ABC PROJECT

BRIGHAM AND WOMEN'S HOSPITAL

Sleep Division

Randomized Trial of Bariatric Surgery for Treatment of Sleep Apnea

BRIGHAM AND WOMEN'S HOSPITAL

Manual of Procedures

221 Longwood Avenue
Funded NIH-NHLBI
R01 HL106410

Introduction

Currently nearly one third of Americans are obese and two thirds are overweight or obese.[1] Obesity is an independent risk factor for diabetes, arthritis, depression, heart disease, and multiple forms of cancer.[2] One of the most common co-morbidities resulting from obesity is obstructive sleep apnea (OSA) characterized by repetitive collapse of the upper airway during sleep resulting in fragmentation of sleep as well as recurrent episodes of hypercapnia, hypoxemia, and wide pleural pressure swings, which leads to substantial morbidity.[3] Obesity is the strongest risk factor for OSA and incidence is high among those with a body mass index (BMI) of 30 kg/m^2 or greater. OSA is associated with excessive daytime sleepiness and impaired cognitive function. In addition, OSA appears to act synergistically with obesity to further increase the risk of diabetes,[4] hypertension,[5] and heart disease,[6] as well as gastroesophageal reflux disease (GERD) and depression.[7, 8] Recent studies suggest OSA also acts synergistically with obesity to increase mortality risk.[9, 10] Beyond the effects of obesity, OSA is independently associated with a reduced quality of life,[11] cardiovascular disease (including hypertension, stroke, and congestive heart failure),[7, 8, 12, 13] and an increased mortality risk.[9, 10]

The primary treatment for moderate to severe OSA is nasal continuous positive airway pressure (CPAP). By applying a pressure to the upper airway lumen that exceeds the surrounding tissue pressure, collapse can be prevented. While CPAP is highly efficacious,[14] its acceptance by patients and long term use is often limited and a large minority if not majority do not use the prescribed therapy regularly. In contrast, bariatric surgery has been reported to be highly successful in improving OSA in morbidly obese patients and is often recommended to obese patients with OSA, although the data on OSA responses have generally not been collected rigorously.[15, 16] Much of the existing literature has relied on self-reported improvement in OSA-related symptoms to characterize cure rather than objectively measuring OSA severity post-operatively.

This study will assess the role of bariatric (weight loss) surgery as compared to continuous positive airway pressure (CPAP) therapy plus weight loss counseling for the treatment of patients with class II obesity and those who have severe obstructive sleep apnea (OSA). If effective, this will provide a strong basis for conducting a future large multi-center randomized trial (RCT).

Funding provided by the NHLBI has resulted in the establishment of the Apnea, Bariatric, CPAP (ABC) protocol which is comprised of two Clinical Centers, a Physiology Measurement Core for processing all physiological data, a Data Coordination core which includes data management and biostatistical analysis, Resource which includes the biochemical processing (Harvard Catalyst), a surgical committee, a Medical Monitor, and an independent Data Safety and Monitoring Board (DSMB).

This Manual of Procedures (MOP) documents the randomized clinical trial to be conducted by the ABC Project Team which aims to provide data to evaluate the comparative effectiveness of laparoscopic gastric banding (LGB) surgery vs. CPAP therapy along with weight loss counseling. The study will focus on patients with severe OSA and class II obesity (BMI 35-40 kg/m^2).

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Chapter 1

1. General Information

1.1. Design, Objectives, and Endpoints

1.1.1. Study Design and Objectives

- The ABC clinical trial will utilize a two-arm, randomized design to study the comparative effectiveness of laparoscopic gastric banding surgery (LGB) versus continuous positive airway pressure (CPAP) therapy for the treatment of moderately obese (BMI 35-40 kg/m^2) patients with severe obstructive sleep apnea (OSA). Participants who meet eligibility criteria: age 18-65, severe OSA (apnea hypopnea index AHI ≥ 30 events/hr) with at least 1 symptom referable to their OSA (excessive daytime sleepiness, frequent awakenings, bothersome snoring, or morning headaches) and with class II obesity (BMI 35-40 kg/m^2), and acceptance of medical equipoise, will be randomized to one of the following arms:
    1. CPAP Treatment
    2. LGB Surgery

1.1.2. Primary Objectives

- To compare the effectiveness of LGB vs. CPAP therapy, the primary outcome of this study will be exposure to residual obstructive respiratory events at 9 months, with a secondary longer term analysis for a subset at 18 months. Key secondary outcomes of this study will be the change in sleepiness assessed by the Epworth sleepiness score and changes in adiposity as assessed by body mass index at the same time points. In addition, the change from baseline on a number of tertiary outcome variables will be assessed to better define the impact of each treatment on these measures. These include both biomarkers and patient-reported outcomes. Biomarkers to be assessed include:
    - 24 hour blood pressure (BP) profile
    - Markers of systemic inflammation
    - Markers of oxidative stress
    - Insulin resistance
    - Lipid metabolism
    - Measures of hemostasis
    - Vascular function
    - Measure of arterial stiffness

- Pulmonary function
- Measures of the oral and pharyngeal spaces
- Anthropometry

- In addition, patient-reported outcomes will be assessed, including:
  - Global health
  - Quality of life (Overall and disease specific)
  - Vitality
  - Sleep and Wake impairment
  - Gastrointestinal (GI) symptoms
  - Mood
- Finally, measures of health care utilization will be assessed including:
  - Medication usage
  - Health care encounters (planned and unplanned)
  - Emergency room visits and hospitalizations

1.1.3. Overview of Timeline and Endpoints

After the screening visit with a sleep specialist and bariatrician and determination of equipoise, participants will be randomly assigned to receive either CPAP therapy or LGB surgery. A total of 80 subjects will be enrolled from sleep clinics affiliated with two academic medical centers. Subjects will be randomized in equal numbers (20 per year at each site). Outcomes will be measured at 9 months, and in a subset at 18 months to identify the extent to which each treatment provides effective apnea control both in terms of exposure to ongoing respiratory events as well as improvements in cardiovascular biomarkers and symptoms related to OSA. In addition, these data may provide insight on the extent to which each of the chosen markers varies with changes in BMI vs. OSA severity.

Per Site Enrollment Goal:

A total of 80 potential subjects will be enrolled, 40 at each site with an estimated 20% dropout rate, 64 completing the 9 month follow up (32 in each arm) and 40 completing the 18 month follow up (20 each arm). Randomization will be stratified by study site.

All screened participants will be between 18 and 65 years of age, BMI 35-40 and a new diagnosis of severe OSA (AHI≥30) which requires validation through a laboratory PSG with at least 2 hours of sleep time recorded either on a full night diagnostic study or on the diagnostic portion of a split night study.

Participants will have a baseline research exam within 2 weeks of the screening visit which will include an overnight sleep study, blood tests, measures of BP, arterial stiffness, weight, height, and body fat, spirometry, pharyngometry, and the completion of questionnaires about health, sleep, medication use, daily activities, and habits. A study health promoter will provide education on improving diet, activity and sleep. At the end of the exam, participants will wear a 24-hour BP monitor at home which they will return the next day.

Participants will be randomized to CPAP or LGB at the end of the baseline visit.

.1. If in the CPAP arm, a CPAP titration study will be done within 2 weeks of randomization (if not already done as part of a split-night study), and receive CPAP equipment within 2 weeks of the CPAP titration study or within 2 weeks of the baseline visit. Follow up appointments with the respiratory therapist (RT) and/or a sleep physician are based on clinical practice at each of the two sleep medicine centers following American Academy of Sleep Medicine guidelines with a follow-up RT visit at 1 week, 1 month, and 3 months and a physician follow-up visit at 2 months and 6 months. For the subset continuing to be followed for an additional 9 months, an RT visit would occur at 12 months and a physician visit at 18 months.

.2. If in the LGB arm, participants undergo routine pre-operative evaluations, including laboratory testing, and more detailed evaluations (upper GI, psychiatric, pulmonary, cardiac as indicated). In addition, all subjects will undergo a supervised weight management program 3 months prior to surgery. Pre-operatively, the participant meets with the surgeon (approximately 2 weeks prior to surgery) at which time they begin a liquid diet and initiate use of an auto-titrating CPAP device (1 week prior to surgery, continuing for two weeks following surgery). After surgery, health care follows accepted standards, (one night hospitalization and a one week rest period at home). Unless a complication is encountered, the first post-operative visit will be at 2-3 weeks after surgery with the surgeon. Follow-up visits with the bariatric surgery team will subsequently occur at 2 months, 4 months, and 6 months post-operatively, and for the subset to be followed for an additional 9 months, additional visits will occur at months 8, 10, and 12 post-operatively. These visits will roughly correspond to months 5, 7, 9, 11, 13, and 15 from randomization.

1.2. General Protocol Policy

1.2.1. Changing the Protocol

The objectives of the ABC project are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol will result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure participant safety or will significantly enhance the scientific validity of the study.

1.2.2. Initiating a Protocol Change

Any member of the ABC project may request a change to any portion of the study protocol. The member wishing to change the protocol should present the proposed change(s) in writing to the Chair of the Steering Committee. The Steering Committee will review the request and decide whether to make any change. Any proposed changes can be implemented only after the Steering Committee reaches a majority vote and the NIH Project Officer approves of the proposed changes. Once a proposed change has been approved, the Data Management/Biostatistical Core will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol. Clinical Centers will then submit the protocol amendment and revised protocol to their local IRB for approval.

Substantive changes to the protocol and ancillary proposals must be submitted to the DSMB for review and approval before implementation can occur.

Chapter 2

2. Study Organization

2.1. The Scientific and Data Coordinating Core (SDCC)

The SDCC located at the Brigham and Women's Hospital and directed by Susan Redline and Sanjay R Patel will provide administrative, biostatistical, and data management / computing leadership for the design and conduct of the clinical trial. This core will be responsible for producing study documents, producing and maintaining a web-base database that includes web-based randomization procedures, produce study progress reports, track Adverse Events, and perform final statistical analyses. It will also coordinate and monitor data flow and integrity across their sites and review study procedures and implementation. Dr. Malhotra will serve as the Study Medical Monitor, and provide oversight for the real-time review of unexpected adverse events and adjudicate potential treatment failures.

Additional SDCC Staff include:

- Statistician – (Wei Wang)
- Lead Medical Monitor – (Atul Malhotra)
- Data Systems Management staff

Responsibilities of the SDCC include:

- Provide leadership in directing the scientific (clinical) aspects of protocol development and study implementation.
- Oversee study governance.
- Prepare and distribute the study protocol and Manual of Procedures (MOP) based on collaboration with the Steering Committee and the NHLBI.
- Lead the development, testing, and use of all CRFs and other study procedures.
- Develop and maintain an efficient data management system to facilitate the collection, transmission, storage and archival of all electronic study data. This system will include the development and application of quality assurance procedures including data tracking and validation.
- Provide training of Clinical Center staff and coordinate site monitoring.
- Coordinate Steering Committee meetings.
- Prepare for the Steering Committee and DSMB detailed reports regarding participant recruitment and retention, data collection activities, and results.

2.2. Clinical Centers

There are two Clinical Centers each responsible for the recruitment, screening, and enrollment of study participants and the collection of study data according to the protocol.

ID #	Clinical Center	
1	Brigham and Women's Hospital	(BWH)
2	Beth Israel Deaconess Medical Center	(BIDMC)

2.2.1. Personnel

Each site is comprised of the following ABC-trained personnel:

- Principal Investigator (Clinical)
- Co-Investigator (Clinical)
- Dieticians
- Local un-blinded Medical Monitor

The study coordinator, health promotion counselor, and research assistants (recruiters, technicians performing data collection, and data entry) will work across both sites to identify eligible subjects, schedule and coordinate visits, and gather safety and endpoint data.

2.2.2. Continuing Review

The following is a suggested list of items to include when submitting your annual review to the IRB. Modifications may be necessary based on your institutional guidelines.

- the number of subjects accrued;
- a summary of any unanticipated problems and available information regarding adverse events (in many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document)
- a summary of any withdrawal of subjects from the research since approval or the last IRB review;
- a summary of any complaints about the research since approval or the last IRB review;
- List of questionnaires and instruments
- DSMB report
- SDCC report
- Minor Violation Report, if there have been any minor violations since last review
- a summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;
- any relevant multi-center trial reports;

- any other relevant information, especially information about risks associated with the research; and
- a copy of the current informed consent document and any newly proposed consent document.

2.3. Measurement Core

This project involves one Measurement Core directed by Sanjay R. Patel and Susan Redline which is responsible for overseeing all procedural aspects of the protocol including overall data collection and quality control. This core will establish standardized procedures for acquisition and processing for all physiological data including: sleep studies, CPAP usage, 24-hour blood pressure recordings, radial artery pressure waveforms, pulse wave velocity, spirometry, and pharyngometry using robust approaches developed and utilized in prior studies. The core will be responsible for providing specific training and technical support related to these specialized measures for all study staff. In addition, it will be responsible for developing quality control measures to certify all staff and track their consistency on all measurement techniques.

2.3.1. Biochemical Resource - Harvard Catalyst

This study will utilize expertise and resources available through the Harvard CTSA program (known as the Catalyst) for the collection and handling of all blood and urine markers. The Catalyst will establish methods for standardized collection, shipment, and storage of specimens, and perform assays using an array of extramural quality assurance programs including the Comprehensive Coagulation module of the CAP Survey, WHO standards for calibration, the CDC certification program for lipids and the Westgard Multi-Rule control procedures for analytical test acceptability.

Harvard Catalyst Core Lab (HCCL) The HCCL will be used as the primary lab for tests and assays. Any tests and assays not handled at the HCCL will be sent to the Laboratory of Clinical Biochemistry Research, University of Vermont ((802)656-8968). HCCL policies and procedures are will be followed and are available at:

http://brighamandwomens.org/research/hccl/policy.aspx

2.4. Steering Committee

Oversight of the study will be through a Steering Committee, which will include the Clinical Center Principal Investigators and Co-Investigators, and the study statistician. Subcommittees that may be assembled include: Operations, Quality Control, Surgical, Publications, and others as needed.

The following areas typically fall under the purview of the Steering Committee:

- General design and conduct of the study;
- Protocol;
- Adherence to the study protocol;
- Review of the essential study documents, including MOP and forms;
- Review of data collection practices and procedures;
- Changes in study procedures;
- Appointments to and disbanding of committees and subcommittees;

- Allocation of resources based on priorities;
- Review of study progress;
- Meeting recruitment goals;
- Review and implementation of recommendations from the DSMB;
- Review and response to other general advice and/or recommendations (e.g., from the NHLBI Program Director).

Subcommittees coordinate activities related to the development, training and implementation of their protocol-specific areas:

- Operations (Chair- Sanjay R. Patel)
- Quality Control (Chairs- Susan Redline)
- Surgical (Chair – Ali Tavakolizadeh)
- Publications (Chair – Sanjay R. Patel)

2.5. Data and Safety Monitoring Board (DSMB)

A DSMB will be convened with representation by 4 experts in statistics, clinical trials, bariatric and sleep medicine. The DSMB will convene and approve the final protocol before study initiation and then will be provided with quarterly updates summarizing study progress and adverse events. Protocol development will include formal procedures for reporting and tracking all adverse reactions to the NIH and IRB and for tracking progress in the study and to identify any need for premature termination of the protocol.

2.6. Communication

2.6.1. Initial and Ongoing communication

Communications, coordination, and standardization of study activities will be accomplished through the following:

- An initial training session with participation of all study investigators and study coordinators in which the protocol will be reviewed and the study coordinators will be trained on all study procedures, including “hands on” supervised practice in making study measurements, brain-storming recruitment approaches, and using the data management system interface.
- Prior to the initiation of the study and then quarterly, meetings will be held with all practitioners at each sleep center to review this protocol, review eligibility and prove a standardized description of the study.
- Weekly Operations meetings with study staff to review pragmatic aspects of study implementation, data, flow, etc.
- Monthly Steering Committee calls to review overall study integration and progress.

2.6.2. Study Registration

This trial has been registered at www.clinicaltrials.gov with a detailed description of the study protocol, eligibility criteria and endpoints. The trial is classified there as an interventional study with randomized, parallel assignment, single blind design. The ClinicalTrials.gov unique identifier is NCT01187771. Any interim changes to the study

design, protocol, endpoints or contact information will be submitted to the website for updating within 30 days.

