Portable Monitoring in the Diagnosis and Management of Obstructive Sleep Apnea

Manual of Operating Procedures

(Version 1.5, August 12, 2008)

Center for Clinical Investigation

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Appendices

1. Overview of Study

This protocol addresses the efficacy and cost effectiveness of an integrated strategy for the diagnosis and treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) utilizing a portable, home-based monitoring (PM) device. The home-based portable monitoring strategy will be compared to the standard of care strategy that uses sleep laboratory- based polysomnography (PSG) studies.

1.1 Background

The role of PM in the management of patients with OSA remains uncertain. A recent tri-society task force comprised of representatives of the American Academy of Sleep Medicine (AASM), American Thoracic Society (ATS), and American College of Chest Physicians (ACCP) performed a systematic evidence based review of studies comparing portable monitoring with attended polysomnography as a gold standard.[Flemons, 2003 #4] A PM guideline statement that was approved by the tri-societies recommended only the use of type 3 devices (devices which use four or more cardiopulmonary bioparameters) in the attended (laboratory) setting. [Chesson, 2003 #5; 2004 #6] Of note, a number of limitations of attended type 3 device studies were also cited. The guideline statement and review both highlighted a number of shortcomings of the existing evidence and made recommendations concerning future studies. However, a simple comparison of apnea and hypopnea values may not be the only way to evaluate the potential usefulness of PM devices.

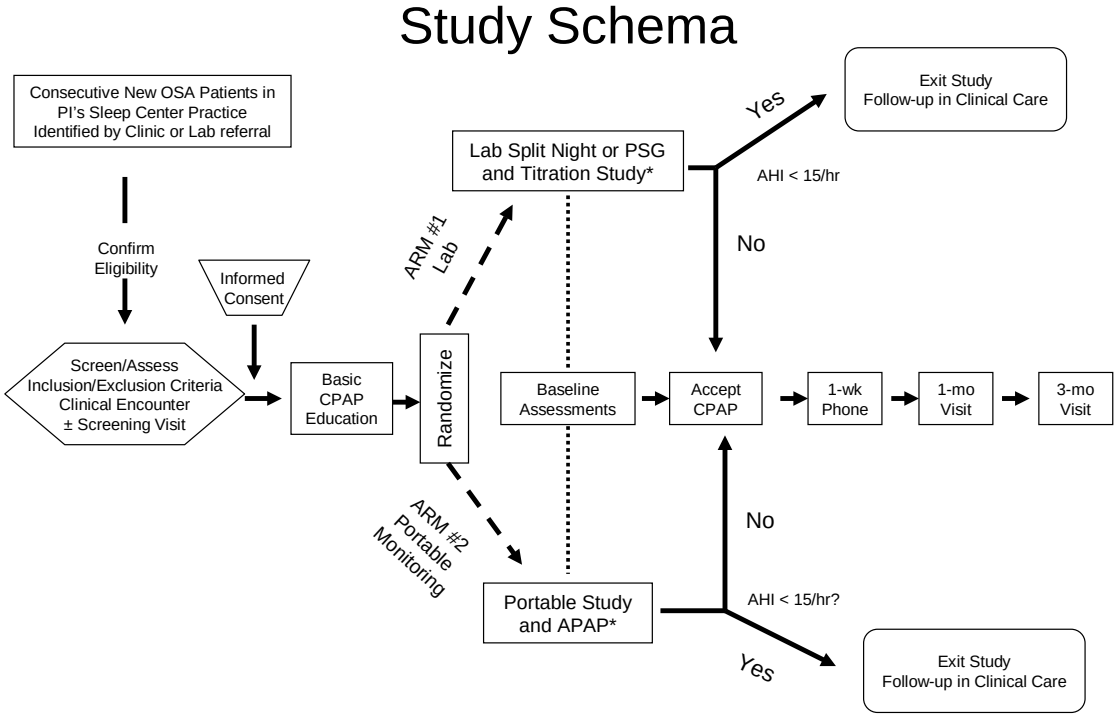
The true impact of the devices on patient outcomes will certainly depend on the patient population evaluated as well as the global algorithm used for diagnosis and treatment. For example, portable testing of clinic populations with suspected sleep apnea often results in a high proportion of positive studies. If these patients then undergo an attended polysomnography positive pressure titration, then this treatment pathway may not result in cost savings or a reduction in time to effective treatment compared to a split polysomnography (combined diagnostic and positive pressure titration). In addition, the utility of any diagnostic test is influenced by the clinical criteria used to identify patients requiring study and the quality of the medical personnel that interpret the results and make treatment decisions based on the derived information. Thus, the utility of the portable monitoring approach will likely be as dependent on the overall algorithm for diagnosis, treatment, and follow-up of patients as the technology of a given monitoring device.

Recently a large multi-center study by Masa [Masa, 2004 #7] and coworkers found generally comparable improvements in the apnea hypopnea index (AHI) and sleepiness scores among three groups of patients randomized to CPAP treatment based on conventional CPAP titration, at home auto-titration, and an algorithm based approach for determining CPAP treatment. All of the participants in this sample had severe OSA, defined by an AHI > 30 and an Epworth Sleepiness Score of $\geq$12, and all tolerated a 20-minute daytime CPAP trial. This trial supported the efficacy of non-conventional approaches for determining optimal CPAP level. However, the generalizability of these findings to a broader spectrum of patients and the overall utility of this approach when combined with home diagnosis were not evaluated. Clinical decision-making will require that the latter be addressed as well as the cost-effectiveness and patient acceptability of each treatment mode. The HomePAP study will help identify whether a combined home diagnosis-treatment approach can be cost effective compared to traditional laboratory-based approaches for diagnosing and treating patients with OSA with CPAP. Overall, the data obtained could have critical implications for many thousands of OSA patients evaluated and treated with CPAP in the US each year.

1.2 Study In Brief

The study is a randomized, parallel group, unblinded, multicenter study that compares two approaches [home-based, portable monitoring (PM) versus attended, laboratory-based polysomnography (PSG) (Lab)] in adults at least 18 years of age with a moderate to high probability of OSA who have been referred to sleep medicine specialists at AASM-accredited sleep centers for evaluation and/or management. The study is designed to compare the utility of the two approaches (PM group vs. Lab group) for the diagnosis and management of OSA in adults.

Approximately 372 eligible adults will be randomized at screening to either the PM or Lab arm (186 per arm), undergo baseline OSA testing to confirm diagnosis and study eligibility, and then receive PAP titration studies to determine the level of pressure needed to treat their OSA. For qualifying participants, the titration study will be lab-based in the Lab group and be home-based using a commercially available portable, automatic PAP device (APAP) in the PM group. All qualifying study participants will have access to study CPAP equipment and supplies to treat their OSA. Primary outcomes (time from diagnosis to effective treatment, patient outcomes, and relative resource utilization) are determined at one and three months after starting CPAP treatment. Study participants who complete all of their study visits will keep their CPAP machine at the end of the study.

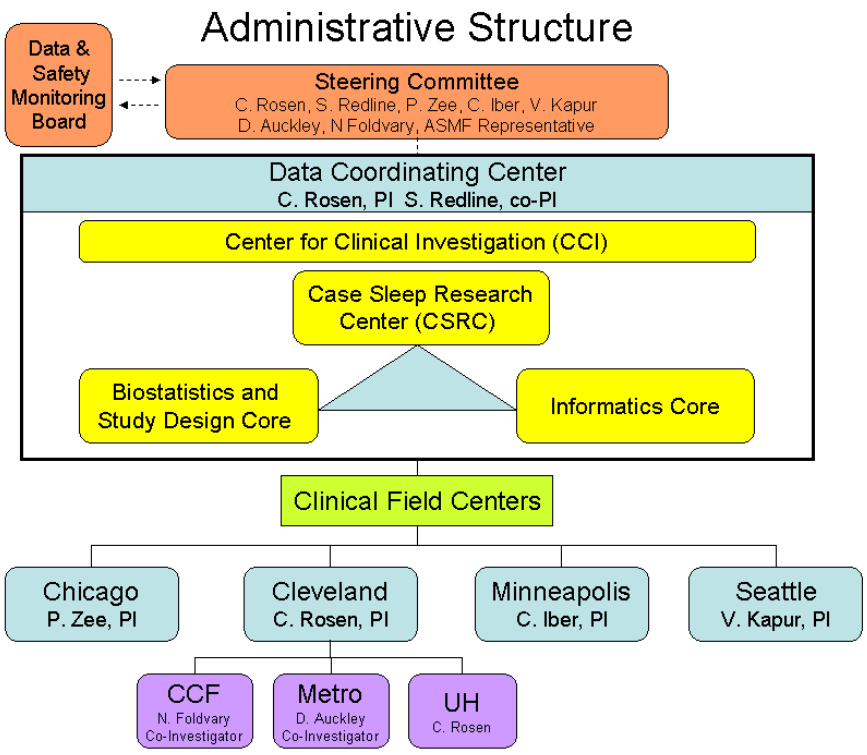


* Decisions for split, repeat or crossover studies to lab studies per protocol for negative or unacceptable studies

