>
3. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definitions and measurement techniques in clinical research. *Sleep* 1999; 22:667-89.
4. American Sleep Disorders Association Report. Practice parameters for the indications for polysomnography and related procedures. *Sleep* 1997; 20:406-422.
5. American Thoracic Society. Indications and standards for cardiopulmonary sleep studies. *Am Rev Respir Dis* 139:559-568, 1989.
6. Condos R, Norman RG, Krishnasamy I, Peduzzi N, Goldring RM, Rapoport DM. Flow limitation as a noninvasive assessment of residual upper-airway resistance during continuous positive airway pressure therapy in obstructive sleep apnea. *Am J Respir Crit Care Med* 1994; 150:475-480.
7. Hosselet JJ, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. *Am J Respir Crit Care Med* 1998; 157:1461-7.
8. Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. *Sleep* 1997; 20:1175-84.
9. Montserrat JM, Farre R, Ballester E, Felez MA, Pasto M, Navajas D. Evaluation of nasal prongs for estimating nasal flow. *Am J Respir Crit Care Med* 1997;155:211-215.
10. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring for sleep stages in human adults. Los Angeles, CA: Brain Information Service, Brain Research Institute, University of California, 1968.
11. American Sleep Disorders Association Atlas Task Force. EEG arousal: scoring rules and examples. *Sleep* 1992; 15:174-178.
12. Slutsky AS, Strohl KP. Quantification of oxygen saturation during episodic hypoxemia. *Am Rev Respir Dis* 1980; 121:893-895.
13. Redline S, Kapur V, Sanders MH, Quan SF, Gottlieb DJ, Rapoport DM, Bonekat WH, Smith PL, Kiley JP, Iber C. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am J. Respir Crit. Care Med* 2000; 161:369-374.
14. Redline S, Sanders M. Hypopnea, a floating metric: Implications for prevalence, morbidity estimates, and case finding. *Sleep* 1997; 20:1209-1217.