2.6.3. Contact Information

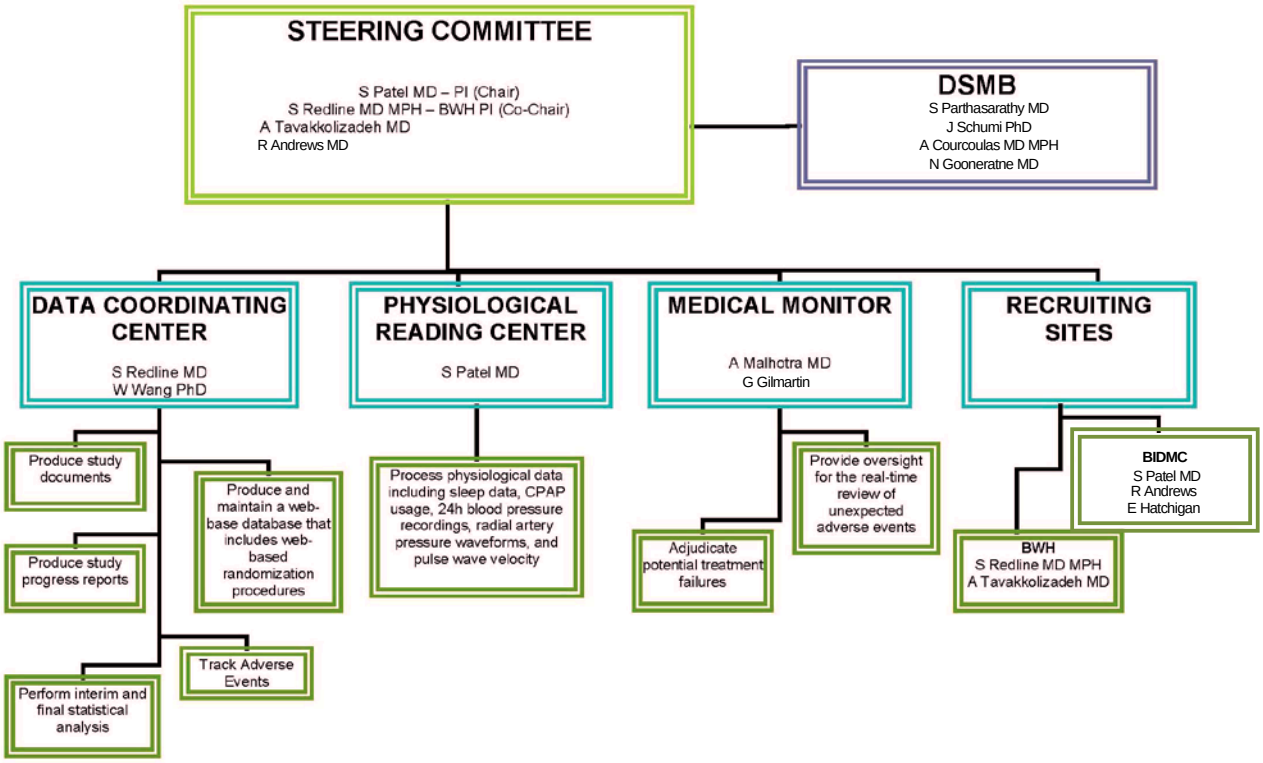
The SDCC Project Manager may be contacted via phone, email or fax at the following address:

Melanie Zibit
Senior Research Assistant
Brigham and Women's Hospital
221 Longwood Ave, 275A
Boston, MA 02115

Voice: 758-307-0337
Fax: 216-732-4015
Email: mzibit@partners.org

Chapter 3

3. Study Administration



3.1. Role of Study Personnel During Visits and Contacts

3.1.1. Site Principal Investigator (PI)

The Principal Investigator will be available to answer any protocol and/or procedural questions, and be responsible for the overall integrity of study data collected at his/her site and for the overall safety of participants in her/his site. To the extent feasible, the PI should be blinded to the randomization arm of given participants and randomization-specific outcomes for the overall study (until its completion).

3.1.2. Study Coordinator and Research Assistants

Research personnel (coordinator/assistant) trained in ABC study procedures may recruit, conduct baseline and final visits and complete phone contacts. The coordinator is essentially the “site project manager” and ensures that all data are collected according to

the guidelines listed in the Manuals of Procedures. For those sites utilizing a Clinical Research Unit (CRU) and nursing staff, an in-service on the ABC protocol and procedures must be conducted according to your institutional guidelines. CRU ABC trained personnel must be listed on the Responsibility Log. The study coordinator/health promotion counselor will be unblinded so as to make phone calls providing treatment specific health promotion (addressing mask issues for CPAP arm and dietary restrictions for LGB arm) as well as to obtain AE information. All other staff including recruiters, technicians and nurses making measurements of primary and/or secondary endpoints will be kept blinded to treatment assignment as much as possible.

3.1.3. Local Medical Monitor (MM)

The local MM will be responsible for reviewing adverse events and treatment failures that may occur and which may require unblinding in order to ensure that the participant's safety is addressed. All decisions to label a subject a "treatment failure" should be reviewed with the Overall Study Medical Monitor.

3.2. Quality Control and Certification

As a multi-center study, there is a strict need to collect high quality, standardized data. To reduce site to site variability, which would reduce the ability to address the study hypotheses, it is critical that all measurements across sites and by different study personnel are performed as similarly as possible. Likewise, all data need to be processed and scored using identical approaches. To maximize study quality, the following approaches will be followed:

- Study coordinators, research assistants and study investigators will participate in a central training session conducted prior to beginning data collection.
- All procedures will be documented in Manuals of Procedures.
- All study specific procedures will be acquired by personnel trained for these procedures using the ABC protocol and certified according to protocol guidelines. Depending on the procedure, certification may require demonstrating the procedure on volunteers at central training or locally under the supervision of an expert or centrally trained individual; completion of an exam, or submission of practice tests showing reproducibility.

3.3. Record Keeping

Participant study documents must be made available to the Scientific and Data Coordinating Core, the IRBs, the DSMB, and the NHLBI when necessary for safety and quality control and/or as required by law for regulatory purposes. These documents should be organized in binders or files (outlined below) and stored in accordance to security and record retention regulations and until further written notice by the sponsor or the SDCC. Each clinical center must maintain the following documents in binders/folders:

3.3.1. Clinic Regulatory Binder (1 per Clinical Center)

This binder contains all essential documents, according to GCP guidelines, required for conducting a clinical trial:

- Protocol/Amendments and Signature Page(s)
- Informed Consent Form/Attestation/HIPPA

- IRB Correspondence
- IRB Membership List, if applicable (current for duration of trial)
- General Correspondence (DSMB, NHLBI, etc.)
- Laboratory Certifications/Laboratory Normal Ranges (Harvard Catalyst; current and updates during the trial)
- Curriculum Vitae and License of all clinical personnel (current within 2 years)
- Signature and Delegation of Responsibilities Log
- Manual(s) of Procedures
- Adverse Events
- Study logs (these can be maintained electronically where appropriate)
- Screening log
- Enrollment log
- Education and recruiting materials
- Reports

A template of the Regulatory Binder Menu will be sent to each site electronically and can be modified as needed. The purpose of the template is to assist each site (including cores) in obtaining and organizing the necessary regulatory documents required to conduct the trial.

Note to file: Documents outlined above may be stored in other/additional binders or electronically during the course of the study; however a "Note to File" should be placed in any section where this occurs as a means to track the document during a monitoring visit.

3.3.2. Case Report Form Binder (1 per study participant)

This binder contains all data collection forms and select administrative forms completed during the course of the trial. No participant identifiers other than participant ID number and name code should be contained in this binder.

3.3.3. Source Document Binder (1 per study participant)

Contains all documentation collected to support and verify information contained on the data collection forms. This includes the following original source documents: participant signed informed consent, eligibility checklist, medical records, laboratory results, CRU admission and nursing notes, administrative forms not contained in the Case Report Form Binder such as the participant contact Information, progress notes, and correspondence. In addition, any copies of applicable source documentation should also be stored in this file. Study documents that have participant identifiers beyond participant ID and participant initials should be contained in this file.

3.3.4. Participant Study Binder (1 per Clinical Center)

This binder contains a Participant ID Assignment Log, a copy of all participant-signed informed consent forms, and all financial documents related the study. Any additional study-specific confidential documents should be contained in this file.

It is suggested that each Clinical Center implement a mechanism to track visit due dates for each participant and record dates that the participant was contacted. This could be an

individual “Participant Contact Log” that is designed to aid in tracking visits and to record the date of contact or attempt at making contact.

In addition, another log each Clinical Center may want to consider is a Deferral Log that is designed to track participants who are interested in participating but cannot participate until one or more of the criteria for deferral has resolved.

3.3.5. Internal Distribution of Study Documents

The SDCC is responsible for maintaining a record of all documents, reports and meeting minutes pertaining to this trial. During the conduct of this protocol, the SDCC will be responsible for the distribution of the Protocol, Manual of Operations and Procedures, and study reports. At the end of the study, these documents will be archived by the SDCC and forwarded to the National Technical Information Service (NTIS). Minutes of all appropriate committee meetings will be maintained in the files at the SDCC. At the conclusion of the study, these minutes will be archived and forwarded to the NHLBI.

3.4. Case Report Forms

CRFs will be developed by the SDCC and will be subject to approval from the Steering Committee. Following Steering Committee approval, final versions of the CRFs will be distributed to each Clinical Center for their own IRB. CRFs will be made available to the Clinical Center as PDF documents.

Clinical Centers will be responsible for entry of CRF data into the Data Management System. Tracking of entry and monitoring of entry and data quality will be performed by the SDCC. Original forms will be retained by the Clinical Center.

3.4.1. Generic Directions for Completing Case Report Forms

The following general guidelines are applicable to all CRFs used in this study:

- Print legibly and clearly.
- Always use a ballpoint pen with ***black ink***. Do ***NOT*** use pencil or multi-colored ink (green, red, blue, etc.).
- Do not use erasers or correction fluid.
- If an error is made, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated.
- Dates ***must*** match any source or supportive chart, lab, or evaluative documentation. The approved format for collecting dates is Month / Day / Year.
- Times are collected in standard (12-Hour AM & PM) format. The CRFs will specify which collection method is being utilized. If only a partial time is available, write in the known data and enter missing codes (-9,-10) for missing hours/minutes.
- Always use patients’ namecode, not full name.
- Avoid using abbreviations.
- Be clear, concise, and to the point when completing CRFs, writing comments, or providing additional / supportive information.

- Provide signature and date as required on forms.
- Do not write comments in the margins or on the reverse side of the CRFs.
- Completely fill in study information at the top of each CRF.
- After the informed consent process, the Coordinator will assist the participant in responding to a series of questions regarding aspects of his / her OSA, sleep, demographic information, medical history (including present and previous treatment histories), etc.
- Where possible, the Clinical Site will maintain a set of original blank CRFs to make copies when needed; or will download and print the necessary CRFs from the study website prior to the participant's scheduled clinic or telephone visit.

3.4.2. Types of Forms

There are two types of forms used for this study:

- DATA CRFs contain participant data and are entered into the database – these include clinical and participant completed forms.
- ADMINISTRATIVE CRFs are used for processing CRFs, data entry and administrative needs.

3.4.3. Case Report Form Completion

The Study Coordinator will verify the CRFs and create a visit packet based on the Baseline, 9 month and for a subset at 18 months before the patient's scheduled visit.

CRF Headers are in the top margin of each CRF and the fields are filled in to match CRF data with the Study ID. These fields are:

Visits and Phone Contacts:	The date of each visit and phone contact is located at the top of the first page of study documents. A visit or phone contact check box is located at the top of all forms that will be repeated at baseline/final visit and interim phone contacts.
Study ID:	A 5-digit number, that is a unique identifier for each study participant, is written on all study documents and specimens. The first digit corresponds with the site code number where the participant is enrolled.
Namecode:	An alphabetic code representing the first two letters from the participant's first and last name. Serves as a check on the ID number and as a quality control check on CRFs.
Site:	Each participating Clinical Center is assigned a unique 1-digit site code number, which is also placed as the first digit of each study ID.
Staff ID:	A 3-digit number, representing the site and a unique identifier

used to identify the person who completed the form.

Serves as a check on the data gathered and as a quality control check for CRFs.

Study staff will fill in the header information prior to giving the CRFs to the participant to complete (or check that the header was accurately populated by any automatic form download procedure). The participant should be reassured that confidentiality is maintained on all collected data, throughout the course of the study.

Questions should not be left unanswered. If a participant chooses to leave a question blank, write “Unknown per participant’s choice” or “Patient refused to answer”, date and initial next to the blank question. Participants should be urged to use their “best estimate” rather than leaving the question unanswered.

Exercise caution that you do not paraphrase or answer questions on the participants’ behalf. Even though medical / chart information may contradict participants’ response, study staff must not alter participant responses on Participant Completed CRFs.

Study staff will review all of the CRFs for inconsistencies and missing information ***before*** the participant leaves the area, and will attempt to collect any missing data. An error by the study staff and/or participant on the CRFs will be corrected by crossing out the error with a single line in ***black ink***, and entering the correct information. The correction ***must*** be initialed and dated. The correct response *may* be circled for clarification, if necessary.

Each CRF is dated and identified with a version date, located in the bottom footer. This number is important should a CRF become revised at a later date.

CRFs may be completed by various individuals as follows: To avoid transcription errors the research coordinator (when applicable) will verify the information for completeness, and query the participant if the information is inconsistent or confusing. Under no circumstances shall the participant take the questionnaire home to complete. The research coordinator may need to assist in the completion of these forms, if applicable.

Participant Completed CRFs

Participant completed forms are completed by the participant.

If the participant makes any mistakes they should be instructed to draw a line across the error response, initial and date next to the error to indicate who made the error correction and when it was made. The correct response should be written legibly above or near the original response.

If the Study Coordinator or other designated site staff believes that the participant may have trouble reading the CRFs, staff may read the questions to the patient but should not answer or complete the CRFs for the participant.

When the participant returns the CRFs, check them for completeness. After the CRFs are reviewed, staff will complete the Staff ID in the top right corner of the master heading of the CRF.

Research Personnel Completed CRFs

Research Personnel completed CRFs can be administered to the participant; or the information can be gathered from clinical methods.

When soliciting information from the participant, the research personnel will attempt to get a reasonable answer from the participant if their answer is unclear, incomplete or irrelevant, by repeating the question and refocusing and redirecting the participant and using the "probing" technique.

Some samples of "probing" techniques that are useful when attempting to broker information from participants:

- ***Basic Probe***: Repeat the question to get the participant back on track; this technique can be used when the participant is "going off on a tangent".
- ***Explanatory Probe***: Used to get clearer understanding by completing the incomplete statements of the participant. The questioner asks questions like, "Can you give me an example of that?" or "Can you explain that?"
- ***Focused Probe***: Used to get particular understanding about a topic. For example, "What type of … did you use?"
- ***Silent Probe***: The questioner maintains silence and waits for the participant to break silence. This type of technique is generally useful when the participant is taking a lot of time to respond or is hesitant to respond.
- ***Drawing Out***: Used when the participant has stopped and is not responding. The questioner restates or rephrases the last question or topic (ergo: "So, the question was…" or "What else can you tell me about…"), which helps the participant start talking again.
- The research personnel will ask the participant to elaborate or reconsider an incomplete or inappropriate answer without leading the patient or influencing the content of the answer (creating bias in his / her answer).
- Be mindful of sensitive or painful issues for the participant and exercise sensitivity when asking questions.
- Reassure the participant regarding the confidentiality of their response and explain the importance of the question if the participant seems hesitant.
- If the information can be obtained from study methods – BP, anthropometry, lab device, etc – make certain that all answers are completed.

After the CRFs are completed, please check them for completeness and legibility, and the research personnel will complete the staff ID.

Administrative Forms

Administrative forms do not get entered into the DMS and are primarily used for QC and administrative purposes. They are designed to help manage and keep organized different aspects of study administration.

Some of the administrative forms contain private and confidential participant information – such as name, address, contact numbers – and should be kept in a secure location. These forms should never be submitted to the SDCC.

3.4.4. Entry/Submission of Case Report Forms

Data Entry / Site Staff Completed forms are used to gather valuable Primary and Secondary endpoint data, safety data, and efficacy data. It is vital to ensure that all questions are answered in their entirety prior to being entered into the DMS.

All CRFs should be entered into the DMS within one week of being received or collected by the RC.

3.5. Data Management

The SDCC will coordinate the development, testing, and distribution of case report forms; will develop a computerized Data Management System to securely house electronic study data; and develop secure web portal to disseminate information, facilitate participant randomization, and allow Clinical Centers to interface with the study database. These systems are described in more detail in this section.

3.5.1. Study Database

The Data Management System for the study will be REDCap (Research Electronic Data Capture). The Data Management System will be housed on secure servers located in a dedicated access- and temperature-controlled data center. Data from various sources will be merged and prepared for analysis by custom programs utilizing the SAS System for Windows (version 9.2).

Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. The REDCap Survey is a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. Both REDCap and REDCap Survey systems provide secure, HIPAA compliant, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry.

Direct access to the Data Management System is limited to select data management personnel within the SDCC. Clinical Center personnel and other study staff can access the data only through the study web portal.