1.3 Time Line Overview

	2007					2008				2009		
	Aug	Sep	Oct	Nov	Dec	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 1	Quarter 2	Quarter 3
Finalize forms, database; Refine protocol; Secure IRB approval	●	●	●	●								
Conduct central training in Cleveland			●									
Enroll / study 372 participants				●	●	●	●	●	●			
Complete 1-month and 3-month follow-up visits						●	●	●	●			
Conduct Site Visits						●						
Evaluate study recruitment, population demographics, screen failures. Estimate time to meet recruitment and visit completion goals. Submit annual report.								●				
Complete data analysis and manuscript preparation. Submit final study report.										●	●	●

2.0 Study Organization



2.1 Steering Committee

The Portable Monitoring Steering Committee (PMSC) is co-chaired by Drs. Rosen and Redline and includes the PIs from each Clinical Field Center and an ASMF Board representative. The PMSC will oversee all scientific and administrative aspects of the study, establish clear lines of authority and responsibility, develop plans for quality assurance, and approve publications, presentations, and ancillary studies. The PMSC will also assemble a nationally constituted external Data Safety Monitoring Board (DSMB), independent of any participating site, which will be charged with approving the final protocol (including proposed safety monitoring), reviewing any protocol violation or adverse events, and making recommendations to the ASMF Board of Directors. The PMSC will meet at least monthly by telephone conference in year one (more frequently during Phase 1) and at least annually in person. Meeting content will include: 1) protocol review and revision, 2) participant recruitment and retention, 3) interim data, and 4) DSMB recommendations. Monthly web postings addressing study progress, meeting minutes, protocol revisions, etc., will be used to facilitate communication.

2.2 Data Coordinating Center

University Hospitals Sleep Center and its research partner, the Center for Clinical Investigation (CCI), will provide clinical oversight, manage a centralized scoring repository, serve as the Data Coordinating Center (DCC), and give biostatistical support for this study.

The CCI, located in the Case Western Reserve University School of Medicine in Cleveland, Ohio, is made up of several cores that will be involved in the coordination of this study.

2.2.1 Case Sleep Research Center

The Case Sleep Research Center (CSRC) has served as the reading center for numerous large research studies, directing the collection, processing and scoring of >15,000 full unattended polysomnograms since 1994, pioneering and setting the standards for performance and analysis of research-quality sleep studies for epidemiological purposes, and assuring quality and reliability. The CSRC will:

- Coordinate with study investigators to select the recording montage most appropriate for meeting the study goals.
- Develop a standardized protocol for PSG data acquisition, processing, scoring, and urgent alert identification.
- Provide training for technicians, research assistants and study coordinators, dedicated to sleep study acquisition, staff certification, and data transmission to the CSRC.
- Provide ongoing technical feedback to field sites relative to acquisition of sleep data.
- Monitor quality of submitted sleep studies; assign quality codes; report findings of study quality and performance to study investigators.
- Review and score sleep studies by certified scorers, following a standardized protocol.
- Monitor quality of central reading and scoring.

2.2.2 Biostatistics and Study Design Core

The Biostatistics and Study Design Core will:

- Collaborate with study investigators in finalizing study design and protocol issues.
- Develop a standardized protocol for data analysis.
- Conduct and report interim analyses, as required for data and safety monitoring.
- Conduct statistical analyses to address specific research hypotheses.
- Participate in the writing of final reports, abstracts and manuscripts.

2.2.3 Informatics Core

The Informatics Core will:

- Design, develop and implement the analytical database for all trial data.
- Develop a standardized protocol for data acquisition, processing, scoring, urgent alert identification, and analysis.
- Provide training/assistance for research staff in the conduct of the RCT and all specialized procedures
- Conduct all phases of protocol quality assurance, validation, query resolution and reporting.
- Electronically archive all scored and raw physiological data.
- Maintain a data dictionary relevant to all study variables.

2.3 Clinical Field Sites

Clinical field sites are responsible for recruitment and data collection. Six field sites have been identified for this study. Each will be

Name and Location	Abbreviation	Site ID

University Hospitals Sleep Center; Cleveland, OH	UH	1
Metro Health Medical Center; Cleveland, OH	MHMC	2
Cleveland Clinic Sleep Program; Cleveland, OH	CCF	3
Sleep Disorders Center at Northwestern University; Chicago, IL	NU	4
Minnesota Regional Sleep Disorders Center; Minneapolis, MN	UMINN	5
University of Washington Medicine Sleep Center; Seattle, WA	UWASH	6

Key field site personnel include the following: 1) an investigator who will oversee all study activities at his/her site, 2) a study coordinator who will recruit participants, schedule study visits, and demonstrate PM equipment, and 3) a liaison from the local sleep laboratory team who will ensure that standardized approaches to OSA evaluation are consistently implemented by the clinical laboratory staff.

All site personnel will be assigned a unique ID that is to be included on study paperwork and CRFs as indicated (Staff ID or Tech ID). These Staff IDs will be three digits, with the first digit identifying the site. For example, the first staff member assigned an id from Minnesota, will have id 501. Study Coordinators will be responsible for informing the DCC of new staff members and will receive their Staff ID

Each field sites will also be responsible to:

- Assist with development and finalization of the protocol.
- Achieve local IRB approval for study conduct.
- Recruit 5-6 patients per month (372 patients over a 12-month recruitment window).
- Obtain standardized data on blood pressure, anthropometry, symptoms, and quality of life.
- Provide standardized CPAP education.
- Randomize patients to usual treatment versus PM arm using web system.
- Perform PSG or PM according to protocol.
- Perform split-night CPAP, lab CPAP, or auto CPAP according to protocol.
- Complete all CRF forms and transmit to the DCC.
- Transmit PSG, autopap, PM, and compliance data electronically to the DCC.
- Complete one-week, one-month and three-month visits.
- Report all adverse events and protocol deviations according to protocol.

3.0 Overview of Study Procedures

3.1 Procedure Outline

3.1.1 Patient Referral

Screen new OSA referrals to PI's or Sleep Center's clinical practice (scheduling, intake, chart review) to identify potentially eligible patients; ascertain study eligibility; assure HIPAA requirements are met.

3.1.2 Visit 1 – Screening Visit (Timepoint 0)

If potentially eligible, confirm further eligibility criteria and complete Eligibility Form. Note: for interested, potentially eligible patients, the screening visit may occur at the end of an initial clinical patient encounter or as a separate screening visit (per patient preference).

If eligible and interested, obtain informed consent and enroll in study. Obtain randomization assignment. Provide study standard CPAP education and mask fitting. Administer self-completed tools on baseline sleepiness, functional status, and mood. Schedule baseline visit and diagnostic assessments.

3.1.3 Visit 1—Screening Visit (Timepoint 1)

Review medical history, complete measurements, and conduct interview to determine eligibility status.

3.1.4 Visit 2 – Baseline Visit (Timepoint 2)

Confirm diagnosis and final eligibility with appropriate diagnostic test according to randomized study arm.

3.1.5 Receipt of CPAP (Timepoint 3)

Finalize prescription, provide study PAP device and PAP education, and begin CPAP therapy.

3.1.6 One-week Phone Follow-up (Timepoint 4)

Clinical phone contact by study staff to assist patient with implementation of CPAP therapy, reinforce CPAP compliance and general study participation, track interval health care encounters, and monitor safety and adverse events.

3.1.7 Visit 3 – One Month Follow-up (Timepoint 5)

Clinical visit with doctor to measure study's primary and secondary outcomes, reinforce CPAP compliance and general study participation, track interval health care encounters, and monitor safety and adverse events.

3.1.8 Visit 4 – Three Month Follow-up (Timepoint 6)

Clinical visit with doctor to measure study's final primary and secondary outcomes, reinforce CPAP compliance, track interval health care encounters, and monitor safety and adverse events.

3.2 Identification of Timepoints

For clarity in reporting, each patient contact will be assigned a Timepoint code, and data collected at that timepoint will be identified with the date of collection as well as with the Timepoint code.