3.5.2. Web Portal

The SDCC will develop a secure web interface in order to provide Clinical Centers and other study personnel with the following functionality:

- General study information including staff directories
- Dissemination of Clinical Report Forms
- Enrollment and randomization of study participants

- Entry of CRF data into the study database
- Review of participant status and data
- Dissemination of study reports

Clinical Centers will only be required to have a web browser through which to access the study web interface. No additional software need be installed on Clinical Center computers in order to access the Data Management System, view reports, or enter data.

Participant enrollment and randomization will be performed through the web interface. Clinical Center staff will enter required information to verify eligibility and will be provided with the randomization assignment. A manual backup system for participant randomization will be implemented in the event that the Data Management System is not available.

Data entry of CRFs will be performed through this secure web interface. Logic and range checks will be built into the interface to prevent invalid or illogical data being entered into the database.

3.5.3. Quality Assurance

The SDCC will be responsible for the validation of study data and the resolution of identified problems. The web data entry interface will provide validation and logic checks to help prevent missing, illogical, or problematic responses from begin entered into the database. Further checks of the data will be programmed into the Data Management System to identify problems. The SDCC will query the database at regular intervals and will provide Clinical Centers with reports to resolve discrepancies and verify suspect values.

The Clinical Center will be required to enter a random sample of records a second time into the database, and the SDCC will request copies of a random sample of CRFs, for quality assurance purposes. Problems identified with a particular staff member will be addressed by retraining or more detailed auditing.

Once entered into the database, any changes to study data are tracked by the REDCap's audit trail feature.

Each Measurement Core will be responsible to provide the SDCC documentation on their own Quality Assurance measures, and the SDCC will perform additional checks of data received from Measurement Cores in order to identify potential problems. Reports will be provided to the Measurement Cores to resolve discrepancies and verify suspect values.

3.5.4. System Maintenance

The SDCC data center is located in dedicated space with monitored access control and isolated temperature control. All servers are equipped with uninterrupted power supply systems, and the data center itself is on an emergency generator system in the case of power outages. Maintenance of the SDCC server hardware and software is performed by dedicated IT personnel. The study database is administered by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group, who will be responsible for database performance, backups, and user access control. Regular maintenance of the systems requires periodic upgrades which result in some down time

during off hours (9:00 pm – 5:00 am EST). All study personnel will be notified if there is anticipated down time of the system during business hours.

All study data and systems are backed up nightly via the Enterprise backup system, IBM Tivoli Storage Management, and maintained on encrypted storage tapes for tapes that are stored off site.

3.6. Adverse Event Reporting

3.6.1. Pre-Existing Conditions and Adverse Events

The following section outlines pre-existing condition information and adverse events information collected during the screening and baseline assessments. The purpose of recording adverse event information related to pre-existing medical conditions is to provide ongoing monitoring of any changes in pre-existing conditions, and to allow comparison of adverse event information related to pre-existing medical conditions with adverse events that may occur once the study period has begun.

3.6.2. Definitions

A pre-existing condition is any chronic or acute sign, symptom, illness, or condition that the participant has at the time of entering the trial. Pre-existing conditions will be collected on the Health Questionnaire at the Baseline visit. If a pre-existing condition worsens during the course of the study, it must be reported on the Adverse Event [AE] CRFs.

Adverse Event (AE)

An adverse event is any unfavorable or unintended sign, symptom or disease occurring in a clinical trial participant at any stage of the study. Adverse events may include the following:

- All suspected adverse medication (or device) reactions, drug interactions, etc.
- Worsening of a pre-existing condition, or apparent unrelated illness.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.
- Any event that could be characterized by the definitions above is an AE, whether or not considered related to the study.
- Abnormal Laboratory Values: A laboratory abnormality should be documented as an adverse event if:
  - The abnormality suggests a disease and/or organ toxicity, *OR*
  - The abnormality is of a degree that requires active management; (e.g. specific treatment, more frequent follow-up assessments, further diagnostic investigation, etc.) *AND*

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.

Non-serious Adverse Event

A Non-serious AE is any adverse event that does not meet the criteria for "serious."

Serious Adverse Events (SAE)

Any event that is life threatening or fatal; results in significant or persistent disability; requires hospitalization or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. The appropriate case report form must be completed for all events in this category according to the guidelines listed in the Manual of Procedures.

Baseline-Emergent Adverse Event

Defined as any event that occurs or worsens during the screening process (after informed consent signing) including the baseline visit up to the time of randomization.

Expected (Anticipated) Adverse Events

Expected Adverse Events are adverse events that are known risks of the study protocol and for the purpose of this study have been identified in the protocol and consent form. Examples of these include:

- Associated with PSG
  1. Skin redness from removal of adhesives
  2. Temporary depigmentation under area of sensor attachment
  3. Poor sleep during PSG
- Associated with Phlebotomy
  4. Temporary Pain
  5. Fainting
- Associated with AMBP
  6. Discomfort from wearing equipment and inflation of cuff
- Associated with CPAP or Oxygen
  7. Nasal stuffiness
  8. Sinusitis
  9. Nasal bleeding
  10. Eye irritation due to mask leak
  11. Discomfort associated with breathing while using CPAP
  12. Facial or nasal irritation near the mask or nasal prongs
  13. Poor sleep due to mask fit or CPAP pressure
- Associated with bariatric surgery
  14. Conversion to Laparotomy
  15. Wound infection
  16. Nausea
  17. Vomiting
  18. Bloating

19. Band Slippage

Unexpected Adverse Events

Adverse events that are not expected and not identified in the protocol or consent form.

Unanticipated Problem Involving Risks to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to a subject's participation in the research
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Serious Adverse Events: Hospitalization, Prolonged Hospitalization or Surgery

- Any adverse event that results in hospitalization, surgery or prolonged hospitalization, should be documented and reported as a ***serious adverse event*** (SAE). Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.
- Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event if it occurred for a diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study follow-up. For this study, the study treatment follow-up is defined as the last scheduled visit.

3.6.3. Recording and Reporting Adverse Events

At each contact with the subject, the Study Coordinator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate AE module of the case report form (CRF). All adverse events occurring during the study period must be recorded.

Consistent with clinical research adverse event reporting guidelines, the reporting of adverse events will be accomplished by collecting information on adverse experiences at all research visits (baseline, 9 month, and in the long term follow-up subgroup, 18 months) and interim monthly contacts. The Research Coordinator should interview each potential participant in a manner that is friendly but solicitous of a response in order to ascertain as many pre-existing conditions as possible (pre-existing medical conditions are asked about

in the Health Questionnaire). Research personnel should refer to this questionnaire when conducting interim phone contacts. All adverse events (serious and non-serious; treatment-emergent and baseline-emergent) must be recorded on the Adverse Event Report Form.

Signs and Symptoms will be graded by the Research Coordinator, in consultation with the local Medical Monitor, utilizing a 5-grade scale and reviewed by the local Medical Monitor. Each event will be assessed by the Medical Monitor for its relationship to study participation according to the guidelines listed in the Manual of Procedures. The Site PI is required to review all AEs and SAEs prior to submission to his IRB.

Any serious adverse event will be reported to the Offices of Human Research at the clinical site of the SAE following their local site's guidelines. The site of the SAE will immediately contact the SDCC project manager, faxing the SAE and Potential Treatment Failure Report form. Also, the site of the SAE enters the SAE CRF into the DMS. The project manger will report the SAE to the study-wide medical monitor, each site PI, the DSMB Chair, and the NHLBI Program Scientist within 14 days of being informed by the site of the SAE for SAEs unrelated to the study and within 7 days for SAEs related to the study.

All adverse events will be reported to each IRB according to its own requirements. In order to appropriately monitor the study, all adverse events need to be reported to the SDCC by completing the Adverse Event form within one month of its occurrence.

In addition to completing the web-based Adverse Event forms, a signed copy of each Adverse Event/Serious Event form completed according to each site's local IRB needs to be provided to the SDCC.

Follow Up of Adverse Events

The clinical course of each adverse event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The Study staff will follow every AE to a satisfactory outcome or stabilization of the event, even when this requires a time period beyond the scope of the study. The Study Coordinator will record each AE outcome on the case report form.

Post-study Adverse Event Follow Up: All unresolved adverse events should be followed until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that they believe may be related to participation in this study.

SAEs that are ongoing at the end of the study period must be followed to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

3.6.4. Participant Assessment

The Study Coordinator with the assistance of the local Medical Monitor should assess each participant for adverse events (AE) throughout study participation. This

includes conducting a thorough investigation on any suspected AE that may come from a variety of sources:

- Spontaneous reports by participant
- Observations by key study personnel
- Reports to study staff by the participant's family or medical care providers
- Possible AE documented in medical records, progress notes, etc.
- Death of participant

In addition to receiving reports of potential AEs, the Investigator and Study Coordinator should develop and implement a plan to consistently and routinely monitor for AE through proactive measures such as:

- Interview participants
- Review lab reports
- Review participant's medical records for additional information
- Communicate with participant's medical providers

This phase will extend until the 9 month Research Visit (or 18 month visit for the long term follow-up subgroup) has been completed, data has been received/collected and entered into the Data Management System.

3.6.5. Summary

AE information will be collected after informed consent signing, and at all visits and interim phone contacts. Pre-existing condition information will be collected by the study staff at the screening visit and at the Baseline visit on the Health Questionnaire. Any AE related to the worsening of a pre-existing condition will be recorded on the AE case report form.

3.7. Medical Alerts- Immediate and Urgent Referrals

3.7.1. Background and Rationale

Certain findings made at the time of the Research Visits or identified during home physiology monitoring –may require medical intervention. The system that has been established is based on the urgency of the finding – either IMMEDIATE (requiring review by a study physician prior to the participant leaving clinic or within 24 hours for laboratory findings), or URGENT (requiring review by a study physician within the next business day). The study physician will be responsible for informing the subject of the finding and developing a plan of action with the subject.

3.7.2. Documentation of Medical Alerts

During the research clinic visit, the examiner will indicate on the applicable forms whether any alert conditions were observed. In the event of any alert condition, a Medical Alerts form is completed, in order to document what, if any, action was taken. There is one alert form for the Study: Research Study Visit Alerts. All forms should be entered into the DMS once verified by local Medical Monitor review.

Similarly, during review of the physiology monitoring (polysomnography or PSG, 24-hour blood pressure monitoring, and overnight oximetry) downloads, the technician will indicate on the "Signal Verification" form whether any alert levels were observed. In case any adverse events are observed during the signal verification process, a "Medical Alerts" form will be completed. This information will be transmitted to the Study Coordinator for updating of the Research Study Visit Alert form.

3.7.3. Immediate Alerts

Immediate alerts are potential emergencies which may require immediate treatment of the participant to prevent serious harm. These are findings made at the time of the Research Clinic visit. Because the research assistants/coordinators are neither trained nor licensed to perform clinical diagnostic assessments, all Immediate Alerts will be referred by the technician to the on-call study physician. This physician, based on information obtained from the technician and/or the participant, will determine whether immediate treatment referral is indicated. Participants receiving immediate referrals are those who would be advised to go directly to their physician or to a hospital or emergency room. With the participant's consent (obtained verbally at the time of the alert), the study physician would contact the participant's referring physician directly. In addition, if referral is indicated, a letter will be sent to the participant's physician (with permission), documenting the event and action, with a "cc" to the participant. Each site will develop an "on-call" list of study physicians available to review Immediate Alerts (e.g., the P.I., Co-I., and local Medical Monitor).

Findings requiring an Immediate Alert at the time of the Research Visits or when laboratory results become available:

- **Blood pressure** (awake, seated, average of the last two readings)**:**
  - Systolic blood pressure ≥ 210 mm Hg
  - Diastolic blood pressure ≥ 120 mm Hg
- **Blood pressure** (mean of 24-hour ambulatory recording)**:**
  - Systolic blood pressure ≥ 210 mm Hg
  - Diastolic blood pressure ≥ 120 mm Hg
- **Heart rate** (awake pulse):
  - >140 beats/min at rest
  - <40 beats/min at rest
- **Overnight Sleep Study**:
  - New atrial fibrillation/flutter
  - Ventricular fibrillation or persistent ventricular tachycardia (more than 2 minutes)
  - Any symptomatic arrhythmia
- **PHQ-8:**
  - Score ≥ 15
- **Blood glucose:** ≥ 300 mg/dL

3.7.4. Urgent Alerts

Urgent alerts are related to abnormalities detected at the time of the clinic visit or PSG download, or upon subsequent review of the physiologic monitors (PSG, 24-hour BP, overnight oximetry) which may require medical attention but generally not on an emergency basis. A study physician (P.I., Co-I., local Medical Monitor) will be charged with reviewing these no later than the next business day following the observation of the alert condition. This physician, based on information obtained from the technician and/or the participant, will determine whether referral for further evaluation and/or treatment is indicated. If referral is indicated, the subject will be informed of the findings by telephone or in person by a study physician. In addition, if referral is indicated, notification of the participant and his/her physician (with permission) should be sent by mail within 10 days. However, certain urgent referrals may require more immediate attention at the discretion (and responsibility) of the study physician. If the study physician judges the condition to require more immediate attention, he/she has the responsibility of contacting the participant directly by phone to seek consent to notify the participant's referring physician about the condition. If the participant refuses, then the study physician should minimally refer the participant to the ER and/or provide a listing of specialists (e.g. bariatric surgeons or sleep specialists) the participant could contact for immediate medical care.

- Findings requiring **urgent referral** at the time of the Baseline or 9 and 18 month visit or when reviewing physiology monitoring downloads:

  - **Triglyceride level:** ≥ 1000 mg/dL
  - **In a non-diabetic, Blood glucose:** ≥ 126 mg/dL
  - **In a diabetic, Blood glucose:** ≥ 200 mg/dL

  - **Blood pressure** (awake, seated, average of last two readings):
    - Systolic blood pressure ≥ 180 mm Hg (but < 210), OR
    - Diastolic blood pressure ≥ 110 mm Hg (but < 120)
  - **Blood pressure** (mean of 24-hour ambulatory recording):
    - Systolic blood pressure ≥ 180 mm Hg (but < 210), OR
    - Diastolic blood pressure ≥ 110 mm Hg (but < 120)
  - **PHQ-8:**
    - Score ≥10 (but < 15)
  - **Overnight Sleep Study**:
    - Previously known atrial fibrillation/flutter but HR>120 or HR<50 for 2 minutes duration
    - Heart rate ≥150 or ≤30 (no a-fib/flutter) for 2 consecutive minutes
    - Mobitz type II AV block or 3rd degree heart block
    - Non-sustained ventricular tachycardia (3 beats duration at rate>120) (upon review of study)

3.8. Treatment Failures

Treatment Failures are defined as changes in health status that require an alternative treatment for OSA to that in the assigned arm. As a change in health status, Treatment Failures are a subgroup of Adverse Events. Examples may include the occurrence of new drowsy driving in a participant in the CPAP or bariatric arm, which the Medical Monitor considers to warrant attention; or subjects in the bariatric arm who are deemed to be at more than low surgical risk after pre-operative screening. Potential Treatment Failures are identified by the study staff as part of interim monitoring with the assistance of the local Medical Monitor and reported to the Central Safety Monitor who will adjudicate these. If an event is adjudicated to be a Treatment Failure, the local Medical Monitor and Study Coordinator will make appropriate referrals to ensure alternative treatment is begun in a timely manner. The “Serious Adverse Event and Potential Treatment Failure Report” should be completed.

Chapter 4

4. Participant Considerations

4.1. Confidentiality

4.1.1. General Information

Extensive efforts will be made to ensure and maintain participant confidentiality, except as may be required by law and/or institutional regulations. All identifying information ***must*** be maintained in a secure area at all times and ***must never*** appear on CRFs. Consent form(s) and source documentation ***must*** be maintained in a separate folder from the CRFs. If source documentation has to be made available for data audits, copies of the source documents should be forwarded to the SDCC with only Study ID number visible and personal information obscured.

The SDCC staff have access to the *Study ID* number for data management purposes. All communication between the SDCC staff and the Clinical Center staff regarding participant data occurs via the *Study ID* number. All CRF's and source documents sent to the SDCC ***must*** have all participant identifiers, other than the *Study ID* number, obscured. However, never obscure information on the original/source documents. The staff at the SDCC ***will not*** have access to any participant locator or identifying information available to the clinical center.

4.1.2. Assignment of Study ID

At the time of screening, potential participants will be assigned a Study Identification (Study ID) number based on the Study ID Log. This log is an administrative form developed in advance by the SDCC for each clinical center. The form includes a column with hard-coded Study ID numbers and a blank column for participant name, namecode, and the date of consent. Each new participant is to be assigned the next available Study ID number.

The Study ID is a 5-digit number that is a unique identifier for each study participant and will only be used once regardless of participant status (screen failure, enrolled, lost to follow up, withdraw, etc.). Each Study ID begins with the 1-digit Clinical Site ID number follow by a 4-digit participant number (refer to sample log below).

The Namecode, an alphabetic code comprised of the first two letters from the participant's first name and the first two letters of the last name, will also be used as an additional identifier for quality control purposes.