Visit	Time point
Visit 1 – Screen/Enroll	1
Visit 2 – Baseline	2
Receipt of CPAP	3
One-week Phone Follow-up	4
Visit 3 – One Month Follow-up	5
Visit 4 – Three Month Follow-up	6

3.3 Schedule of Measures

HomePAP SUMMARY OF FORMS & PROCEDURES

	Pretreatment Period		Treatment Period			
	Screening	Baseline	Day 0	Week 1	Month 1	Month 3
	Visit 1	Visit 2	CPAP Receipt	Phone Contact	Visit 3	Visit 4
	Timepoint 1	Timepoint 2	Timepoint 3	Timepoint 4	Timepoint 5	Timepoint 6
FORMS						
Contact Form	x					
Physical Measurements: Screening	x					
Physical Measurements: Baseline		x				
Physical Measurements: Month 1					x	
Physical Measurements: Month 3						x
Eligibility Form	x					
Informed Consent Form	x					
Sleep Habits Questionnaire: Baseline		x				
Sleep Habits Questionnaire: Month 1					x	
Sleep Habits Questionnaire: Month 3						x
(ESS) Epworth Sleepiness Scale		x			x	x
(EQ-5D) European Health Status Questionnaire		x			x	x
(SF-36) Your Health and Well-being Questionnaire		x			x	x
(FOSQ) Functional Outcomes of Sleep Questionnaire		x			x	x
(SAQLI) Calgary Sleep Apnea Quality of Life Index: Part 1		x			x	x
(SAQLI) Calgary Sleep Apnea Quality of Life Index: Part 2					x	x
Mood Questionnaire ((CESD-10) Center for Epidemiologic Studies Depression Scale)		x			x	x
Signal Evaluation Form		x				
Embletta Evaluation Form (PM Arm only)		x				
CPAP Education Form		x				
Titration Study Form		x				
Diagnostic Study Flow Form		x				
CPAP Prescription Form			x			
APAP Follow-up Phone Call Form (PM Arm ONLY) one night post APAP titration		x				
CPAP Follow-up Phone Call Form				x		
CPAP Compliance Report				x	x	x
Incoming Participant Phone Call Form	COMPLETE AS NEEDED					
Missed/Incomplete Visit Form	COMPLETE AS NEEDED					
Participant Withdrawal/Removal Form	COMPLETE AS NEEDED					
Summary Log of Internal Adverse Events Report (Excel sheet)	COMPLETE MONTHLY QUERY					
Adverse Event Case Report Form	COMPLETE AS NEEDED					
PROCEDURES						
Medical History Screen	x					
CPAP/Sleep Education		x				
Randomization		x				
Lab or PM Studies*		x				
CPAP Acceptance Review			x			
CPAP Adherence Monitoring					x	x

* Complete CPAP/Sleep Education BEFORE Lab/PM Studies.

4.0 Recruitment and Enrollment

4.1 Target Population

This study will involve participation of consenting patients, males and females, ages ≥ 18 years who have been referred to a sleep medicine specialist in an AASM-accredited sleep center from one of six study field sites. This patient group must have an intermediate to high risk of OSA and clinical sleepiness based on study criteria as described in the study protocol. A brief summary of inclusion and exclusion criteria follows.

4.1.1 Inclusion Criteria

Participants must meet ALL of the criteria below:

1. Intermediate to high probability of having OSA based on an adjusted neck circumference > 43 cm (17 inches). [Flemons, 1994 #9]

NOTE: Adjusted neck circumference = neck circumference + 3 cm (if habitual snorer (i.e., snores at least 3 nights/week)) + 4 cm (if hypertension present (i.e., on BP medications and/or SBP≥140 or DBP≥90)) + 3 cm (if apnea, gasping, choking at least 3 nights/week)

2. Presence of excessive daytime sleepiness (Epworth Sleepiness Scale ≥ 12)

4.1.2 Exclusion Criteria

Participants must NOT meet ANY of the criteria below:

- Severe chronic insomnia, circadian rhythm disorder, or other condition resulting in < 4 hours of sleep per night.
- Unstable medical conditions (e.g., new onset or changing angina, a myocardial infarction or congestive heart failure exacerbation documented within the previous 3 months, uncontrolled hypertension [SBP > 180 or DBP > 100], NYHA stage 3 or 4 heart failure; or a non-skin cancer diagnosed within the last 2 years).
- Alcohol abuse (currently drinks>5 alcoholic drinks/day).
- Untreated major psychiatric diagnoses who have 1) behaviors that would interfere with adherence to study procedures and PAP therapy or 2) active suicidal ideation
- Unable to undergo home testing due to living arrangements, distance from lab, etc.
- Concerns about unsafe driving (i.e., report of automobile accident or near-miss accident due to falling asleep behind the wheel in the last year).
- Severe COPD or restrictive lung disease (FEV1/FVC < 70% or FEV1% < 50%) or regular use of supplemental oxygen.
- Chronic narcotic use (i.e., use of narcotics for > 10 days in prior three months).
- History of cataplexy (a key finding of narcolepsy, another primary sleep disorder associated with sleepiness).
- Moderate to severe restless leg syndrome symptoms (e.g., report of irritable sensations in legs either worse in the evening or relieved with movement occurring > 3 days per week).
- Pre-existing diagnosis of sleep apnea.
- Prior experience with CPAP or bilevel PAP.
- Anticipated upper airway surgery or gastric bypass surgery in the next four months.
- Decisional impairment for consenting.
- Hypoventilation syndrome identified in the medical record.
- Waking oxygen saturation < 92%.

4.2 Recruitment Procedures

The process of subject recruitment must be reviewed and approved by each site's local IRB to help assure that privacy protections are consistent with federal HIPAA regulations.

Recruitment is limited to patients newly referred for evaluation of suspected sleep apnea or snoring. Specific approaches may vary from site to site, but in all cases procedures must ensure that 1) follow-up care is directed by a sleep specialist and 2) sufficient time for eligibility verification and informed consent discussion are provided.

4.2.1 Identifying Study Participants

The PIs and study staff at each site will identify newly referred patients who potentially meet eligibility criteria. It is noted that most practices strive to evaluate all patients referred for sleep studies at a clinic appointment prior to a scheduled PSG. However, because of access issues, some sleep centers may allow some patients to be referred directly for PSG without prior sleep clinic assessment.

The following suggestions may be helpful in developing procedures:

- Regularly review patients referred to the sleep laboratory or sleep clinic, clinic schedules, patient intake forms, electronic records and/or medical charts (according to HIPAA and institutional guidelines).
- Incorporate questions from Eligibility Checklist into all sleep center clinical records as part of routine patient care (neck circumference, Epworth score, age, BMI, medical co-morbidities)
- Approach patients during their clinic visits with consent procedures conducted at that clinic appointment or during a subsequent screening visit.
- Approach patients referred for diagnostic PSGs by telephone, scheduling a subsequent screening or clinic visit (according to the practice of that sleep center) or by telephone (using an IRB-approved telephone script) to invite participants to consider study enrollment
- Provide information about the study to sleep center patients. This can be done by the PI, PIs sleep center, referring physician colleagues, or study staff. Information materials must be IRB-approved and will include:
    - Information sheets within the sleep center's clinical practice area (see Appendix A).
    - Brochures for potentially eligible participants (see Appendix A2).
    - Information sheets to referring physicians. Some centers may provide expedited clinic appointments for patients identified by their referring physicians as potentially meeting study eligibility criteria. However, an expedited clinic visit does not require the patient to agree to participate in the research study (see Appendix A3).
- Use telephone scripts for study staff to contact patients who have indicated interest in the study (see Appendix A4).

4.3 Enrollment Procedures

4.3.1 Confirm Eligibility

All potential participants who meet initial eligibility criteria will be evaluated by completing the Eligibility Form. Note that once one exclusion criterion is identified, screening may be stopped. Data from each completed Eligibility Form is submitted to the DCC using the web entry system, regardless of the final eligibility decision or participation status. After entry using the web system, the user will receive the Screening ID that is to be transcribed onto each page of the Eligibility Form. The Eligibility Form is then also transmitted to the DCC per the procedures for CRF Transmission outlined in section 8.2.2.

Items on the Eligibility Form that are used in assessing eligibility include:

- Demographic information
- Recruitment source
- Clinical Criteria
    - Epworth Sleepiness Scale
    - Adjusted Neck Circumference
- Inclusion Criteria
- Exclusion Criteria

A final decision for eligibility is then made by the field site PI, is indicated on the form, and the form is signed and dated. Also recorded is the participant's response, whether they agree to participate in the study or not.

Eligibility criteria are confirmed by the DCC at the time of enrollment.

Note: In the event that ESS is completed more than once, be sure to document the highest ESS as the study qualifying score.

4.3.2 Informed Consent

Each field site will be responsible for obtaining informed consent from each participant prior to enrollment in the study. Informed Consent forms will have been approved by the site IRB and will minimally contain a description of the purpose of the research, description of procedures at each study visit, expected and potential risks, benefits, burden, subject rights and alternative treatments. The Informed Consent document will be reviewed with the participant according to IRB guidelines and the instructions in the protocol. In brief, study staff will review the details of the consent form verbally with the participant in a face-to-face discussion, answer any questions concerning participation in the study, and inform participants that participation is voluntary and that they have the right to withdraw from the study at any time without affecting their medical care.

After the Informed Consent form has been signed and a signed copy given to the participant, they can be formally enrolled into the study using the procedures below. The original signed Consent Form will be kept in the participant study file at the field center.

4.3.3 HIPAA Authorization

Following mandated federal Health Insurance Portability & Accountability Act (HIPAA) regulations and according to local IRB guidelines, the use and disclosure of the subject's protected health information (PHI) will be explained and participant authorization will be obtained. HIPAA Authorization forms are also to be completed, signed and dated during the consent process according to the protocol.

4.3.4 Deferral

There may be some situations or conditions in which a participant will be deferred study entry. Once it is formally ascertained that the reason for deferral is not present or has subsided according to the timeframe identified, the participant will be reconsidered for study entry. Deferred study entry can be considered for participants who:

- Are enrolled in another interventional or longitudinal study.
- Request additional time to consider other treatment options for OSA.
- Are experiencing an intercurrent, self-limited illness that would interfere with OSA diagnosis or CPAP treatment.