All communication regarding individual participants must be through the Study ID number. Once a Study ID number has been assigned, it should never for any reason be reassigned. The Study ID Log form should be stored in a secure, locked

filing cabinet. A backup copy of this log should be made at the end of every other week and the copy stored in a separate, secure location.

Study ID Assignment Log Example (BWH site 1 is used in this example):

Study ID	Participant's Name (First, Last)	Namecode	Date Consent Signed
11001	*Jonathon Doe*	*JODO*	*11/25/2009*
11002	*Kimberly Lacy*	*KILA*	*11/27/2009*
11003	*Terry Church*	*TECH*	*11/30/2009*

4.2. Eligibility Criteria

4.2.1. Rationale

We have targeted a sample of patients ages 18-65 with severe OSA (AHI ≥30) with at least one symptom referable to OSA and class II obesity (BMI 35-40 kg/m^2) since this is a population at risk for co-morbidities including heart disease and other life-threatening diseases. Patients will be excluded who have previously used CPAP for the treatment of OSA or who have previously undergone bariatric surgery, have severe sleepiness as evidenced by any history of drowsy driving in the past year, have co-existing hypoventilation syndrome (baseline oxygen saturation <90% or documented daytime hypercarbia), esophageal dysmotility or other anatomic disorders precluding LGB, or have disorders that increase peri-operative surgical risk:[29] active smoking in the past 3 months, prior history of venothromboembolism, history of coronary artery disease or heart failure, or poor functional status (inability to walk 200 feet). In addition, individuals who cannot provide informed consent themselves or who have other unstable medical or psychiatric conditions that might reduce ability to complete the study protocol or raise surgical risk will be excluded Because tonsillectomy is the first line treatment of choice for pediatric OSA, children will be excluded from this study. Due to the increased morbidity of bariatric surgery as well as unclear evidence for any therapeutic benefit of treatment of OSA in older populations, the elderly will similarly be excluded.

4.2.2. Inclusion Criteria

1. Age 18-65 years
2. Key criteria for the project
    a) Severe obstructive sleep apnea defined as AHI ≥30 with at least 1 symptom (e.g., snoring, sleepiness, fatigue, frequent awakenings, morning headache)
    b) Class II obesity (BMI 35-40 kg/m^2):
3. Ability to provide informed consent

4. Seen in one of the Sleep Disorders Clinics diagnosed with severe OSA
5. Patient and physician have equipoise about randomization to either treatment arm.

4.2.3. Exclusion Criteria

1. Prior treatment with CPAP for OSA
2. Prior bariatric surgery
3. Has co-existing hypoventilation syndrome (baseline oxygen saturation <90% or documented daytime hypercarbia)
4. Disorders that increase peri-operative risk
    i. Active smoking in the past 3 months,
    ii. History of venothromboembolism
    iii. History of coronary artery disease or congestive heart failure
    iv. Poor functional status (inability to walk 200 feet)
5. Disorder of esophageal dysmotility or other anatomic disorder impacting LGB placement
6. Severe sleepiness (e.g. drowsy driving within the past year)
7. Pregnancy (or intention to become pregnant in the next year)
8. Other unstable medical or psychiatric conditions (e.g., renal failure, cirrhosis, active malignancy)

4.2.4. OSA Eligibility Criteria

In order to be eligible for the study participants must have been diagnosed with severe sleep apnea:

- An apnea hypopnea index (AHI) ≥ 30 with the majority of events obstructive in nature. This diagnosis should be made on polysomnography with a minimum of 2 hours of total sleep time and using AASM criteria for definition of a hypopnea.

- At least one symptom referable to the sleep apnea. This includes but is not limited to: bothersome snoring, daytime fatigue or sleepiness, unrestful sleep, frequent nocturnal awakenings, and morning headaches.

4.2.5. Deferral Criteria

There may be some situations or conditions for which a participant will be found ineligible for participation because of either a temporary exclusion or an unclear history about an exclusion criterion. In these cases, rather than being excluded, the subject will be deferred from entry into the study. Once it is formally ascertained that the exclusionary condition is not present or has resolved, the participant will be reconsidered for entry into the study. The following list identifies some of the conditions for deferment:

1. Subjects currently enrolled in another intervention study.
2. Subjects who have received an investigational drug or device within 30 days prior to screening will be deferred until off study for a period of at least 30 days.
3. Participant requests additional time to consider treatment options.
4. Participant has an uncontrolled medical problem and can be deferred until determined stable by physician (e.g., having quit smoking for 3 months).

Some participants may be poor historians and/or have a limited understanding of their health problems and associated treatments. For those questions which are denoted in your records as reported by participant, it is advisable that the response be verified with a medical record/report whenever possible.

Each site should establish a tracking system for deferred cases to serve as an administrative tool and will not be entered into the DMS. Since this will contain identifying information, it should be kept separate from other files in a locked, secure cabinet. Once a deferred subject is entered in the study, the study is over, or if information arises that disqualified the subject from entering the study, any identifying information on these subjects is destroyed.

To determine the re-screening date for a participant who has been deferred for more than one criterion, the coordinator will select one date that allows sufficient time for all deferral criteria to have been resolved. The coordinator should contact the participant by telephone close to the ending date of the deferral period which in most cases will not be more than 30 days to:

- Review the study with the participant
- Determine whether the deferral condition is resolved if applicable
- Ascertain if the participant is still interested

4.2.6. Screen Failures

A participant who does not complete the screening procedures for whatever reason will be considered a screening failure and will not be randomized to the trial. For example, a participant who goes through the screening visit, meeting with the study internist and surgeon and does not return for the baseline visit will be considered a screening failure.

Potential participants who do not meet <u>one or more</u> of the following criteria are considered *screen failures* and will not be enrolled (randomized) into the study:

- Does not meet all inclusion and exclusion criteria on the Eligibility form
- Does not have established equipoise to be randomized to participate in either CPAP or LGB surgery

4.2.7. Baseline Failures

A participant who does not complete baseline procedures for whatever reason will be considered a baseline failure and will not be randomized to the trial. For

example, a participant who goes through the overnight sleep study visit and decides not to participate will be considered a baseline failure. Additionally, a patient who decides that they would prefer to have gastric bypass or sleeve gastrectomy instead of LGB surgery at this point will be considered a baseline failure.

A participant who is randomized to one treatment and only then decides that they would like to participate in the other treatment will not be considered a baseline failure but rather be considered a treatment failure for the assigned treatment and a cross-over.

4.2.8. Bariatric Intervention Failures

In the LGB Group, subjects who did not lose a targeted amount of weight during supervised weight management (usually a minimum of 10 pounds, determined during the initial surgical assessment) will be considered an inappropriate surgical candidate (per routine clinical practice) and not be offered surgery. These subjects will be deemed surgical treatment failures.

Subjects who are deemed to be at high operative risk on pre-operative evaluation (e.g., active cardiac ischemia) will also be deemed surgical failures. Patients who are surgical treatment failures will be offered CPAP (i.e., “crossed over to the alternative study arm”).

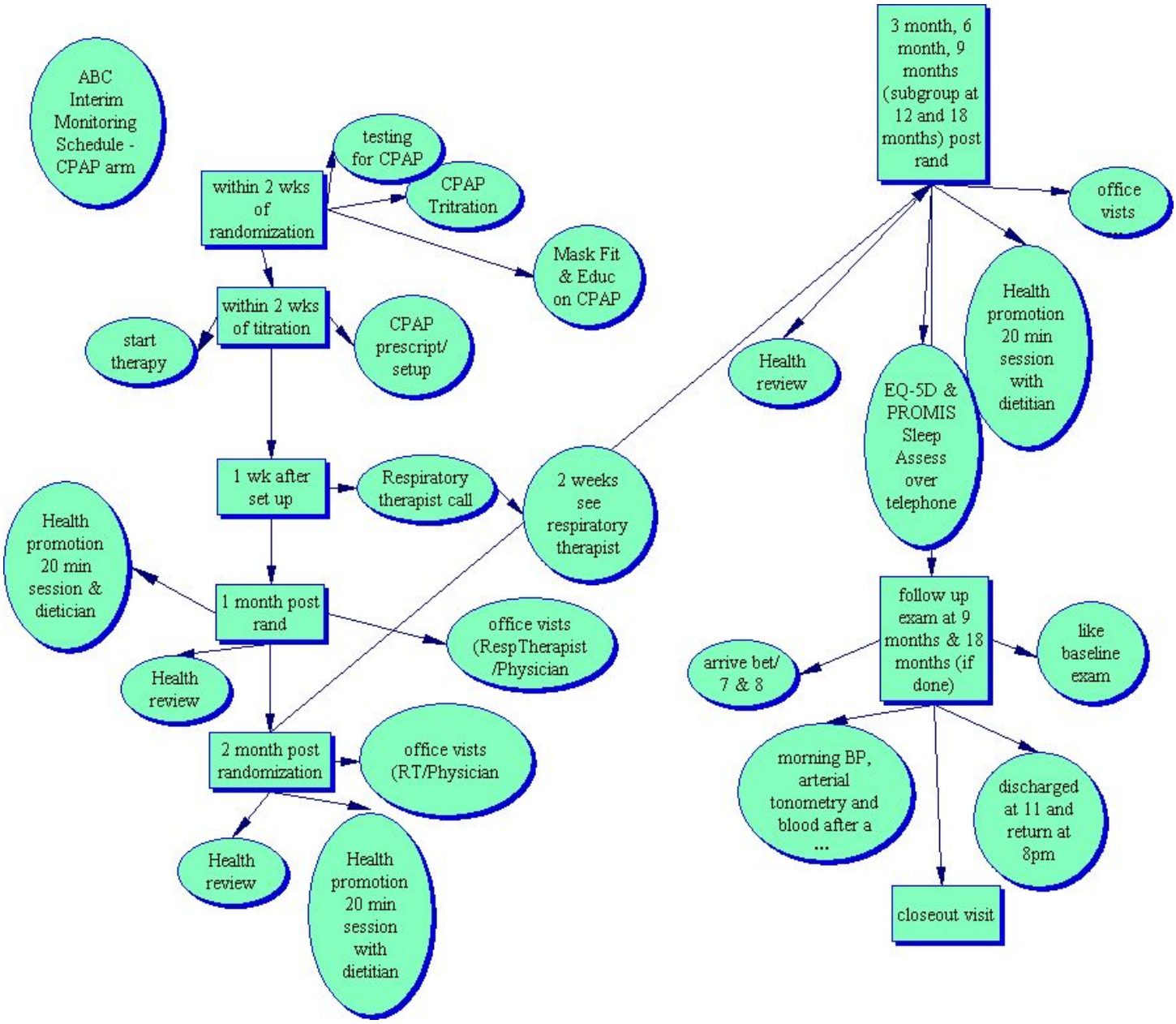
4.3. Interventions

4.3.1. Baseline

After the screening visit and once eligibility and equipoise are confirmed, the participant will be scheduled for a baseline health assessment which includes an overnight exam in the inpatient Clinical Research Unit (CRU). The subject will arrive at the CRU in the evening, have blood pressure measured and complete a battery of questionnaires and a standardized overnight polysomnogram (PSG) ensuring comparable OSA data on all participants. At 7 AM the following morning, participants will be awakened and blood pressure will again be measured and anthropometry performed. Morning urine and fasting venous blood samples will be obtained. Radial artery tonometry will be performed to assess arterial stiffness as well as pulse wave velocity. An ambulatory BP monitor will be placed on the patient’s non-dominant arm and they will be asked to wear this device for 24 hours. The BP monitor will be removed the next day by the subject and returned by courier or direct retrieval. All measurements will be made by CRU staff blinded to treatment assignment.

Prior to discharge from the CRU, participants will be scheduled to meet with a research staff member trained to provide health counseling. She will provide Lifestyle Modification education consistent with good clinical practice. Lifestyle intervention will consist of three components: diet, exercise, and sleep optimization. Education in these areas will be standardized, with use of a common protocol, educational brochures, diet diary, work sheets, and a customized slide show.

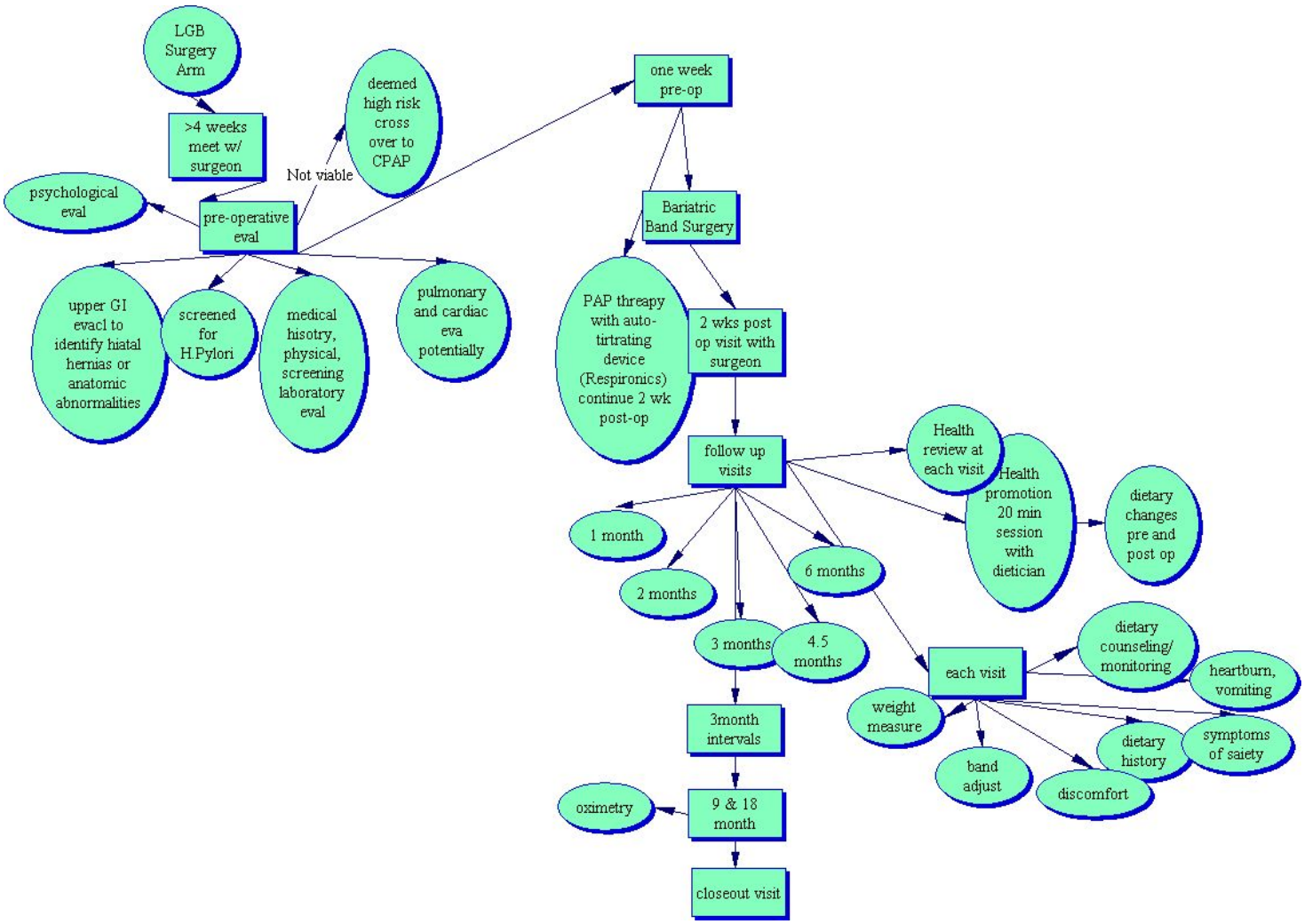
4.3.2. CPAP Group



CPAP arm will undergo a CPAP titration within 2 weeks of enrollment unless a split-night study was already performed as part of their diagnostic polysomnogram (PSG) providing a reliable CPAP therapeutic pressure. As soon as an appropriate pressure is identified, CPAP therapy will begin with routinely scheduled follow-up visits to maximize CPAP adherence.

Participants will be educated on the use of CPAP and will have an opportunity to try various CPAP mask interfaces in order to optimize fit. Verbal and written directions on the use of these materials will be provided, with instructions reinforced after the initial period of CPAP titration is completed, and then at interim telephone calls and health promotion visits. Participants will be prescribed nasal CPAP (Respironics, Murrysville PA) therapy with a heated humidifier within 2 weeks of the CPAP titration study. If the results of the titration study suggest a pressure greater than 20 cm H2O is required to maintain airway patency, a bi-level PAP device will be prescribed as per the titration study recommendations. All PAP machines will contain Smart Cards© or will contain software (Encore Anywhere©) that allows remote monitoring of PAP use through daily electronic transmission of PAP pressures to a secure central server. This will provide the means to monitor residual events as well as PAP usage/adherence. The PAP machines will also have the option for a ramp and expiratory pressure release (C-flex, Philips-Respironics) to be used as needed to improve adherence. Participants will receive CPAP support as per routine care, including a follow-up phone call or visit to a respiratory therapist at one week to address early CPAP issues and follow-up visits with a respiratory therapist and/or physician as per standard of care guidelines at each clinical site. At or prior to each visit, CPAP usage data will be downloaded and reviewed and adjustments to equipment (mask replacement, use of chin strap, addition of expiratory pressure release) will be performed as needed to improve adherence per standard care. Decisions about changes in prescribed PAP settings including level of pressure, switch from CPAP to bi-level PAP and/or re-titration of pressure requirements will be made by the clinicians caring for the patient independent of the research team although information about any such changes will be collected as part of this study.

4.3.3. LGB Group



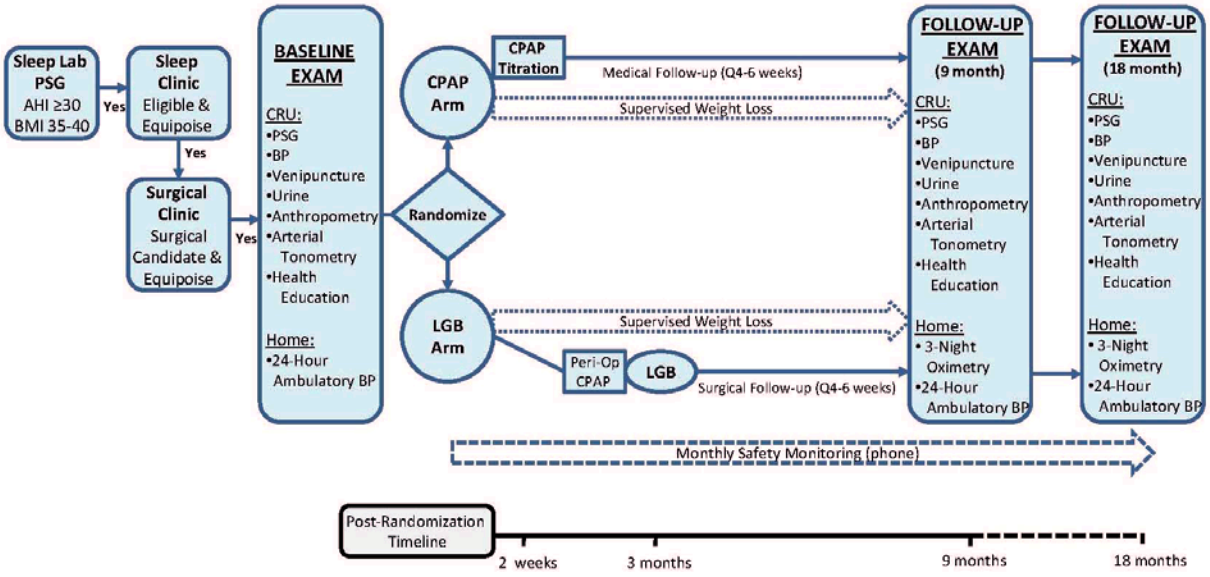
Participants randomized to surgical therapy will be scheduled for additional pre-operative assessments per routine clinical guidelines that will include screening laboratory evaluation (chemistry and hepatic panel, TSH, PT, vitamin D and B12 levels, ferritin levels). Further pulmonary, cardiac or psychiatric evaluation may be required based on initial evaluation, as per routine care and will be handled according to routine clinical procedures. In addition, and according to routine clinical procedures, subjects will undergo an upper GI evaluation to identify hiatal hernias and other anatomic abnormalities and be screened and treated for H. pylori. Participants will also meet with a registered dietician on a regular basis through the pre-, peri-, and post-operative periods out to 12 months as is standard of care for the bariatric programs at both sites. This will be to review specific dietary changes required for success of LGB in addition to general weight loss counseling which will be provided in both arms by the study Health Promotions Counselor.

Within three weeks of surgery, patients will be scheduled for a routine pre-operative visit with the bariatric surgical team to document that weight gain did not occur and to assess adherence to lifestyle recommendations and to ensure that new medical issues did not arise. Two weeks prior to surgery, subjects will begin a liquid diet as prescribed by the dietician to reduce liver size and facilitate laparoscopic surgery. One week prior to surgery, the subject will begin PAP therapy with an auto-titrating PAP device and continue this treatment until the 2 week post-operative evaluation. Subjects will undergo laparoscopic adjustable gastric banding with the LAP-BAND (Allergan) under general anesthesia. Patients will be extubated in the operating room to CPAP. Post-operative pain will be treated with intravenous narcotics until oral medications can be administered. Post-operative care will follow standards of care including a one night planned hospitalization and a planned 1 week recuperative period at home. Subjects will be seen between 2 and 3 weeks post-operatively by the surgeon to ensure proper wound healing and functioning of the band. Follow-up visits with the bariatric team per routine care at each clinical site will then occur roughly at 2 months, 4 months, and 6 months post-operatively corresponding to months 5, 7, and 9 in the study (and in study months 11, 13, and 15 in the long term follow-up subset). Additional follow up visits will be scheduled on an individual basis according to routine care. Decisions about adjustments to the band will follow standard guidelines. At each visit, dietary history will be obtained, symptoms of satiety as well as heartburn, vomiting, and discomfort elicited and weight measured. Fluid addition to the band will be considered if the subject reports rapid loss of satiety after meals, increased volume of meals, hunger between meals, or a weight loss less than 0.5 kg/week. Fluid removal will be considered if the subject reports restrictive symptoms, maladaptive eating behaviors, or weight loss in excess of 1.0 kg/week. Participants will continue to receive nutritional counseling by the bariatric dietician for up to one year of follow-up to reinforce the personalized dietary plan and identify barriers to achieving sustained weight loss. Dietary counseling will address the specific dietary changes required pre- and post-operatively. In addition, monthly calls from the Health Promotions Counselor for the duration of study participation will be used to supplement dietary counseling and support.

Chapter 5

5. Study Flow

5.1. Overview of Study Flow



5.2. Participant Recruitment

5.2.1. Participant Population and Recruitment

This study will recruit participation of adult patients, 18 to 65 years of age with severe Obstructive Sleep Apnea (OSA) with Apnea-Hypopnea Index of AHI ≥ 30 and BMI 35-40. kg/m^2 with at least 1 symptom referable to their OSA (e.g., excessive daytime sleepiness, frequent awakenings, bothersome snoring, or morning headaches). The diagnosis of severe OSA (AHI≥30) requires laboratory PSG with at least 2 hours of sleep time recorded either on a full night diagnostic study or on the diagnostic portion of a split night study. Patients will be recruited from Sleep Health Centers (SHC), a multi-site private clinical comprehensive sleep medicine program affiliated with

the Brigham and Women's Hospital as well as the sleep disorders clinics at Beth Israel Deaconess Medical Center.

5.2.2. Sources of Referral

Research staff will review all new sleep studies at the clinical sites and identify patients meeting major inclusion criteria (age 18-65 yrs, AHI ≥ 30, BMI 35-40). The patient's sleep physician will be contacted by study staff to let them know of the potential eligibility for this study. The physician will be asked to determine whether they feel the patient would be appropriate for this study (there is equipoise on the part of the patient's physician about the two treatment options). Subjects whose physicians agree that he or she may be appropriate for the study will ask the subject whether he or she would be willing to speak with the study recruiter to learn more about the study.

5.2.3. Recruitment Procedures

The Research Coordinator (RC) will oversee recruitment efforts at the two clinical sites. This will involve:

1. To enhance awareness about the ABC study, IRB approved protocol-specific materials which consists of a brochure will be distributed to potentially eligible subjects. These materials can be mailed or provided to patients and families during a clinic visit. These also will be disseminated at the clinics targeted for recruitment. In addition, prior to beginning recruitment, the site PI will present an overview of the study to the sleep clinicians at their site to make referring physicians aware of the study.
2. Equipoise (willingness to have the patient participate in either arm) will be ascertained for the referring physician at the Sleep Clinic visit as well as whether the patient would be interested in participating.
3. Subjects whose physicians agree that he or she may be appropriate for the study will be asked by their physician if they would be willing to speak with the study recruiter to learn more about the study. If agreeable, the subject will meet with the recruiter at the time of the sleep clinic visit or arrangements will be made to meet with the subject at a separate time or over the telephone. Some patients may be referred for sleep studies and a sleep consultation (but not OSA management). In those cases, the referring physician also will be contacted to ascertain permission to contact the patient for study enrollment.
4. At the initial interview, a study recruiter will explain the two treatment arms and protocol requirements. This explanation will include review of study brochures and a slide show that will present each treatment (CPAP and LGB), as well as other potential treatment options including other bariatric procedures not offered in this protocol (such as gastric bypass and sleeve gastrectomy). In addition, more detailed information will be gathered from interview following an IRB-approved script as well as medical chart review to determine eligibility. This should be done to ensure not only the participant's *preliminary* eligibility, but also his/her willingness and ability to meet the demands/responsibilities of the study.
5. Obtaining informed Consent. Those individuals who appear to meet eligibility criteria and appear interested and willing to participate will be scheduled for a screening visit. This visit will be scheduled to include meetings with the Study Coordinator/Health

Promotion Counselor, a Study Sleep Physician, and a Study Bariatrician (either medical or surgical). At this visit, the study protocol including the two treatment arms will again be reviewed in detail with the potential research subject. Details about the pros and cons of CPAP therapy will be reviewed by the Study Sleep Physician and pros and cons of LGB surgery will be reviewed by the Study Bariatrician. Detailed medical history will be elicited by the study physicians to confirm eligibility and clinical equipoise in the minds of both the Sleep Physician and Bariatrician. Once all questions are answered, clinical equipoise in the mind of the subject will be confirmed by the Study Coordinator. Only at this point will informed consent be obtained.

6. At each of these potential recruitment points, data collection forms will be used to capture the reasons for ineligibility or patient/physician preferences. This will be critically important in assessing the recruitment pipeline and specific eligibility issues that would impact future trials and to best understand perceptions of equipoise.

7. Scheduling the Baseline Visit. Subjects meeting the criteria (ages 18 to 65 years of age with severe Obstructive Sleep Apnea (OSA) with Apnea-Hypopnea Index of AHI ≥ 30 and BMI 35-40 kg/m^2) will be scheduled for a baseline visit where additional data are collected. At the conclusion of this Baseline visit, the subject will be randomized to one of the two treatment arms, as described below. Visits should be scheduled within 2 weeks of confirming eligibility and obtaining consent.

5.2.4. Recruitment Methods

Physicians who evaluate patients at the sleep clinic will ascertain whether the patient seems eligible and interested in the study. If the patient is interested in hearing more about the study, they will speak with a study coordinator or recruiter who will be available at the clinic visit or will arrange to meet the subject at a separate time). Additionally, once the sleep physician has given permission to contact the patient, a letter briefly introducing the study will be sent to the patient along with the Study Coordinator's contact information.

Successful recruitment and retention is critical for the success of this trial. Each of the Clinical Sites has a recruitment goal of 40 participants **over a two year period or a recruitment rate of 1-2 subjects per site per month.**

Recruitment data will be monitored by the SDCC in order to continually assess recruitment rates at each site and to monitor deviations from projections. Sites which fail to meet projections for 2 consecutive months will be asked to provide a report, with an analysis and action plan to the Steering Committee. If continued lags are observed alternative(s) will be discussed with the Executive Committee.

Each clinical center is responsible for determining how best to recruit participants from its local population. Other recruitment methods are described below:

Investigators' Own Clinical Practice: Potential participants can and will be identified by considering the current participant population at an investigator's practice. The success of this method depends largely on the number of participants who are potentially eligible and interested in the study. When considering this as a source of recruitment, investigators should not only evaluate how many participants will meet the study criteria, but also what percentage will be willing to participate in and comply with the study protocol.

Referral from Medical Practices of Other Physicians: In order to facilitate participation from multiple referral sources (Sleep Clinics), the PI/Co-I at each site must maintain contact with his/her colleagues. Access to patients in large clinical populations and excellent relationships with colleagues will facilitate research responsiveness (or equipoise).

It is also likely that each clinical center will need to rely on the referral of potential participants from the medical practices of other physicians to supplement enrollment from their own practice. In order to succeed, this method of recruitment requires the support of colleagues more than any other method. If potential referring physicians are not advocates of the study the number of referrals will be minimal, and the method not reliable for recruiting participants. Each site PI/Co-I is encouraged to present the study regularly at scientific or other meetings held at collaborating practices.

Recruitment Materials for Potential Participants: Clinical centers will use a variety of IRB-approved materials for recruitment. In general, these are materials that will be developed with input from the Steering Committee, and may be modified for local use. Modifications should be submitted to the SDCC for review to ensure the study is presented fairly and equipoise is not disturbed. Recruitment materials include brochures, flyers, or advertisements that can be used in a variety of settings (e.g. clinics, sleep lab, educational or promotional events) and/or may be mailed to potentially eligible participants. An educational slide show that describes each intervention, its potential side effects and role in treatment of obesity and sleep apnea will be shared with potential participants during pre-screening and the screening visit. The material will be designed to describe the trial and participant study requirements as simply but accurately as possible and should include the name and contact number of the research coordinator (RC) and/or study PI. Recruitment materials designed with the purpose of circulating to potential participants must be approved by each respective local IRB prior to use, with a copy of the approved material sent to the SDCC.

5.2.5. Recruitment Tracking

The Steering Committee and its Operations Subcommittee will oversee recruitment efforts. The Operations Subcommittee will include participation by the Study Coordinator and study recruiters. It will meet twice a month to share ideas to potentially enhance overall recruitment, to discuss recruitment challenges and to share recruitment strategies.

The Study Coordinator will also be responsible for maintaining records of all recruitment efforts and track these with locally maintained files. For every record which is systematically reviewed, an Eligibility form will be initiated and these data entered into the RedCap database. Sufficient data will be collected to provide reporting of the status of subjects approached for recruitment according to the Consolidated Standards of Reporting Trials Statement [CONSORT].[18] Eligibility forms should be entered within one week of their data collection, and entered regardless of the participants eligibility status (participant does not have to be randomized to enter these data).

This report will be officially reviewed by the Steering Committee on a monthly basis and more frequently if recruitment milestones are lagging behind.

5.2.6. Retention

The success of this study requires that 80% or more eligible participants complete the study. We expect to have 64 individuals completing the 9 month follow-up exam (32 in each arm) and 40 completing the 18 month follow-up exam (20 in each arm).The Steering Committee and its Operations Subcommittee will also oversee retention. Ideas for maximizing retention with

appropriate incentives, collecting multiple alternative contacts (name and phone number), etc. will be shared. Sites which experience greater attrition will be identified through monthly reporting to the Steering Committee which will identify procedures for remediation.

If any given site consistently fails to meet recruitment or retention goals, the study PI (Dr. Patel) in consultation with the NIH will prepare a plan for reallocating funds to ensure that study-wide goals are met.

5.3. Screening Contact and Data Collection

5.3.1. General Information

Sites may mail out brochures to research database populations after physician's agreement that the patient is an appropriate candidate, or meet with patients in person at clinic visits.

The Screening Phase of the study consists of the following which could occur at one time or in steps:

- Initial contact with participant to complete screening, ascertain interest, and determine eligibility.
- A Sleep Physician and Bariatrician have met with the patient and each has determined clinical equipoise regarding the specific subject's potential randomization to either study arm and study eligibility
- Presentation of an educational slide show that clearly presents the benefits and risks of both treatments – CPAP and LGB surgery.
- Additionally the participant will work with the Study Coordinator to fill out a decision support tool for their own use to determine their information needs, review their expectations, and how participation in either of the arms fits with their needs and values
- Establishing equipoise
- Informed consent completed
- Status of participant should be updated in RedCap.

5.3.2. Screening visit

Pre-screening may be conducted in the clinic or over the telephone according to institutional guidelines. If pre-screening determines that the potential participant is eligible and willing, the research staff will schedule a screening visit with a Study Sleep Physician and Study Bariatrician and a time to view the educational presentation that clearly reviews the treatment arms and the benefits and risks, work through a personal decision tool, and complete the informed consent.

In addition to the pre-screening summary data, sites will be requested to track weekly recruitment efforts based on inclusion/exclusion parameters.

5.3.3. Screening visit components

The following may apply:

- For participants who had been asked to participate, if during the screening process it is determined that the participant is ineligible for the trial, the participant must be informed as soon as possible.

- Study staff will review with participants, standardized brochures and a power point presentation that describes each intervention, its potential side effects and role in treatment of obesity and sleep apnea. This is intended to ensure that participants are fully educated and they themselves have equipoise regarding potential randomization.
- Once determined eligible and interest is established, the informed consent process must take place prior to the baseline visit and before any study related data collection/testing.
- Potential participants must meet eligibility criteria before undergoing the baseline visit and randomization.
- A participant who is initially deferred from entry based on the deferral criteria may be reconsidered for inclusion at a later date, if the condition(s) **stabilizes** based on a physician evaluation.
- The participant ID number will not be re-assigned for any reason.