4.3.5 Confidentiality

Extensive efforts will be made to ensure and maintain participant confidentiality. The assignment of research IDs for submission of data and other study correspondence will allow the study database to be devoid of all participant identifiers.

When the Eligibility Form is submitted to the DCC, each potential participant will be assigned a Screening ID, which uniquely identified each potential participant without any patient identifiers. Once enrolled, participants receive a Study ID which will be used on all study data and CRF to identify the participant. At no time should the DCC receive any personal identifying information from any field site.

All communication between the DCC and field sites refers only to the Study ID (or the Screening ID in the case of patients screened but not enrolled). The DCC will not have access to any participant identifying information available at the field site.

4.3.5.1 Screening ID

The **Screening ID** is a five-digit number that is generated by the DCC database management system upon receipt of data from a new Eligibility Form. Each Screening ID begins with the one-digit Site ID followed by five numbers. Site staff are responsible for entering this Screening ID onto the Eligibility Form after receiving it from the web system.

4.3.5.2 Study ID

The **Study ID** is a four-digit number generated by the DCC database management system upon enrollment of a new participant. Each Study ID begins with the one-digit Site ID followed by three numbers. Site staff are responsible or recording this Study ID onto the Eligibility Form after enrolling a participant. Once enrolled, the Study ID is used on all CRF and other transmitted data to identify the participant.

4.3.5.3 Namecode

In order to confirm the correct Study ID appears on each form, a participant **Namecode** will be used as a secondary identifier. The Namecode is an acrostic code that is made up of the first two letters of the participant first name and the first two letters of the participant last name. This code should be recorded on the Eligibility Form at the time of completion, and on all subsequent CRF. The Namecode if not necessarily a unique identifier, and is not a personal identifier, but is used to confirm that the proper Study ID has been recorded on each CRF.

4.3.6 Enrollment and Randomization

Participants who meet all eligibility criteria and agree to participate are enrolled in the study after informed consent is obtained. Enrollment requires verification that eligibility has been met, confirmation that consent has been obtained, and then receipt of the Study ID.

Enrollment is performed by field site staff entering the Eligibility Form into the DCC web entry system, confirming eligibility and participation information, and submitting the entry. The DCC web application returns to the user the appropriate Study ID and randomization assignment.

The randomization assignment is determined by an application using the stratified block design outlined in the protocol.

In the event that the HomePAP web entry system is unavailable, field site staff are touse a manual randomization system provided by the DCC. Each site will receive 10 white envelopes containing one of two available treatment assignments. The treatment assignments are randomized and prerecorded by the DCC. If the HomePAP web entry system is unavailable for randomizing, then the field site staff are to open the first available envelope following the consecutive order of one to ten. Any unused randomization envelopes should be stored securely in the event a future randomization assignment is needed, and the web entry system is unavailable.

If an envelope is opened, then the site study staff must contact the DCC immediately by email to inform the DCC of the manual randomization assignment obtained. The email must include the following: 1) SCREENING ID, 2) SITE ID, 3) NAME CODE, 4) STAFF ID, 5) AGE, 6) ESS, and 7) ADJUSTED NECK CIRCUMFERENCE. Do NOT send any participant identifying information to the DCC.

Depending on the reason for the web entry failure, the DCC will provide the corresponding STUDY ID to the field site staff as soon as possible. All completed data collection forms must then be completed and sent to the DCC as usual. The DCC and field site will document the use of the randomization contingency plan.

Note: In order to remain in the study and continue onto PAP titration, participants must meet OSA diagnostic criteria, that is, an AHI ≥ 15 based on the findings from their diagnostic study. Participants who are randomized, but who don't meet diagnostic criteria for study participation because of an AHI < 15 will continue to be followed clinically in the sleep center as part of routine patient care.

4.4 Participant Withdrawal and End of Protocol

In the case that a participant ends participation before completing the protocol, either due to withdrawal, loss to follow-up, or administrative removal from the study, site staff complete and submit the Participant Withdrawal/Removal Form.

When reaching the end of the protocol, participants will continue to be followed as needed by the sleep center physicians. At this point, decisions are made as would occur in routine clinical care.

5.0 Specific Measurements

5.1 Blood Pressure

Blood pressure will be measured after the participant has been sitting quietly for **at least 5 minutes** following standardized guideline using a calibrated sphygmomanometer. Cuff size will be determined by measuring the circumference of the upper arm at the midpoint and identifying the appropriate bladder size from a standard chart. First peak inflation pressure is identified. The arm is raised between measurements. Measurements are repeated three times and recorded on the Measurements Form. See **Appendix B** for detailed instructions.

5.2 Anthropometry

Anthropometric measures are performed as indicated below and recorded on the Measurements Form. See **Appendix C** for detailed instructions.

5.2.1 ***Height*** is measured once to the nearest cm with the subject in stocking feet, using a wall-mounted stadiometer.

5.2.2 ***Weight*** is measured once to the nearest 0.1 kg with a calibrated scale.

5.2.3 ***Neck circumference*** is measured 3 times with a non-stretchable measuring tape to the nearest 0.5 cm. while the subject is seated with the head in the Frankfort horizontal plane, measuring below the thyroid prominence, perpendicular to the neck's vertical axis. Measurements are made three times and recorded.

5.2.4 ***Waist circumference*** is measured 3 times the nearest 0.1 cm. The measurer stands behind the subject and palpates the hip area for the right iliac crest. The measurer places a tape over this point and asks the participate to turn slowly, holding the tape in position so that the tape wraps around in a line horizontal to the floor. This assures that the tape is parallel and that the tape is snug but does not compress the skin. The measurement should be taken at the end of a normal expiration.

5.3 CPAP Education

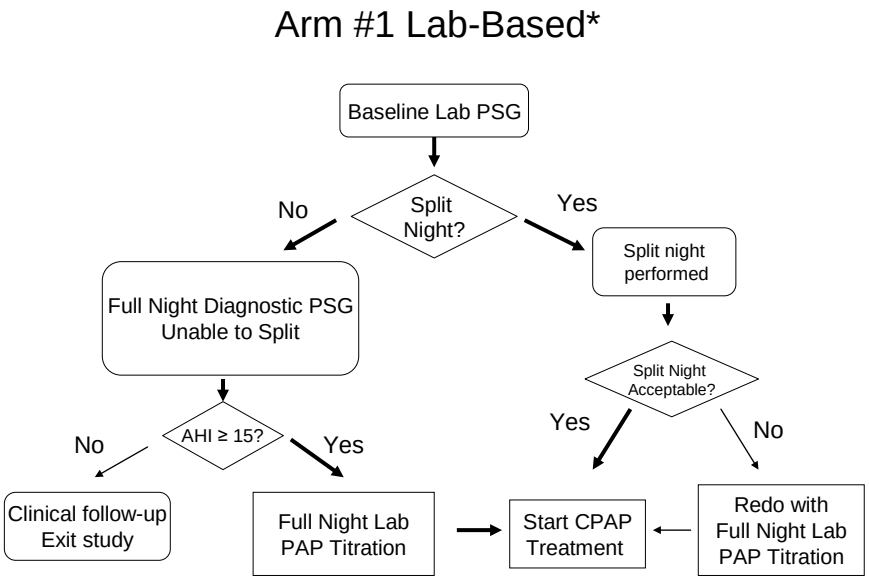
To assure standardization, all participants will receive initial education on CPAP use during the enrollment visit. All participants will receive standardized educational materials (patient care brochures about sleep and health, sleep hygiene, obstructive sleep apnea and snoring, and positive airway pressure for sleep apnea developed by the AASM) as part of general supportive care. The educational intervention targets self-efficacy and enhances cognitions related to CPAP. Study staff will present CPAP education at the enrollment visit, prior to randomization. Participants will have an opportunity to try various interfaces in order to optimize fit prior to PAP administration. The interface may be changed during the study and/or a chinstrap added at the patient's request or to address problems related to suboptimal function. Participants will be given verbal and written directions on the use of these materials at the time of the visit. At the conclusion of this session, the coordinator will ask the participant to rank his/her expectation of improving on CPAP. CPAP education will be reinforced at the time of diagnostic testing, at PAP titration (for lab arm), at APAP dispensing (for PM group), at telephone follow-up, and at scheduled clinic visits.

At the conclusion of the education session, the staff member will complete the CPAP Education form indicating the time spent, and administering to the participant one question regarding perception of benefit.

5.4 Lab Arm Diagnostic and Titration Studies

For participants randomized to the Lab arm, overnight polysomnography (PSG) is used to confirm the diagnostic criterion for participation. Lab diagnostic studies are scheduled according to bed availability and participant schedule, but should be within two weeks of randomization.

The diagnostic and titration studies for the Lab arm will be based on the following algorithm:



*Decisions for split, repeat, or cross-back studies per protocol for negative or unacceptable studies

Each field site will use a standardized approach but will use existing laboratory equipment. Data will be standardized by requiring the use of the same montage, and comparable sensors, sampling rates and filters across sites. Overnight monitoring will be accomplished by local sleep technicians who are supervised by a centrally trained sleep technician. PSG data that will be used for confirmation of eligibility criteria will be based on centrally scored PSG studies at the DCC.

5.4.1 Laboratory PSG Montage

Polysomnography will reflect new (2007) AASM standards as closely as acquisition instrument will allow. PSG will be collected using 15 EEG electrodes with face and scalp placements consistent with 2007 AASM guidelines: E1, E2, F3, F4, C3, C4, O1, O2, M1, M2, L Chin, R Chin, C Chin, patient ground and common reference. In addition, the following cardio-respiratory and other ancillary data are continuously recorded: Chest and abdominal wall motion by inductive plethysmography with a sum signal; oronasal airflow by thermal sensor or CPAP mask flow (for titration studies); nasal airflow by nasal air pressure transducer (non titration studies only); CPAP mask leak; pulse oximetry (spO2) numeric and plethysmography waveform; heart rate by ECG with a standard 3-lead precordial placement; right and left leg

movements (by EMG); position sensor and snore sound sensor. A method for assessing snoring should be included in the montage; sawtooth patterns in the unfiltered airflow or mask pressure tracings and/or detection of vibration by piezo-electric transducers or microphones applied to the neck are acceptable methods for detecting snoring. Other sensors may be included at discretion of the site but will not be mandatory. Since PSG data will be collected on acquisition instruments from various manufacturers but centralized scoring will be done from a single software scoring platform, channels must be standardized to the request of SPRC. All obligate signals must carry through to EDF conversion and import successfully.

5.4.2 Standard Sensors and Placement

Sensors, sampling rates, filter and notch settings, and peak-to-peak ranges will be standardized with respect to the limitations of various recording instruments. In brief, EEG and EOG signals are sampled at a minimum of 200 Hz, ECG and EMG (chin and leg movement) channels at 200 Hz, and respiratory signals at 32 Hz, except for nasal pressure which is collected at 128 Hz. Respiratory belts and airflow cannula are placed using standardized placements. Oximeter sensors are attached to a finger of the non-dominant hand. Scalp electrodes are attached according to the International 10-20 system as well as behind the ears at the left (M_1) and right (M_2) mastoid areas and three over the submental muscles (one in the midline 1 cm above the inferior edge of the mandible; one 2 cm below the inferior edge of the mandible and 2 cm to the right of the midline; one 2 cm below the inferior edge of the mandible and 2 cm to the left of the midline). EOG electrodes are applied 1 cm below and 1 cm lateral to the outer canthus of the left and right eye and will be referenced to an electrode at FPz. When possible, electrodes are secured using water-soluble pastes, increasing the holding power by using an adhesive enhancer and cleaning agent. Isopropyl alcohol will not be used for any phase of participant preparation or electrode placement. Sensors are placed, calibrated, and signal quality/impedance checked, recording these data on study forms (see Appendix E2). Sensor positions are modified as needed to improve signal quality, replacing electrodes if impedances > 5k ohms. Acquired PSG data are reviewed in the local sleep laboratory the morning following acquisition when a Signal Verification form is completed, and then electronically transmitted to the DCC within one day of review.

5.4.3 Lab PAP Titration

The starting pressure will be between 4-5 cm water and then will increase by 2.0 cm H_20 for obstructive apneas and/or hypopneas with desaturation and then by 1.0 cm H_20 for flow limitation or snoring. Guidelines: approximately 20 minutes to assess response to 2cwp increases and 15 minutes to assess response to 1 cwp increases. All attempts will be made to include REM supine time. Down titrations should be considered particularly if central events emerge after obstructive events resolve. If a “down” titration is implemented, it should be conducted when at least 30 min has elapsed without obstructive breathing events and the titration has included REM supine time of 15 minutes. In order to perform a split-night study, the baseline AHI in the diagnostic portion of the study must be at least 40/hr for the first two hours of the study and there must be least three hours of sleep time available for the PAP titration.

5.4.4 Acceptability of Lab PAP Titration

If the technician-attended, in-lab titration study does not meet minimum acceptability criteria *(for adequate titration), then the titration study needs to be repeated, per routine clinical practice*. Criteria for acceptable Lab titration studies are as follows:

- An **optimal** titration reduces RDI < 5 for at least 15-min duration and should include supine REM sleep at the selected pressure that is not interrupted by arousals or periodic awakening.

- A **good** titration reduces RDI < 10 or by 50% if the baseline RDI < 15 and should include supine REM sleep at the selected pressure.
- An **adequate** titration does not reduce the RDI < 10 but reduces the RDI by 75% from baseline (especially in severe OSA patients), or one in which supine REM sleep did not occur at the selected pressure or with AHI < 10/hr on optimal pressure.

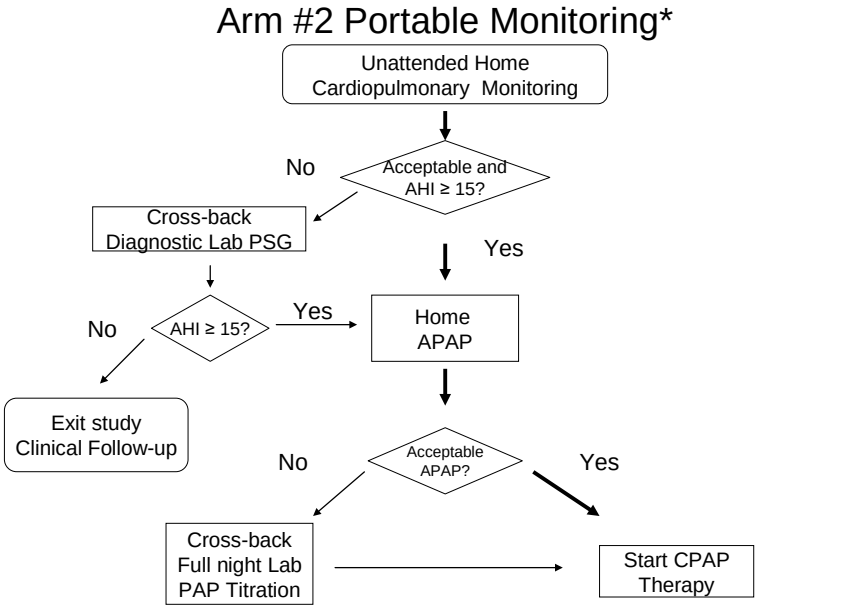
5.4.5 Lab CPAP Pressure

Pressure level is initially determined by the field center staff (technician plus sleep physician) based on the level of pressure that is both tolerated and leads to greatest resolution of airflow limitation, apneas and hypopneas without inducing central apneas. CPAP review is initially made locally, after the sleep study and after the patient is discharged from the laboratory, following routine scoring procedures of the lab, using data from a split or full night titration study.

5.5 Portable Monitoring Diagnostic and Titration Studies

For participants randomized to the Portable Monitoring (PM) arm, the diagnostic and titration study will be accomplished using the Embletta X-30 as provided by the ASMF. Ambulatory auto-titration will be accomplished using the Respironics REMstar® Auto-M Series with C-flex™ technology and heated humidity, as provided by ASMF.

The diagnostic and titration studies for the PM arm will be based on the following algorithm:



*Decisions for split, repeat, or cross-back studies per protocol for negative or unacceptable studies

5.5.1 Portable Monitoring Equipment Distribution

Study staff will provide participants with the diagnostic PM device and patient-friendly, simple-to-use instructions on its home use at the time of the screening/enrollment visit. Study staff will

be available by telephone 24/7 for troubleshooting calls related to equipment use. See Appendix D for detailed instructions on using the Embletta.

5.5.2 Portable Monitoring Equipment Return

Equipment will be promptly returned to the local field site sleep center (preferably by the following morning but maximally by 72 hours) either by the participant or by a courier, as needed. Field site staff will download and preview the PM diagnostic device for technical adequacy of recording, then the data file transferred electronically to the coordinating center for quality review and determination of diagnostic eligibility (AHI ≥ 15/hr) within one working day.

5.5.3 Acceptability of Portable Monitoring

Per study protocol, if the PM recording is technically unsatisfactory, then a second attempt at a diagnostic PM study is made. If two attempts at home APAP titration are unacceptable, then the PM participant "crosses back" for a Lab PAP titration.

If the PM recording is technically satisfactory, but the AHI is < 15 events/hr, the participant "crosses back" to a diagnostic Lab PSG. If this Lab PSG meets diagnostic criteria (AHI ≥ 15 confirmed by the DCC), then the PM participant "crosses back" to the PM arm for APAP titration per protocol.

5.5.4 Portable Monitoring Titration

If PAP eligibility is confirmed by the DCC, the participant will be scheduled to return to the local sleep center as soon as possible, and generally within two weeks, for instruction on the APAP unit, review of CPAP education, and confirmation of mask fitting.

5.5.4.1 APAP Instruction

Participants are educated about the APAP device by study staff at the sleep center in preparation for their home titration study. Study staff stays in contact with the participant by telephone during the 5-7 day APAP titration, as needed for troubleshooting. Participants complete a basic sleep log indicating what time they fell asleep and what time they awoke.