5.3.4. Educational materials and slideshow

The Study Coordinator will review with the participant a 10 to 15 minute slide show (Appendix J) that describes each intervention, its potential side effects and role in treatment of obesity and sleep apnea. The study coordinator will sit down with the participant at a computer and go through each slide explaining the information. The purpose of the slideshow is to present a balanced view of the risks and benefits for each treatment arm, address questions as they come up, and ascertain that the patient's expectations are realistic. The Study Coordinator will also provide the subject with a Decision Support tool that will help the subject think what additional information they might need, what they see as important regarding the benefits and risks in participating, seeking additional support if needed and creating a list of questions that they would like answered.

5.4. Informed Consent and Enrollment

5.4.1. Overview

Each clinical center is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of its local Institutional Review Board (IRB). The SDCC provides a Template Consent Form (Appendix B). The template language undergoes reviews by the SDCC, Steering Committee and DSMB before being placed into the protocol. Each clinical center should use the template consent language as the basis for preparing their consent as per local IRB guidelines. **The SDCC must approve all local consents to ensure their consistency with the template language prior to being submitted to the IRB.** Each site must also forward a copy of their local consent to the SDCC once it receives IRB approval. The informed consent form must be obtained (signed and dated by the participant) **prior** to initiation of any study related activity. Specifically, the following must be accomplished during the informed consent process:

- The participant must be informed that participation in the study is **voluntary** and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed that the study involves **research**.
- The participant must be informed of any **alternative procedures**.
- The participant must be informed of any reasonable foreseeable **risks**.
- The participant must be informed of any **benefits** from the research.

- An outline of safeguards to protect participant's **confidentiality** must be included, as well as an indication of which parties are allowed to review the record.
- The participant's right to withdraw without penalty. This should be balanced with a discussion of the effect withdrawals have on the study, and the responsibility a participant has, within limits, to continue in the study if they decide to enroll.
- The participant must be informed of his/her right to have **questions answered** at any time. The Study Coordinator should allow the potential participant time to consider the study obligations and discuss the study with his/her family members before signing the consent form.
- The informed consent form must be signed in the presence of a study physician and the Study Coordinator or qualified study staff, prior to collection of any study-related data or blood specimens are performance of study procedures.

An informed consent must be obtained from the participant before any study-related data are collected and study procedures are performed.

5.4.2. Administration of Informed Consent

To confirm a participant's eligibility, the inclusion, exclusion and deferral criteria will be reviewed by a study physician.

Once deemed eligible, the coordinator/study staff will provide the potential participant with the Informed Consent Form and ask the participant to read a few sentences out loud to ascertain whether the potential participant needs assistance with the written material. If the participant cannot read the written material or speak and understand the English language, they are ineligible for enrollment. After the participant has had a chance to ask questions, the consent form must be signed and dated.

The informed consent form should be reviewed in a comfortable setting where the participant is able to make a free choice without pressure. Ample time should be given to allow the participant to thoroughly read, process the information, and ask questions. If the participant wishes to take the Informed Consent home before reaching a decision, they may do so. At the subsequent visit, the coordinator/study staff and/or study physician should answer any questions raised by the participant.

The participant should be made aware of their responsibilities throughout the Screening process, during the baseline visit, after the randomization assignment is known and during the follow up contacts. The importance of continued follow-up should be stressed and balanced with a discussion of the effect of participant withdrawal on the study.

The Informed Consent Form **must** be signed and personally dated by the **participant**, and by the persons "obtaining consent". A participant should not be asked to sign the consent statement if s/he has any doubts about enrolling or if the clinical staff believes s/he does not understand what participation would involve. Under ***no*** circumstance is any study information to be collected or

study procedures performed for the specific purpose of the trial before the participant has signed the informed consent form.

The Study Coordinator will maintain the original consent document in the participant's confidential file with other confidential documentation, and provide a copy of the signed and dated informed consent(s) to the participant who should be urged to retain the document for future reference. A second copy of the informed consent should be made as a back up and stored together in the "study-confidential file". In addition, a signed and dated progress note must be made in each participant's file affirming that the informed consent process took place prior to any study procedures.

To ensure confidentiality, study staff will not send copies of the informed consent form(s) signed by the participant to the SDCC and must keep copies of the informed consent form with the CRFs.

5.4.3. Participant Withdrawal and Withdrawal of Consent

Participants are free to withdraw (or be withdrawn) from the study at any time. There are many reasons a participant may want to do so. They include:

- Adverse Event/Serious Adverse Event (AE/SAE)
- Significant concurrent illness
- Protocol noncompliance
- Investigator's discretion
- Withdrawn informed consent
- Relocation
- Dissatisfaction with treatment
- Loss of interest in the study
- Loss to follow-up

Reason(s) for withdrawal will be documented by the Clinical Center and recorded at the SDCC. For those participants who withdraw (or are withdrawn) due to AE/SAE, the Adverse Event Form must be also completed.

If a participant indicates that they no longer wish to participate in the study (withdraws consent), the Study Coordinator will provide a letter on the institution's letterhead for the participant to sign. If this document is mailed to the participant, it must be sent certified mail. The certified mail receipt should be kept with the participant's records. The letter should contain the following information:

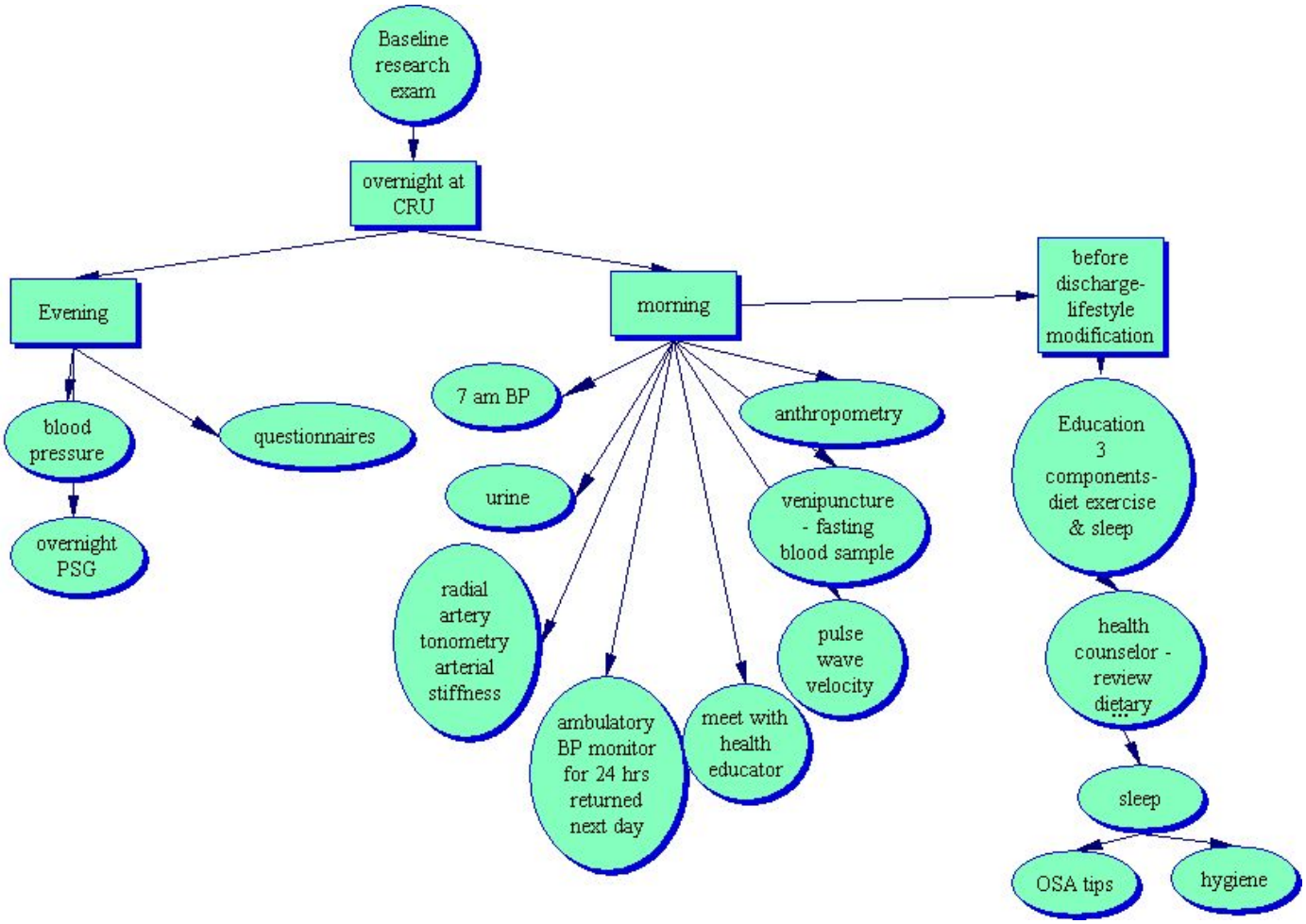
- I voluntarily withdraw my consent to participate in this study.
- I no longer wish to be contacted by the clinic regarding this study.
- I understand that my records will be kept confidential.
- I can continue to receive my regular care and treatment at this clinic.

The coordinator will complete the Participant Withdrawal/Removal form selecting the most representative reason for withdrawal. It should be made clear to the participant that a decision to refuse the assigned treatment or cross-over to the other treatment group is a separate decision from withdrawing from the study. Every effort should be made to encourage participants to

continue with study visits even if they stop treatment early or cross-over to the alternative treatment.

The withdrawal request can be made in person or during a phone contact. Participant data folder must be clearly marked to indicate withdrawal and will be maintained at the clinical center where the participant was recruited and followed. The SDCC Project Manager is informed of the participant's withdrawal, so that the data archival process at the SDCC can be initiated.

5.5. Baseline Visit



5.5.1. Scheduling and Preparation

Following confirmation of initial eligibility and the screening visit, participants will be scheduled for a baseline overnight visit with consideration for any intervening medical illnesses. If the participant has been ill, testing should be scheduled to occur at least 1 week after resolution of an acute illness.

After the screening visit, where eligibility and equipoise are confirmed and initial education on each intervention is provided, the participant will be scheduled for a baseline health assessment which includes an overnight exam at the Clinical Research Unit (CRU).

5.5.2. Orientation

On arrival to the research facility, participant will be introduced to the research staff and provided with a brief tour of the facilities.

The subject will be asked to arrive at the CRU in the evening, have blood pressure measured and complete questionnaires and be hooked up for a standardized overnight PSG (ensuring comparable OSA data on participants in both arms at both sites as well as pre- and post-treatment). At 7 AM the following morning, participants will be awakened and blood pressure will again be measured and anthropometry, spirometry and pharyngometry (using acoustic reflectometry) will be performed. Morning urine and fasting venous blood samples will be obtained. Radial artery tonometry will be performed to assess arterial stiffness as well as pulse wave velocity. An ambulatory BP monitor will be placed on the patient's non-dominant arm and they will be asked to wear this device for 24 hours. The BP monitor will be removed the next day by the subject and returned by courier or direct retrieval. All measurements will be made by staff blinded to treatment assignment. Subjects will be asked to not mention their treatment arm with CRU research staff in order to maintain blinding. The research exam schedule will be:

Evening
6:00PM: Arrive/Dinner
7:00PM: Questionnaire Completion
9:00PM: PSG Hook-Up
10:00PM: Resting Blood Pressure*3
10:30 PM: Lights Out-Sleep Study

Morning
7:00 AM: Lights On/Blood Pressure*3
7:15 AM: Venipuncture
7:30 AM: Urine collection
7:45 AM: Radial arterial tonometry
8:15 AM: Anthropometry
8:30 AM: Breakfast

9:00 AM: Spirometry and Pharyngometry (may be done the prior evening)
9:15 AM: Meet with Health Promotion Educator
10:00 AM: 24 Ambulatory BP Monitor hook-up
10:30 AM: Randomization & Discharge

Lifestyle Modification

Prior to discharge from the CRU, participants will be scheduled to meet with a research staff member trained to provide health counseling. She will provide Lifestyle Modification education consistent with good clinical practice. Lifestyle intervention will consist of three components: diet, exercise, and sleep optimization. Education in these areas will be standardized, with use of a

common protocol, educational brochures, diet diary, work sheets, and a customized slide show. The health counselor will review with the participant his/her dietary history and level of physical activity. All subjects will be prescribed a personalized exercise plan to obtain 180 min/wk of moderate intensity activity such as brisk walking or swimming. Dietary instruction will review caloric needs and goals, methods to track calories, types of foods to avoid, and sizes of reasonable portions of food. It will also review common maladaptive eating behaviors including non-hunger related eating, eating due to stress or other emotions, binge eating and nocturnal eating.

Sleep optimization will include review of good sleep hygiene measures such as ensuring the sleep environment is conducive to sleep, ensuring adequate time for sleep, and keeping a regular sleep schedule. Ancillary treatments for OSA will also be addressed including avoiding alcohol close to bedtime, avoiding sleeping in the supine position, and treatment of nasal congestion if present. Education on the importance of sleep for cognitive performance and psychological well-being as well as findings linking inadequate sleep with obesity risk will be reviewed.

If the CRU has the capability, weekend time slots may be desirable to accommodate the participant's work schedule.

The Study Coordinator will also review next steps, including setting up a clinical appointment schedule based on the assigned treatment arm as well as the schedule of research phone contacts and follow-up research visits. The SC will reaffirm the importance of compliance with therapy and following up on all study phone contacts and the final visit.

5.5.3. Measurements

5.5.3.1. Overnight Oximetry

At the nine month and 18 month follow-up (post-randomization) visits only, participants will be asked to wear a finger pulse oximeter (Respironics 920m Plus, Philips Respironics, Murrysville, PA) for 3 consecutive nights prior to their research visit. The probe clips on a finger and attaches to a battery pack worn on the wrist. The instrument can record for 72 hours and provides the frequency of desaturations per hour at both a 3% and 4% threshold. Further details are presented in Appendix I.

5.5.3.2 Polysomnography

Research polysomnography (PSG) will be performed using the Compumedics E-series system (Abbottsford, AU) which includes 3 cortical electroencephalograms, bilateral electro-oculograms, chin electromyogram (EMG), thoracic and abdominal respiratory inductance plethysmography (by auto-calibrating inductance bands); airflow (by both oro-nasal thermocouple and pressure recording from a nasal cannula); electrocardiography, bilateral leg movements with tibialis EMGs, and finger pulse oximetry, according to AASM criteria.[19] PSG will be performed on the night prior to physiology measurements at the baseline visit for convenience. At the follow-up visits, PSG will be performed off of CPAP both to assess OSA severity when non-adherent as well as to maintain blinding of CRU staff. To prevent any confounding of short term CPAP withdrawal on cardiovascular or other measures, at the follow-up visits PSG will be performed the night after these measurements are made rather than the night prior.

5.5.3.3 Resting Blood Pressure

Blood pressure (BP) 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, measured at the midpoint, and identifying the appropriate bladder size from a standard chart. Measurements are repeated three times, elevating the arm between measurements, and recorded. Further details are presented in Appendix C.

5.5.3.4 Fasting Venipuncture

Phlebotomy will be performed using standard techniques by trained staff following a written protocol, for withdrawal of 40 cc of blood. Pre-labeled, bar coded tubes will be used for improved specimen tracking. The sample will be divided into tubes for the varied analyses (10 ml clot for serum, 15 ml EDTA, 5 ml special anticoagulant tube, 5 ml citrate). Clots will be centrifuged and the serum removed within 1 hour of venipuncture. Aliquots of serum, plasma, and urine will be stored in alarmed, dedicated -80° freezers until they assayed at the Harvard Catalyst Core Lab.

5.5.3.5 Anthropometry

Height is measured with the subject in stocking feet, using a wall-mounted stadiometer; *weight* with a calibrated digital scale. *Neck circumference* is determined 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 horizontal axis. *Waist* is measured at the smallest area between the lower ribs and iliac crest, and *hip* at the widest area around the buttocks using non-stretchable tape. Circumferences are measured in duplicate by a two-person team, one recording and the other measuring. If differences of > 2% are observed, a third measurement is made. *Bioelectric Impedance* (*BIA)* is obtained applying electrodes to each extremity while supine on a firm bed, after voiding, with arms and legs at 45°. Total body fat is determined by prediction equations using anthropometry and bioelectric resistance and reactance. Further details are provided in Appendix D.