At the time of APAP instructions, the study coordinator will review CPAP education materials, measure for optimal mask fit, provide a 10-15 minute period for acclimatization and provide the patient with an opportunity to view a CPAP educational video.

5.5.4.2 APAP Distribution

The pressure is set to start automatically, after 20 minutes for adaptation (4 cm H_2O up to a maximum of 20 cm H_2O). Patients are scheduled to use the home APAP titration for each major sleep period, occurring over the subsequent 5-7 days.

5.5.4.3 APAP Clinic Follow-up

Arrangements are made with the participant to return the APAP device after 5-7 days of APAP monitoring. At that time, optimal pressure is reviewed by the study coordinator, CPAP mask or machine questions are addressed, and the APAP machine is set to deliver the fixed optimal pressure. The local polysomnologist or study coordinator will visually determine the optimal pressure from the raw data from the APAP device by analyzing the pressure that included 90% of the periods with acceptable leak, then will select a fixed pressure for the participant's CPAP management. The participant is discharged with this machine.

5.5.5 Acceptability of APAP Titration

The recording and titration period are considered to be acceptable if (1) the recording period in the APAP device averaged at least four hours/night for at least two nights; (2) excessive leak (defined on a flow sheet per pressure level) is absent; (3) machine was used for an average of ≥ four hours/night with residual AHI < 10/hr.

If the first APAP study is unacceptable, a second 5-7 day recording is performed. A titration failure is defined when neither of the two 5-7 night recordings obtained is acceptable. PM participants with a failed APAP study "cross back" to the sleep laboratory for a full-night titration study (as part of routine care) to determine a fixed PAP pressure for treatment.

5.5.6 Confirmation of Optimal Pressure by DCC

Quality control of determination of both CPAP and APAP pressures will be accomplished by electronically transmitting either the lab titration study (split or full) or the AutoPAP data. The PAP titrations will be reviewed at the DCC where an independent determination of the optimal pressure is made. Optimal level of agreement is considered to be +/-2 cm water. If greater differences are identified on more than three studies per four-week period, then discrepancies will be reviewed by local and central staff. If continued discrepancies are observed and attributed to field site departures from protocol, field site personnel will be retrained.

5.6 Diagnostic and Titration Studies Failure Procedures

5.6.1 Lab Arm

Participants with full night diagnostic Lab PSG showing an AHI < 15/hr will exit the study and will continue to receive usual clinical care

Participants with a PM diagnostic with prolonged periods of hypoxemia (< 88% for > 10 consecutive minutes) unrelated to discrete respiratory events PSG will exit the study and will continue to receive usual clinical care

If split PSG criteria are met, but the Lab CPAP titration does not meet study criteria for acceptability (see above), then a repeat full night Lab PSG CPAP titration will be offered to the participant

If a full diagnostic PSG (split criteria are not met) shows an AHI ≥ 15/hr, but the subsequent PSG titration is unacceptable, then a repeat full night Lab PSG titration will be offered to the participant

5.6.2 Portable Monitoring Arm

Participants with a PM diagnostic with prolonged periods of hypoxemia (< 88% for > 10 consecutive minutes) unrelated to discrete respiratory events PSG will exit the study and will continue to receive usual clinical care

Participants who do not meet diagnostic criteria (AHI < 15/hr) from a technically satisfactory diagnostic PM study will "cross back" to receive a diagnostic Lab PSG* and this Lab PSG will be part of usual clinical care.

If this Lab PSG shows an AHI < 15/hr, then the participant will exit the study, but will continue to receive usual clinical care

If this Lab PSG AHI ≥ 15/hr, then the participant will cross back to the PM arm for APAP titration per protocol.

5.6.3 Crossover Procedures

Participants whose first attempt for a diagnostic PM study is technically unsatisfactory will have a second attempt. When both attempts are unsatisfactory, the patient will cross back for diagnostic Lab PSG.

If the Lab PSG AHI < 15/hr, then the participant will exit the study but will continue to receive usual clinical care.

If the Lab PSG AHI is ≥ 15, then the participant will cross back to the PM arm for APAP titration per protocol.

Participants who meet diagnostic criteria based on their baseline PM study (AHI ≥ 15) will have a 5-7 night in home APAP titration with treatment per protocol

If two attempts at a home APAP titration are unacceptable, then the patient will cross back to have a Lab CPAP with treatment per protocol.

5.7 CPAP Compliance

Objective adherence to therapy as measured by compliance monitors inside the CPAP device (average daily time at pressure, percentage of days with > four hours of CPAP use). These data are downloaded using the electronic “smart” card, are viewed and reviewed with the participant, and transmitted electronically to the DCC using the methods outlined in section 8.2.3.

6.0 Follow-up Contacts

6.1 Telephone Contact

Telephone contact is part of standard of care after initiation of CPAP and is used for early troubleshooting to optimize utilization. At enrollment, study staff will identify optimal times to make phone contacts, including alternative phone numbers. In addition to troubleshooting implementation of CPAP therapy, study staff will complete the Phone Call Follow-Up Form for standardized collection of self-reported CPAP adherence, safety monitoring and other health events (e.g., new clinical encounters). The time spent at each telephone contact is documented on the corresponding CRF.

6.2 Follow-up Clinic Visits

As part of the provision of clinical care, both arms will receive equivalent follow-up with visits at month one and three after CPAP initiation with a standardized algorithm to intervene for common problems (e.g., mask leak, mask discomfort). All attempts will be made to keep the time of the clinic appointment similar across visits. One and three month visits should occur as close to the scheduled date as possible. If participant scheduling conflicts arise (e.g., long distance travel, intercurrent illness, family emergency), the visit may be scheduled as much as 5 days before the targeted date or as much as 2 weeks after. If either visit is scheduled outside of the two weeks, then it should be scheduled for as soon as possible and not later than 4 months from the start of CPAP. If the last visit cannot be completed by four months, a phone termination visit will be conducted.

Study staff will arrange to meet with participants to collect the following data using the same approach as used for the baseline examination:

- Epworth Sleepiness Scale
- Change in health-related quality of life measures and mood
- General quality of life (SF-36 and EuroQol ED-5)
- Sleep-specific: Functional Outcomes of Sleepiness Questionnaire (FOSQ) and SAQLI
- CES-D
- Change in systolic and diastolic blood pressure
- Weight (3 month visit only)

7.0 Adverse Events

7.1 Adverse Event Definitions

Definitions for *adverse events* are documented in the Office for Human Research Protections (OHRP) Department of Health and Human Services (HHS) *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.pdf).

7.1.1 Adverse Event

An *adverse event* (AE) is "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research" (OHRP Guidance on Unanticipated Problems and Adverse Events, p. 5).

Any condition necessitation surgery must be documented as an AE.

An abnormal laboratory value is considered an AE if the value is confirmed as abnormal on repeat testing and either (1) the abnormal value suggests disease and/or organ toxicity, **or** (2) the abnormal value necessitates active clinical management (e.g., more frequent assessment, specific treatment, diagnostic intervention.

7.1.2 Serious Adverse Event

A *serious adverse event* (SAE) is an AE that "(1) results in death; (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred); (3) results in inpatient hospitalization or prolongation of existing hospitalization; (4) results in persistent or significant disability/incapacity; (5) results in a congenital anomaly/birth defect; or (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition" (OHRP Guidance on Unanticipated Problems and Adverse Events, pp. 9-10).

Any AE that results in surgery, hospitalization, or prolonged hospitalization must be documented and reported as an SAE.

7.1.3 Preexisting Condition

A *preexisting condition* is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition **worsens** during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition.

In the event that the subject undergoes diagnostic or elective surgery for a **preexisting condition**, neither the surgery nor the hospitalization needs to be reported as an AE.

7.1.4 External Adverse Event

With respect to multicenter clinical trials, an *external adverse event* is defined as an AE "experienced by a subject enrolled by investigators at other institutions engaged in the clinical trial" (OHRP Guidance on Unanticipated Problems and Adverse Events, p. 20).

7.1.5 Internal Adverse Event

With respect to multicenter clinical trials, an *internal adverse event* is defined as an AE "experienced by a subject enrolled by the investigator(s) at that institution" (OHRP Guidance on Unanticipated Problems and Adverse Events, p. 20).

7.1.6 Unexpected Adverse Event

An *unexpected adverse event* is any AE that is **inconsistent** with either the known or foreseeable risk of AEs as described in the current IRB-approved research protocol and/or consent form **OR** the "expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event" (OHRP Guidance on Unanticipated Problems and Adverse Events, p.7).