5.5.3.6 Arterial Applanation Tonometry

Arterial applanation tonometry is a noninvasive technique that provides the basis for high fidelity analysis of central and peripheral blood pressures through pulse wave analysis. Waveforms of radial artery recordings will be calibrated with sphygmomanometric brachial artery mean and diastolic pressure measurements in the same arm. Measurements will be performed using the SphygmoCor (AtCor Medical, AU) device with use of a probe containing a solid state high fidelity Millar transducer over the radial artery with a minimum of two consecutive measurements to obtain pulse wave analysis results. Orientation and pressure applied to the transducer will be adjusted to optimize applanation of the artery between the transducer and the underlying tissue. Pulse wave velocity will be obtained by assessing time delay using lead II ECG (LL, LA, RA) recording as well as carotid and femoral applanation tonometry. Pulse wave analysis will provide a measure of central aortic pressure which has been found to be a better predictor of cardiovascular and renal disease than systemic blood pressure.[34, 35] Pulse wave velocity provides an assessment of

arterial stiffness, an indirect measure of atherosclerosis. Further details are provided in Appendix E.

5.5.3.7 24 Hour Ambulatory BP Monitoring (ABPM)

The Spacelabs 90207 ABP monitor will be used for measuring blood pressures at 30 (during the day) or 60 (during the night) minute intervals for 24 hours, beginning at the time of discharge from the CRU. Prior to discharge from the research facility, cuffs will be secured, and subjects instructed on how to re-move them as needed, and check placement (using marks placed on the arm to ascertain position). These data will provide data on temporal and diurnal blood pressure changes, of particular relevance with regards to OSA given the association between OSA and a non-dipping nocturnal profile, and between non-dipping and cardiovascular events. Further details are provided in Appendix F.

5.5.3.8 Pharyngometry

Pharyngometry (*Eccovision, Hood)* will be obtained with the subject sitting, with the head in a Frankfort horizontal position and supine, with use of a mouth piece positioned with the tongue forward and down. Following an initial maneuver using nasal breathing (to identify the velum), oral maneuvers are obtained during quiet breathing to obtain 3 curves that exhibit characteristics seen on a reference diagram, i.e., a well-defined oral cavity segment between 0-5 cm, a distinct oropharyngeal segment, and no evidence of tongue occlusion or leak. Each measurement consists of a plot of cross-sectional area (CSA; cm^2) as a function of distance (cm) from the oral cavity. Further details are provided in Appendix G.

5.5.3.9 Spirometry

Spirometry will be obtained with the subject seated and supine with nose clips on, using a calibrated device. Subjects will be instructed to take a maximal breath in and exhale forcefully for at least 6 seconds and until an expiratory plateau is observed (and not more than 15 seconds). Up to 5 maneuvers will be obtained in each position until 3 acceptable and 2 reproducible curves are obtained in each position. Further details are provided in Appendix H.

5.5.3.10 CPAP Data

For those patients using CPAP therapy, the effective OSA exposure will utilize data on average nightly usage as well as residual AHI on treatment to obtain a weighted average of effective exposure to respiratory events. Average nightly usage will be obtained by downloading data from the web-based adherence program Encore Anywhere© (Philips Respironics, Murrysville PA) and for those subjects who do not have home wireless internet access by interrogating the SmartCard© in the patient's CPAP machine over the 30 nights prior to the CRU appointment. In addition, the residual AHI will be obtained from the Encore Anywhere© or SmartCard© data which records residual apneas and hypopneas detected by an internal pneumotachograph in the machine. This measure has been demonstrated to correlate well with the AHI obtained on laboratory PSG.[39] The effective AHI is computed as the average of the off-CPAP AHI obtained from PSG in the CRU and on-CPAP AHI obtained from Encore Anywhere© or SmartCard© data with appropriate weighting for the level of adherence. Further details are provided in Appendix K.

5.6. Questionnaires

All of the proposed questionnaires other than the Calgary Sleep Apnea Quality of Life Index are self-administered. Questionnaires will be administered in two randomized orders (maintaining the same order for each subject at his baseline and post-intervention study), to minimize the possibility that any apparent relative superiority of a given instrument will not be due to the order of presentation.

5.6.1. Medical History and Medications

Modified Cleveland Sleep and Health Questionnaire
A standardized questionnaire will be used to ascertain medical history, exposures (tobacco, alcohol), and socio-demographic characteristics at the baseline visit.

Medications
Subjects will be asked to bring all medications to each of the CRU visits and a review of all medications including frequency of usage will be performed.

5.6.2. Sleep Related Outcomes

The Hispanic Community Health Study Sleep Questionnaire will be asked at each CRU visit. It is a 23-item instrument that includes questions from: the *Sleep Heart Health Study Sleep Habits Questionnaire* (on snoring symptoms, sleep duration and timing) as well as:

The *Epworth Sleepiness Scale* (assessing the likelihood of falling asleep in 8 common situations), which has good internal reliability (α=0.88) and test-retest reliability over 5 months (r=0.82), and has been shown to discriminate among patient groups with various degrees of objectively determined sleepiness and to respond to OSA therapy.

The *Women's Health Initiative Insomnia Rating Scale* (WHIIRS) which has been validated and used in a trial of more than 100,000 women to assess insomnia symptoms.

The *Calgary Sleep Apnea Quality of Life Index (SAQLI),* which is designed to assess responsiveness to OSA treatment, will be administered at each CRU visit to obtain a measure of OSA-specific quality of life. This instrument correlates with global quality of life measures, has a high 2 week test-retest reliability (r=0.92), and a large responsiveness index (1.9) and effect size (1.1) to CPAP therapy.

5.6.3. General Health and Functional Status

Medical Outcomes Survey-SF 36 (MOS-SF), a standardized tool for assessing general health status, physical and social functioning, and fatigue will be administered at each CRU visit. Its subscale, Vitality, has demonstrable sensitivity to CPAP therapy.

EuroQol (EQ-5D) The EQ-5D is a five question instrument that is especially easy to administer and has been previously used in studies of OSA to assess quality of life. Valuation of scores from this instrument has been done in many countries allowing for its use in future cost-effective analyses. This instrument will be administered at each CRU visit as well as every three months by the Study Coordinator in person or over the telephone as part of the monthly safety/AE evaluation and health promotion counseling session.

Patient-Reported Outcomes Measurement System (PROMIS) The sleep and wake impairment scales of this tool provide an integrated and efficient assessment of self-reported health that are predictive of health care utilization and mortality, and may be used to assess health utility states in future cost-effectiveness analyses. These questions will be administered at each CRU visit.

5.6.4. Gastrointestinal (GI) Quality of Life

Because both obesity and OSA are commonly associated with gastric reflux symptoms, and side effects of surgery predominantly affect the GI tract, we will assess a quality of life measure specific to the GI system. We will use the *Gastrointestinal Quality of Life Index (GIQLI)*, which was designed to be responsive to change and assesses a wide variety of symptoms, including heartburn, dysphagia, diarrhea, ability to eat foods, and bloating. It contains 36 questions each with five response categories which are summed to give a numerical score. It been validated in a number of GI conditions, with high internal reliability (α=.70-.86) and standardized response means ranging from .45 to .86. The GIQLI will be administered at each CRU visit.

5.6.5. Depression

Depressed mood commonly occurs in both obesity and OSA and may improve with treatment of both obesity and OSA. As such, it may be an important intermediary mechanism by which OSA (and obesity) treatment improves quality of life and other relevant outcome measures. As such, depression will be assessed using the Patient Health Questionnaire-9 (PHQ), a psychometrically valid measure of depression at each CRU visit in this study.

5.6.6. Physical Activity

Physical activity is an intermediary behavior relevant to both obesity and OSA and which may change with treatment and thus, influence study outcomes. As such, physical activity will be assessed with the MESA Typical Week Physical Activity (TWPAS) questionnaire, adapted from the Cross-Cultural Activity Participation Study, providing estimates of the level of physical activity in the last month. It has been validated in both men and women in relation to 8 days of physical activity records. This questionnaire will be asked at each CRU visit.

All questions are to be completed. The Study coordinator double checks questionnaires to make sure there are no missing answers, especially when participant completes the forms without the assistance of the study coordinator. A Question by Question guide will be available to help clarify ambiguities that may arise. If the participant does not feel comfortable answering a question, study coordinator indicates this next to the questionnaire field, study coordinator initials and dates note. There will be a code when handling missing data to provide the reason why the response is missing.

5.7. Health Utilization Indices

5.7.1. Medication use

Participants will be asked to bring all medications to their baseline and follow-up exams. A detailed medication list including dosages and frequency of administration will be recorded by the study coordinator. The study coordinator should retrieve all missing information during phone contact and/or refer to participant's medical chart. Medication use will also be updated at the time of the monthly interim phone calls. Although this approach is inferior to querying actual pharmacy records, our sample will likely utilize a number of different pharmacies, as will likely occur in a later multi-center trial. To assess potential misclassification, we will compare the recorded medication with the pharmacy records in a sample of individuals who utilize the BWH or BIDMC pharmacy as their sole provider of medications

5.7.2. Health Care Encounters

Standardized case report forms (CRFs) will be used at each scheduled encounter to record the reason for the encounter, duration, professional and non-professional staff time, administration of procedures, etc. In addition, during interim assessments, subjects will be queried on other scheduled clinic visits unrelated to OSA treatment, any unscheduled clinic visits, emergency room or urgent care visits, and hospitalizations.

5.8. Biomarkers

Biomarker assays will be performed by the HCCL Core Laboratory using samples that have been labeled only using de-identified study ids. Blood samples will be being processed immediately at the time of venipuncture. Blood and overnight urine sample will be stored locally at -80°C until shipped to the Core Laboratory.

Assays were selected based on their known value in predicting clinical important outcomes and because prior literature or our own preliminary data indicate their responsiveness to CPAP or bariatric surgery interventions. The battery will allow interrogation of the following biological pathways: insulin resistance and glucose regulation (insulin, glucose, hemoglobin A1C and adiponectin); lipid metabolism (total, LDL and HDL cholesterol and triglycerides); inflammation (C-reactive protein, interleukin-6, and soluble TNFaR1); hemostasis (fibrinogen and plasminogen activating inhibitor, PAI-1); oxidative stress (oxidized LDL), and markers of end organ damage (N-terminal pro-B-type natriuretic peptide, NTproBNP, a marker of cardiac ventricular dysfunction; and glomerular endothelial function measured by the urinary albumin to creatinine ratio). Urine will also be stored for future analyses, such as catecholamines and isoprostane levels. Additional serum aliquots will also be stored and available for future analyses, such as hepatic function.

5.9. Blinding

The study is single-blinded due to the nature of the interventions. Attempts will be made to blind study investigators (other than the physicians providing direct patient care - including the study surgeons – as well as the Medical Safety Monitor) to the study arm to which the subject was randomized. This will include scorers, data entry staff, and CRU nurses who obtain questionnaire and physiologic measurements. The Study Coordinator, who needs to ensure appropriate scheduled visits are made and needs to perform follow-up calls to ascertain treatment specific issues will not be blinded. Unblinded personnel will not administer tests that could be influenced by interview or administration technique. Participants will be encouraged not to discuss their treatment with the CRU nursing staff (who will make study measurements). However, if blinded

individuals are accidently unblinded, this will be recorded and its impact on the study measurements evaluated.

5.10. Randomization

After completing the baseline visit, the study coordinator will use a web-based randomization system to enter eligibility criteria. After electronic verification, the participant will be assigned a randomization code for study arm (CPAP vs. LGB) using a secure, pass-word protected, HIPAA compliant 24/7 web site. Randomization will be done within strata defined by site and gender to ensure comparable distributions of these key variables. Within each stratum, randomization will be performed using a permuted block scheme.

Only participants who have completed the entire screening process through the end of the baseline visit and have met eligibility requirements will be randomized. The following items will be assessed to confirm eligibility prior to randomization:

- The inclusion and exclusion criteria will be reviewed (eligibility form and sleep study/AHI results).
- Equipoise is established following assessment by the patient's sleep physician (at the time of routine clinical evaluation) and after a semi-structured interview at the screening visit between the patient and both a study Sleep Physician and Bariatrician.
- In order to obtain the randomization assignment, study staff must complete the Baseline Visit Checklist and Randomization CRF and follow the instructions listed on the form.
- The online Randomization form will only display after all the data are entered correctly into the required fields. Upon submitting the form, the database will compare the fields on the form and return a randomization code if all conditions are satisfied. If not entered or data doesn't match, the system will not return a randomization code and the discrepancy will have to be resolved.
- After randomizing, the staff person should log on to REDCap, initiate the participant in his/her arm, and start the real "meat" of data entry.

  As study staff are preparing for the baseline visit, they should attempt to access the OnWard web entry system to check that it is operational and that the Clinical Center has a working internet connection. In the event the OnWard web entry system is not available or internet connectivity is unavailable, study staff will call the SDCC randomization phone number available during the hours of 7:30 a.m. to 6:00 p.m. (Eastern Time Zone), Monday through Saturday. Should an SDCC representative not immediately take the call, study staff should leave a voicemail with the following information concerning the potential subject: Study ID, Name Code, Staff ID, Site ID, Date of Enrollment, and a return phone number. Based on this information, the SDCC representative will look up the next randomization assignment and provide it to the Study Coordinator.

  After receiving the randomization assignment from the SDCC representative, study staff should record the assignment on the Randomization CRF. SDCC representative will notify the Study Coordinator when the web entry system is operational again. Study staff should return to the web entry system at this point and confirm the entry of the Randomization CRF for the manually randomized participant.

5.11. Health Promotion Sessions

For all participants, 20 minute health promotion sessions will be scheduled monthly with the Study Coordinator/Health Promotion Counselor for the duration of study participation. As much as

possible, these sessions will be coordinated to occur with other visits to the health center (e.g., to the surgical or sleep center) to allow for face to face meetings. These appointments will reinforce good sleep hygiene and exercise recommendations. Participants will also review dietary recommendations to reinforce the personalized dietary plan and identify barriers to achieving sustained weight loss. Dietary counseling will address the specific dietary changes required pre- and post-operatively., and the personalized weight loss plan. If a given face-to-face meeting is not possible, follow-up sessions will be arranged to occur by telephone. Adherence with each visit and time to administer each session will be closely monitored for use as process or secondary outcomes.

5.12. Monthly Telephone Calls

Monthly interim health review contacts will also be performed by the Study Coordinator to assess for problems with therapy, assess for safety concerns such as drowsy driving, review any changes in medication usage, and ascertain health care utilization (scheduled or unscheduled health care encounters, and medical procedures). In addition, every 3 months, the EQ-5D will be re-administered over the telephone to provide updated assessments of quality of life and utility weights for cost-effectiveness assessments. Any new concerns will be evaluated by the local physician medical monitor. These contacts will either occur by telephone or, to minimize participate burden and if possible, through collection of these data at the time of scheduled health promotion visits or surgery/sleep clinic follow-up appointments.

Being enrolled in ABC does not substitute for the participant's regular healthcare or relationship with their personal physician. All medically related questions (e.g., about symptoms, medications, etc.) should be directed to his or her bariatric surgeon (if LGB arm), sleep physician (if CPAP arm) or primary care physician. Study staff are responsible for providing general information and should **NOT** try to give medical advice that should be reserved for the participant's physician. It is appropriate for the Health Promotions Counselor to reinforce all healthy lifestyles—nutrition, exercise, sleep, etc. It is possible that through review of the participant's history and through discussion of healthy lifestyles, areas of potentially suboptimal medical management are identified. If the participant questions his own management, study staff should indicate that treatment approaches often need to be individualized for specific patients and encourage the participant to discuss his concerns with his physician. If the participant is resistant to do this, the Study Coordinator may indicate that she will ask the local Medical Monitor to review the participant's history and determine if feedback to the patient's physician is indicated. It is also important that in reviewing this information with the participant, strict equipoise is maintained.

5.13. Follow-Up (9 and 18 month Examination

All subjects will have a follow-up examination at 9 months. Those subjects recruited in the first 27 months of the study (long term follow-up subgroup) will also be invited to return for a follow-up visit at 18 months. Subjects recruited after the first 27 months will not be invited back for an 18 month follow-up because the study will have come to an end before their 18 month time point. The follow-up visits will be nearly identical to the Baseline Exam. However, because the computation of a residual/effective AHI for subjects in the CPAP arm will require the research follow-up PSG to be conducted while off of CPAP, the research PSG will be performed the night *after* rather than before the morning research exam. Participants will be asked to arrive at the CRU between 7 and 8 AM on the morning of the follow-up exam rather than the evening before (thus, by obtaining BP, arterial tonometry and blood/urine assays after a typical night at home, those measurements are

likely to be more reflective of their usual physiology compared to measurements made after requiring or discontinuing CPAP in the controlled CRU environment). After morning research data are collected (approximately 11 AM), subjects will be discharged from the CRU and asked to return by 8 PM for the follow-up sleep study. To further assess “effective” levels of OSA in the participants’ home environments, we also will arrange for each participant to use an overnight oximeter each night at home for three nights prior to their follow-up CRU visit.