7.1.7 Expected Adverse Event

An *expected adverse event* is any AE that is identified in the current IRB-approved research protocol and/or consent form and may or may not warrant reporting. All foreseeable events that are expected to occur as part of routine clinical care and do NOT exceed threshold definitions are **not** considered AEs and do not require formal reporting. Expected Adverse Events for this study that do not qualify for AE reporting are as follows:

Associated with PSG

- Skin redness from removal of adhesives
- Temporary depigmentation under area of sensor attachment
- Poor sleep quality during PSG

Associated with CPAP Treatment

- Mild skin irritation (requiring nothing more intensive than local treatments only)
- Mild nose bleed (not requiring specific therapy and lasting less than 30 minutes)
- Mild worsening of sinus condition (not requiring more than additional nasal decongestants, local steroids and/or antibiotics and not associated with fever)
- Mild bloating of stomach

Associated with Blood Pressure Assessment

- Mild discomfort from cuff inflation

Other

- Anxiety associated with study assessment and/or testing

Any of the above expected events that exceeds threshold definitions is considered an AE and **does** merit formal AE reporting.

7.1.8 Urgent Referrals/Medical Alerts

- Heart rate > 150 bpm for $\geq$ 2 minutes
- Heart rate < 30 bpm for $\geq$ 2 minutes
- Ventricular tachycardia (NSVT) observed
- Atrial flutter/fibrillation noted with no known diagnosis (as recorded at the clinic and communicated to CSERC) or known atrial flutter/fibrillation occurred with heart rate exceeding limits (>120 or <50).
- Oxygen saturation <85% for >15% TST

Note: An urgent referral/medical alert event **during PSG study** does not constitute an adverse event; therefore, completion of the HomePAP Adverse Event Form is not required.

7.2 Recording and Reporting Adverse Events

7.2.1 Adverse Event Reporting Period

The time period for documenting and reporting AEs begins at the start of study enrollment and concludes at the time of final study follow-up (or at the time of subject's study withdrawal, removal, or loss to follow-up). Non-serious AE documentation and reporting will cease following completion of Visit Four (or following the time of subject's study withdrawal, removal, or loss to follow-up).

7.2.2 Identifying Adverse Events

During each subject contact, the investigative team must determine through specific questioning and/or examination whether an AE has occurred. All AEs occurring during the study period must be recorded and reported as appropriate.

7.2.3 Adverse Event Severity

Any possible AE must be reported to a member of the site's research clinical team (MD or RN) **within 48 hours** of discovery. In response, the site MD or RN will date and sign a written note describing the occurrence (including any need to contact the subject and/or secure additional medical records) and detail any recommendations regarding care or follow up. This note will be kept in the participant's research binder and a copy made for inclusion in the patient's medical record. AEs will be also reviewed by the site Principal Investigator (PI) to assess its severity and relationship to study participation. AE signs and symptoms will be graded on the following five-point Severity Grading Scale:

Severity Grade	Description
1	**Mild**. Awareness of sign, symptom, or event, but easily tolerated; does not interfere with usual daily activities or tasks.
2	**Moderate**. Discomfort enough to cause interference with usual daily activity; may warrant therapeutic intervention.
3	**Severe**. Incapacitating; unable to perform usual activities and daily tasks; significantly affects clinical status; requires therapeutic intervention.
4	**Life-threatening**. Adverse event is life-threatening.
5	**Fatal**. Adverse event causes death.

7.2.4 Reporting Adverse Events

All unexpected AEs are to be reported to the DCC in one of two ways: the Adverse Event Form or the Internal Adverse Event Log. Only the expected AEs identified in section 7.1.7 and within the severity limits described are exempt from reporting.

Additionally, each site must report any AE to its own Institutional Review Board (IRB) according to individual institutional guidelines. Copies of all IRB correspondence must be maintained in each site's regulatory binder.

7.2.5 Adverse Event Form

The **Adverse Event Form** is the primary document for recording all adverse events, regardless of the level of severity, related/ unrelated or expected/unexpected determinations.

Immediately following the notification of an adverse event, an Adverse Event Form is required to be completed. For purposes of contacting the Coordinating Center, research staff will enter information from the Adverse Event Form into the **HomePAP Web Entry System for Adverse Event Reporting.** An **Adverse Event Submission Number** will be generated and displayed once the event has been entered and submitted into the Web Entry System. This unique submission number identifies the report for tracking purposes. Often, separate follow-up reports will be submitted on the same event when additional information becomes available.

Automatic Email Alert

When an adverse event has been submitted through the HomePAP web entry system, an automatic email is sent to the HomePAP Coordinating Center at homepap@case.edu.

Submitting Adverse Event Report Form

All completed Adverse Event Report Forms, regardless of severity, must be submitted to the DCC through the fax server

7.2.6 Internal Adverse Event Summary Log

The **Adverse Event Summary Log** is for tracking purposes only. All adverse events and corresponding submission numbers will be recorded on the Summary Log. The sites will print the Log from the HomePAP website and hand-write relevant adverse event information. This tracking information will assist in IRB adverse event reporting at the time of the progress report. To ensure thoroughness, the DCC may collect the summary log periodically to compare Adverse Event Form submissions versus Summary Log tracking.

7.2.7 Special Procedures for Serious Adverse Events

Field Sites must report any SAE to the DCC by telephone or email within 24 hours of first learning of the event. The Adverse Event Form must also be completed and submitted to the DCC within 48 hours of first learning of the event as outlined above. In addition, the field site PI must provide more detailed information on the SAE in written narrative form. Any significant new information regarding ongoing SAEs should be provided promptly to the DCC.

Each field site must also report any SAE to its own IRB according to individual institutional guidelines. Copied of all IRB correspondence must be maintained in each field site's regulatory binder.

Any SAE presumed to be possibly related to study participation will be reported by the DCC to the University Hospitals Case Medical Center Office of Human Research and the Data Safety Monitoring Board within seven days of notification.

Submit Adverse Event Form and accompanying source data to:

Lisa Fardy, MSN, MPH, RN
Center for Clinical Investigation
Case Western Reserve University
11400 Euclid Avenue, Suite 290D
Telephone: (216) 844-4836
Fax: (216) 844-6265
Email: homepap@case.edu

7.3 Adverse Event Report Generation

The DCC will generate AE reports for submission to and review by all field sites. These reports will be available on the DCC web site and will be distributed to each field site PI on a regular basis.

7.4 Adverse Event Follow-up

The clinical course of each AE must be followed to a satisfactory conclusion (i.e., stabilization, resolution, or determination that AE was unrelated to study participation). An SAE that is ongoing and thus unresolved by the conclusion of the overall study period must be followed until the outcome is determined. Any SAE that occurs following the end of the study period **AND** is considered to be at least **possibly related** to study participation must be recorded on the Adverse Event Form and reported immediately.

At the last scheduled visit, the site investigator will instruct the subject to report any subsequent events that he or she believes to be related to study participation. All unresolved AEs must be followed until resolution or loss of subject to follow-up.

A treatment failure is generally defined as a condition or situation discovered on routine examination or follow-up that warrants discontinuation of active study participation due to identified need for additional/alternative treatment. The condition or situation may or may not qualify as an exclusion criterion; however, its presence places the subject at increased risk. Examples of clinical status changes that merit consideration include:

- A new serious medical condition causing disability and preventing participation in the study (e.g., acute stroke requiring extensive rehabilitation)
- A serious sinus exacerbation or skin reaction preventing use of PAP therapy for four or more weeks.
- Newly discovered complicating condition, such as narcolepsy, which would have disqualified the patient had the condition been noted on screening.
- Occurrence of profound hypoxemia requiring supplementing oxygen during sleep.

If the subject meets the terms of treatment failure, then his/her study participation ends and appropriate referrals will be made for alternative therapy.

8.0 Protocol Deviations & Exceptions

8.1 **Protocol Deviation** is any alteration/modification to the IRB-approved protocol that is not approved by the IRB prior to initiation or implementation.

8.1.1 **Minor Protocol Deviation** is an incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data.

8.1.2 **Major Protocol Deviation** is a more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data. A major protocol deviation can also be called a protocol violation.

8.2 **Protocol Exception** is a temporary deviation from the protocol that has been approved by the IRB before its initiation. Protocol exceptions are usually for a specific participant (e.g., allowing enrollment of a participant who is close to, but outside of, the age eligibility).

8.3 Reporting Procedures

Each site must adhere to its own IRB guidelines regarding appropriate report and documentation. Timely report and documentation must also be made to the CSERC to ensure continued participant safety and data quality.

9.0 Data Management

9.1 Case Report Forms

9.1.1 Overview

All Case Report Forms (CRF) are created using Cardiff TeleForm which allows for scanning of data into the DCC database management system using optical character recognition. The field sites will be responsible for assuring completeness and quality of data recorded on the CRF.

Each CRF has a Form Name that is appears at the top of the first page, and in the footer of each page of the form. The footer also contains a version date so any needed changes to CRF can be tracked. A full description of each CRF, as well as more detailed instructions for acquisition and completion, is included in Appendix F.

9.1.2 Acquisition and Preparation

Because the CRF will be scanned and read by the DCC TeleForm system, CRF are to be printed for each participant; photocopies of CRF should not be used. In order to facilitate this printing and to make any updated immediately available to field sites, all CRF will be obtained via the DCC web site at the time of or shortly before each participant visit.

CRF will be available as Portable Document Format (PDF) files. Adobe Reader is required to acquire and print CRF, and is freely online by following the link included in Appendix F. Individual CRF will be available, but they will also be prepared as Visit CRF Packets. Each packet is a single PDF file that contains all of the necessary CRF for a particular participant visit according to the Schedule of Measures.

In preparation for a visit, the appropriate Visit CRF Packet should be opened using a web browser. Site personnel then enter the Study ID by typing it into the appropriate boxes on the Visit CRF Packet cover sheet. This will place the appropriate Study ID on each page of each form in the packet. The Visit CRF Packet can then be printed and prepared for use.

9.1.3 Completion

9.1.3.1 General Considerations

The use of TeleForm CRF requires that data be entered legibly using black ink. Field site staff should instruct participants on completing the CRF.

9.1.3.2 Headers

The top of page one of each CRF contains important administrative information which should be completed by study personnel before the rest of the form is completed. The header information is essential to match the CRF data with the proper participant and timepoint. Header fields include:

Header Field	Description
Study ID	The unique identification number assigned to the enrolled participant as described in section 4.3.5.
Time Point	The code corresponding to the particular visit, as described in section 3.2.
Date Completed	Date the form was completed, or the date of visit.
Name Code	Acrostic identifier code for the enrolled participant, as described in section 4.3.5.
Staff ID	The site personnel ID (as described in section 2.3) of the individual completing the form or reviewing the form in the case of participant-completed CRF.

9.1.3.3 Categorical Responses

Many responses on CRF are completed by selecting the appropriate value from a set of choices. For these responses, the appropriate bubble should be filled in completely. Check marks and slashes through the bubbles will not scan as accurately.

9.1.3.4 Fixed Text Responses

Responses that require numbers, dates, or other fixed sets of characters will use one box per character or digit. Numbers and letters should be written inside the box legibly.

9.1.3.5 Free Text Responses

Responses that require longer text, such as specifying an “Other” response or entering comments, should be concise, clear, and legibly written.

9.1.4 Review

Field site staff will carefully review all CRF for completeness, accuracy, and legibility before transmittal to the DCC. For CRF completed by participants, forms should be reviewed during the visit in order to capture any missing data before the end of the visit. If missing responses are found after the visit, attempts should be made to acquire complete information before the CRF is transmitted to the DCC.

When necessary, corrections to CRF should be made with a single line through the incorrect value and the correct value written in above or near the incorrect response. Under no circumstances are erasers or correction fluids to be used to edit CRF. Any change or correction to a CRF is to be initialed and dated.

9.2 Transmittal of Data to the DCC

All research data collected in the study protocol will be electronically transmitted to the DCC using one of three methods. A chart of each measure and its corresponding transmittal method, as well as detailed instructions for each transmittal method, is included in Appendix G.

9.2.1 Web Entry

The DCC has established both a public, generally accessible, and an internal, password-protected web site for this study. The internal portion of the web site contains data entry screens for specific CRF and data logs. Data entered into the web system will go directly into the DCC database management system. Users will need to have approved registration on the DCC web site, including a unique username and password, in order to view, edit, or enter records into this web system. Field site computers will need a high-speed internet connection, and it is recommended that they use Internet Explorer 6 or 7.

9.2.2 Fax Scan

All CRF will be submitted via fax to a specialized fax server at the DCC, which incorporates submitted CRF into the TeleForm system where data is scanned and verified before inclusion into the database. The dedicated fax number for this study will be supplied to field sites. Field sites will be able to use standard fax machines to transmit CRF data.

9.2.3 FTP

Electronic data from PSG, portable monitoring devices, and CPAP compliance, will be transmitted to the DCC using File Transfer Protocol (FTP) over a Secure Sockets Layer (SSL) which not only provides secure access to the DCC system, but provides encryption of data during transmission. In order to send data via FTP, field site computers will need FTP client software that can handle FTP/SSL transmission (Internet Explorer, while useful for FTP downloading and uploading, cannot handle these secure transmissions). FileZilla is a free FTP client that is recommended, but many other client software packages are available.

Detailed instructions for FTP Transfer to the DCC is included in Appendix G. In brief, field site staff will prepare data for transmittal, following naming conventions as described. Then using the FTP client software, field site staff will connect to the DCC server using their username and password, and will transmit data.

10.0 Quality Control

Quality control will be addressed at several levels: development of standardized CRF and MOPs; centralized training of research staff and investigators; certification procedures for selected procedures; ongoing tracking, reporting and Steering Committee review of site-specific and overall study progress (recruitment and retention, study quality; PAP quality; timeliness of data transmission); and central re-reading of sleep diagnostic and titration data. The centrally read AHI data will be used as final criteria for determining AHI eligibility and for analyses that utilize PSG data. The centrally determined optimal PAP pressures, however, are used as a quality control check only; i.e., the CSRC will independently determine all PAP titrations and pressure selections, and record these as "centrally determined pressures". If systematic differences > 2 cm water pressure are noted in any given 10 consecutive studies performed at a given site using locally adjudicated pressures, quality control measures will be implemented, including staff retraining. These aberrations, or other protocol deviations, systematic problems with study quality or recruitment will be discussed by the Steering Committee, which will make recommendations for remediation (e.g., retraining, site visits, etc.).

10.1 Practice Studies and Certification

Practice studies on volunteers are conducted to assure that all staff are familiar with the study equipment and protocol before enrolling research participants. Ideally, these volunteers should include individuals who are already familiar with equipment used in the diagnosis and treatment of OSA and who are motivated to assist with quality assurance exercises for this research project.

10.1.1 Practice and Certification Volunteers

Adult volunteers may include:

- Current research or clinical staff at field sites as determined by field site PI.
- Individuals with OSA who currently use CPAP, but who do not currently have active patient care problems related to diagnosis or treatment of OSA.
- Volunteers will not be active clinical patients who are being newly evaluated for OSA. Data from these volunteer studies will not be used for research or for clinical care. There will be no compensation to these individuals. Given the minimal risk of our study procedures and the nature of the proposed volunteer pool, a waiver of written consent for these practice studies will be requested.

10.1.2 Certification Specifics

Practice studies and Certification will be required for measurement of waist and neck circumferences and for BP. In addition, each field site will be required to certify each laboratory PSG instrument that will collect study data prior to any practice studies. This will be followed by collection and transmission of one successful practice study performed using the laboratory PSG montage, the Embletta, and one using an autoPAP unit to the CCI (with local staff identification of optimal pressure). In addition, each site will be asked to submit a de-identified and re-identified split night lab CPAP titration (done for clinical purposes), providing their estimated optimal CPAP pressure and their estimated AHI in the diagnostic portion of the study.

Each field site will be required to transmit one successful practice study performed using the PSG montage, the Embletta and one using an autoPAP unit to the CCI (with local staff identification of optimal pressure). In addition, each site will be asked to submit a de-identified split night lab CPAP titration (done for clinical purposes), providing their estimate of optimal

CPAP pressure and their estimated AHI in the diagnostic portion of the study (see Appendix E).

10.2 Data Collection

Field site staff will use standardized data collection forms to collect baseline and outcome data and to monitor safety, adverse events, and other health events (for example, new clinical encounters) needed to determine the effectiveness and costs of each evaluation and management pathway. These data will be recorded and monitored by the DCC. Study data are collected on optical scanning forms when appropriate, or other CRF. Validated questionnaires are administered using recommendations of the authors. Study staff verify complete data prior to transmitting to the DCC. All data should be transmitted to the DCC within 7 days of data collection.

10.3 Central Scoring

Studies from each arm will be re-scored centrally using well-developed quality assurance approaches. The DCC will provide over-reading of all diagnostic studies within 72 hours of receipt, confirmation of study eligibility and communicate with the sites about the quality of studies. Quality control for sleep data acquisition is ensured by central review of signals and quality reporting. After each study is received, it is assigned quality codes. The DCC Clinic Coordinator will contact sites if consecutive studies demonstrate poor quality or if any one study shows evidence of faulty technique or malfunctioning equipment, or needs to be repeated. Signal and study quality codes, specific to each technician, monitor, and field center, are summarized and reported on a monthly basis via postings to the study's web page for review by the Steering Committee and relevant subcommittees. Sites and individual technicians who do not meet pre-defined levels of performance are identified. Any downward trending of quality or deviation of specific technicians will require a written response from the PI of that respective field center. If needed, the DCC also will lead periodic Sleep Quality Control for the purposes of facilitating dissemination of information regarding problem identification as well as developing solutions.

A dedicated certificated registered polysomnologist will be assigned to score all sleep studies. A sample of studies will be re-circulated after re-labeling their identifying information to assess intrascorer reliability. Further thresholds for requiring remediation include retraining or removing a scorer.

Because central scoring might introduce a delay in determining study eligibility and in initiating PAP therapy, the time from the diagnostic PSG/home study to the time when AHI eligibility data are received at the local site will be tracked. These data may be used to explore any difference in time intervals between diagnostic study and initiation of CPAP therapy. It is recognized that intervals between scoring a study and determining CPAP appropriateness may vary widely from lab to lab and may vary according to the complexity of the study (Lab vs PM). This study design feature will be considered in all interpretations of study findings.