5.14. Final Study Visit

Subjects will be asked to return for a close-out visit with an unblinded (as possible) study physician within one month after their last (9 or 18 month) research follow-up exam to discuss the results of the research testing including: polysomnography, sleepiness symptoms, CPAP adherence (if applicable), weight loss, and blood pressure. This visit should take no longer than 30 minutes. They will also be provided a follow-up visit with their sleep physician and/or bariatric surgeon to ensure ongoing clinical care.

Chapter 6

6. Statistical Analysis Plan

6.1. Outcome Measures and Data Analysis

As a planning grant, a major goal is to provide estimates of the mean and standard deviation of the differences before and after each intervention, including estimation of effect sizes, for markers of intermediate biological pathways and for patient-reported outcomes. Hypotheses regarding intervention differences in the response of these indices between baseline and 9 months after intervention for each arm (CPAP vs. LGB) will be assessed using mixed-effects models where the dependent variable is the response at 9 months post-randomization while the independent variables will be baseline measurement and treatment arm.

6.1.1. Modeling Approach

The primary analysis will be based on an intent-to-treat analysis while secondary analyses will be based on an as-treated analysis.

6.1.2. Preliminary Data Analysis

Data will be summarized using standard descriptive statistics (e.g., means; inter-quartile values for continuous variables and frequencies/proportions for categorical variables). Initial analyses will investigate any imbalance in baseline variables among the 2 groups. Histograms and scatter plots will be used to evaluate the distribution of each variable and change in the variable between baseline and 9 months after randomization within a subject.

6.1.3. Missing Data

Although every effort will be made to obtain complete data on all patients randomized to a treatment arm, we conservatively estimate that follow-up data will only be available for 80% of subjects. Sensitivity analyses will be performed to assess the effect of drop-out on the results of the primary and secondary analyses. For instance, linear and generalized linear mixed-effects models will be used to investigate the effect of treatment on each of the outcomes of interest. Such models assume that data is missing at random and allow all data to be analyzed within the same framework, even though follow-up data on some subjects is not available.

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The following tables summarize the outcome measures and data analysis by Aim

6.1.4. Specific Aim 1

Specific Aim 1: **Assess the feasibility of the proposed implementation of the RCT** .		
Category	**Measures**	**Additional descriptions**
Recruitment Yields.		
	Numbers (%) of eligible participants at each site	Reasons for not enrolling contacted subjects, including patient/provider preferences (equipoise).
	% of eligible subjects successfully contacted	
	% of contacted subjects successfully enrolled	
Fidelity of Randomization		
	Number of subjects studied (and % of complete data) at each site	
	Monthly rates of accrual	
	Numbers of crossovers from one arm to another	
CPAP Adherence		
	Proportion accepting CPAP	Reasons for not accepting CPAP
	Effective duration of treatment (time spent at the prescribed pressure)	Data exported from CPAP units
	Proportion of nights with at least 4 hours of use at prescribed pressure.	
Surgical Adherence		
	Proportion undergoing surgery	Reasons for not receiving surgery
	Adherence with post-operative care	Attending follow-up visits, maintaining prescribed diet
Study Retention		
	Ability to contact for monthly interim visits	
	Numbers returning for 9 and 18 month visits	
Safety		
	Number of AEs, SAEs, and Treatment Failures per study arm	Categorized according to their severity, expectedness and relationship to the study

		intervention • specifically peri-operative morbidity and mortality • changes in surgical plan (e.g., conversion to laparotomy) • deviations from expected recovery (1 night in hospital and 1 week out of work)
	Quantify treatment specific side-effects	Use CRFs obtained during respiratory therapy visits in the CPAP arm and data from the GIQLI for the LGB arm

6.1.5. Specific Aim 2

Specific Aim 2: **Assess the effectiveness of LGB vs. CPAP therapy on OSA severity** by the "effective" AHI at 9 months post-randomization (subset of 50 at 18 months)		
<u>Primary Outcomes</u>		
OSA severity -#1		
Measures		**Additional description**
LGB	**CPAP**	
9 month AHI **minus** the baseline AHI	baseline AHI **minus** an estimated weighted mean of the follow-up AHI **weighted mean calculation:** • Hours per day of CPAP use in the month prior to the follow-up exam • Residual AHI on CPAP during prior month (estimated from the PAP device algorithm). • AHI off CPAP (measured at the follow-up exam in the CRU) • Average sleep duration (estimated by self-report)	AHI at 9 months post-randomization (and in a subset of 50 participants, at 18 months).

OSA severity-#2	
Measures	**Additional description**
• Follow up oximetry home-based average desaturation index **minus** baseline value obtained from PSG • **Average desaturation index -** Number of desaturations ≥3% and 4% per hour of sleep	
Primary analysis #1 ***Each treatment arm separately***	
Measures	**Additional description**
Intervention minus baseline (effective AHI and desaturation index) for each arm • **Paired t-tests measured at baseline and 9 month (or 18 month) follow up** • **Adjusted for site and gender** • **Intention to treat analysis**	Each treatment arm separately
Primary Analysis #2 ***Between two treatment arms***	
Measures	**Additional description**
Intervention minus baseline (effective AHI and desaturation index) for each arm measured at baseline and 9 month (or 18 month) follow up • **Two sample t-tests measured between two treatment arms** • **Adjusted for site and gender** • **Intention to treat analysis**	Between two treatment arms
If significant differences in key baseline variables (age or BMI)	
Multivariable linear regression models	Change in outcome measures across treatment groups conditioned on baseline variables that differ between 2 arms.

<table>
<tr><td colspan="3">Longitudinal patterns of change</td></tr>
<tr><td colspan="2">Repeated measure linear (or generalized linear) mixed-effects model
effective AHI measured at baseline, 9 month and 18 month follow-up
treatment arm being the covariate and subject being the random effect</td><td></td></tr>
<tr><td colspan="3">Descriptive analysis of both groups</td></tr>
<tr><td colspan="2">Baseline statistics</td><td></td></tr>
<tr><td colspan="2">Pearson’s correlation coefficient or Spearman’s rank correlation</td><td>Correlation among variables within each group
The inter-relationships among the various subsets of data (demographic, anthropometric, metabolic, and sleep)</td></tr>
<tr><td>Categorical variables</td><td>Summarized - Frequency and Proportions
Group comparison – Fisher’s exact test</td><td></td></tr>
<tr><td>Continuous Variables</td><td>Group comparisons –
Two sample t-tests (normally distributed variables)
Mann-Whitney U Tests (non-normal distribution)</td><td></td></tr>
<tr><td colspan="3">Secondary Analysis – efficacy</td></tr>
<tr><td colspan="2">Intervention minus baseline (effective AHI and desaturation index) for each arm
Paired t-tests measured at baseline and 9 month (or 18 month) follow up
Adjusted for site and gender</td><td></td></tr>
<tr><td>CPAP arm</td><td>CPAP vs LGB</td><td></td></tr>
<tr><td>Residual AHI compared to baseline AHI</td><td>Based on change in AHI from baseline to residual</td><td></td></tr>
</table>

6.1.6. Specific Aim 3

Specific Aim3: **Assess the effect sizes (and responsiveness to intervention) Bariatric surgery vs. CPAP therapy on a targeted group of intermediate markers of treatment response and patient-reported outcomes**		
Primary Outcomes		

Measures will be determined by:
• Calculating the statistical distributions of each outcome
• Assessing potential ceiling and floor effects by estimating the minimum and maximum values for each measure at baseline and follow-up and quantifying the proportion of the sample with values at these extremes.
• Responsiveness of each outcome will be assessed by calculating three indices:
  • Change Ratio (mean change/mean baseline * 100)
  • Effect Size (mean change/standard deviation of baseline value);
  • Standardized Response Mean (mean change/standard deviation of change value).		

Outcome	**Measures**	**Description**
• **Change in sleepiness**	Epworth Sleepiness Scale (ESS) score	(assessed by improvement in ESS score)
• **Change in adiposity**	Body mass index (BMI)	(assessed by improvement in BMI)
• **Change in medication usage**		Careful collection of medication data to perform sensitivity analyses to address the extent to which medications and change in medications may influence response variables

Additional Outcomes* [identify the most robust signals for future large multi-center studies] *in publications and elsewhere these latter analyses will be identified as exploratory and any significant findings will require confirmation		
	Measures Example indices	**Description**
Improvement in disease specific quality of life	Sleep Apnea Quality of Life Index (SAQLI)	
Improvement in overall quality of life	MOS SF-36, EuroQOL-5D	
Improvement in mood	PHQ-8	
Blood pressure	Systolic and Diastolic BP (average day and night)	24-hour Ambulatory Blood Pressure Monitoring
	24-hour BP variability	
Arterial stiffness	Augmentation Index	Pulse Wave Analysis
	Pulse Wave Velocity	
Biomarkers		
Dyslipidemia	HDL, LDL, TG	
Glucose Regulation/Insulin Resistance	Fasting insulin, HOMA, adiponectin	
Oxidative stress	Oxidized LDL	Expressed as a ratio of oxidized LDL/total LDL
Fibrinolytic activity	PAI-1	
Inflammation	CRP, IL-6, sTNF receptor	
Subpopulation measurements		
Diabetics using hypoglycemic medication	Glucose control will be measured with the HgbA1C	
Statin medication		
Blood pressure lowering meds		Investigate whether possible to measure despite potential confounding

Mechanisms of improved outcomes
Change in each of the outcomes correlated with: • AHI/desaturation index • change in BMI/waist circumference/percent body fat
Assess outcomes most responsive to change in OSA vs. change in obesity.
Interaction term to explore the interactive effects of BMI and AHI change on the various intermediate and patient-reported outcomes.

6.1.7. Specific Aim 4

Specific Aim 4: **Identify modifications of the trial study design that will improve the feasibility of the subsequent RCT.**	
Evaluation components	• Qualitative • Study team feedback at regular intervals
Examination of process measures	• Identify potential bottlenecks • Perform exploratory analyses by subgroups (e.g., gender, diabetes status, etc.)

6.1.8. Specific Aim 5

<table>
<tr><td colspan="3">Specific Aim 5:
Obtain estimates of the health service utilization.</td></tr>
<tr><td colspan="3">Health Care Utilization</td></tr>
<tr><td colspan="2">Description</td><td>Source Documents</td></tr>
<tr><td colspan="2">• Direct medical costs
• Based on current best practices for RCT-based cost-effective analyses
• Intention to treat
• Discount rate – costs in 2010 dollars
• All subjects even if drop out</td><td>• Hospitalizations
• Physician encounters</td></tr>
<tr><td colspan="3">Medication Use</td></tr>
<tr><td>Category</td><td>Measures</td><td>Description</td></tr>
<tr><td>• Totals</td><td>• Total overall number
• Number used for treating pre-defined conditions (hypertension, diabetes, dyslipidemia, depression, GERD/peptic ulcer disease, sleep aids)</td><td></td></tr>
<tr><td>• Δ changes</td><td>• Total number used
• Number in each class
• Dosages at 9 & 18 month</td><td></td></tr>
<tr><td>• Reduction in medication usage</td><td>Mean number used (overall & in each class)
Intervention minus baseline
• Paired t-tests measured at baseline and 9 month (or 18 month) follow up
• Adjusted for site and gender
• Intention to Treat analysis</td><td>For both arms separately</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

	Mean number used (overall & in each class) **Intervention minus baseline measured at baseline and 9 month (or 18 month) follow up** • **Two sample t-tests between two arms** • **Adjusted for site and gender** • **Intention to Treat analysis**	Between two arms
Cost basis determination		
Medication Costs	Average wholesale costs Nonparametric bootstrap methods (small numbers of high resource use patients skews data to right) • Compare means between the two treatment arms • Calculate confidence intervals	

Global Measures of Health

Category	Measures	Description
Quality-adjusted life years (QALY)	• EQ-5D • PROMIS	Foundation for cost effectiveness studies EQ-5D utility weights based on established validity PROMIS evidence of the robustness of system

Direct Medical costs

Category	Measures/costs	Description
• Surgical Arm	Surgery = Physician + Hospitalization costs • Complication treatment • Outpatient clinic visits (Surgeon + physician) o Pre-operative evaluations o Pre-operative + post operative laboratory and radiology testing	1. Case Report Forms (CRF) 2. Every planned encounter 3. Monthly phone calls

	o Peri-operative CPAP rental o Band-adjustment visits	
• CPAP Arm	• CPAP Titration Study • Purchase of the CPAP machine • Outpatient follow-up visits with the sleep clinician and respiratory therapist • Additional testing (e.g., repeat CPAP titration)	
• Both arms	• Medication costs • Unanticipated costs (e.g., additional physician visits, emergency room, hospitalization	
Cost basis determination		
• Direct Medical Costs	• Unit costs based on Medicare fee schedules (convert health care usage to $$s) Used to determine cost/QALY for each treatment arm.	

6.1.9. Power

<table>
<tr><th colspan="3">Power
addressing Specific Aim 2 (comparing AHI in each arm)</th></tr>
<tr><th>Category</th><th>Measure</th><th>Assumptions</th></tr>
<tr><td>Mean baseline AHI</td><td>50 ± 10 (SD)</td><td></td></tr>
<tr><td>Total randomized</td><td>80 subjects (20% dropout)</td><td></td></tr>
<tr><td>9 month follow up</td><td>64 (32 in each arm)</td><td></td></tr>
<tr><td>18 month follow up</td><td>40 (20 in each arm)</td><td></td></tr>
<tr><td>CPAP arm usage</td><td>50% AHI reduction (from 50 to 25 AHI)</td><td>Use of CPAP 4hrs/night
8 hrs sleep</td></tr>
<tr><td colspan="3">CPAP arm – 9 months</td></tr>
<tr><td colspan="2">Measure</td><td>Assumptions</td></tr>
<tr><td colspan="2">32 subjects
99% power to detect 50% reduction in AHI
• 50% AHI reduction (from 50 to 25 AHI)
• 2-sided paired t-test alpha 0.05</td><td>• Assume SD=10</td></tr>
<tr><td colspan="3">LGB arm – 9 months (6 months post operative)</td></tr>
<tr><td colspan="2">32 subjects
99% power to detect 31% reduction in AHI
• 12% reduction in BMI starting with a mean BMI 37.5kg/m^2
• 31% reduction in AHI (reduction from 50 to 35)
• 2-sided paired t-test alpha 0.05</td><td>Studies suggest BMI reduction of 12% is assoc 31% reduction in AHI
• SD=10</td></tr>
<tr><td colspan="3">Compare change between two treatment arms at 9 months</td></tr>
<tr><td colspan="2">32 subjects in each arm
97% power to detect change in AHI
(25 CPAP vs 15 LGB)
• 2-sided t-test alpha 0.05</td><td>• SD=10</td></tr>
</table>

Detection - 9 month follow up within each arm	
32 subjects **90% power to detect a reduction in AHI as small as 6.0** **80% power to detect a reduction of 5.2** • 2-sided paired t-test alpha 0.05	• SD=10
Detection - Compare change between two arms at 9 months	
32 subjects in each arm **90% power to detect a reduction in AHI as small as 8.3** **80% power to detect a reduction of 7.2** • 2-sided t-test alpha 0.05	• SD=10
CPAP 18 month follow up	
20 subjects **99% power to detect 50% reduction in AHI** • 50% AHI reduction (from 50 to 25 AHI) • 2-sided paired t-test alpha 0.05	• SD=10
LGB - 18 month follow up	
20 subjects **99% power to detect a 78% reduction (50 to 11)** • 2-sided paired t-test alpha 0.05	• Study found 78% reduction in AHI from 62 to 13 after 17.7 months for 25 patients w/ severe OSA • SD=10
Compare change between two treatment arms at 18 months	
20 subjects in each arm **99% power to detect change in AHI** **(25 CPAP vs 39 LGB)** • 2-sided t-test alpha 0.05	• SD=10

Detection - 18 month follow up within each arm	
20 subjects in each arm **90% power to detect a reduction in AHI of 7.7** **80% power to detect a reduction of 6.7** • 2-sided paired t-test alpha 0.05	• SD=10
Detection - change between two treatment arms at 18 months	
20 subjects in each arm **90% power to detect a reduction in AHI of 10.6** **80% power to detect a reduction of 9.1** • 2-sided t-test alpha 0.05	• SD=10
<u>Secondary outcome</u> **Epworth Sleepiness Scale (ESS) score**	
Measure	**Description**
Baseline for both groups	
Mean ESS score 12 ± 2	meta-analysis-effect of CPAP in severe apneics suggest treatment produces a drop in ESS of 4.75 SD = 4.85
CPAP arm	
32 subjects at - 9 months > 99% power 20 subjects at 18 months 98% power • Detect a change in ESS of 4.75 • Assume SD=4.85 • two-sided paired t-test at alpha=0.05 level.	

LGB arm	
32 Subjects at 9 months 99% power • detection of a reduction in ESS of 4 points 20 subjects at 18 months 99% power • Detection of a reduction in ESS of 6 points Assume SD=4.85 two-sided paired t-test at alpha=0.05 level.	Study - mean ESS falls by 4 points at 3 months and 6 points by 24 months

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