Protocol and Background

Title **PAP to PAP: CPAP vs ASV for Insomnia (Title Abbreviation = P2P)**

Date November 7, 2014

P.I. Barry Krakow, MD
Sleep & Human Health Institute (SHHI)
Maimonides Sleep Arts & Sciences, Ltd (MSAS)
6739 Academy Rd. NE, Suite 380
Albuquerque, NM 87109
(505) 998-7204

NCT NCT02365064

Synopsis

Insomnia is the most common sleep disorder affecting millions of adults and is linked to daytime impairment. Insomnia is typically thought of as a symptom, secondary to a primary disorder, and often goes untreated for years. Medication (over the counter or prescription) and sleep hygiene are typical insomnia symptom treatments but they do not address the cause of the insomnia. Newer guidelines view insomnia as a co-morbid disorder needing independent treatment. Recent research has discovered high rates of sleep-disordered breathing (SDB) among insomnia patients; this co-morbid pairing is referred to as "complex insomnia." Several studies have revealed that treatment of SDB decreases insomnia.

This study will determine which of two different types of positive airway pressure (PAP therapy) modes are more effective in reducing sleep breathing events in chronic insomnia patients and in decreasing insomnia severity. Patients presenting to the clinic with a primary complaint of insomnia will be potential participants for this study. Following diagnostic polysomnography (PSG) testing, insomnia patients diagnosed with SDB and meeting inclusion criteria will be randomized to a PAP treatment arm, CPAP or ASV. No experimental devices will be used in this study, both CPAP and ASV are FDA approved for treatment of SDB and are in wide use in the USA. Participants will complete a series of three titration studies with their assigned PAP mode and attend a minimum of five clinical follow-up appointments over a 14-16 week timeframe. Titration PSG studies will assess PAP pressure needs to ensure that patients are receiving optimal therapy at all times during this study. Clinical follow-up visits occur every two weeks at which time objective data download information and subjective measures will be collected. PAP adaptation barriers will be addressed as they arise during the study, because it is important that participants are able to use PAP therapy nightly during participation in this protocol. Baseline scores on insomnia severity, sleep quality, subjective insomnia parameters, sleep related impairment, and quality of life will be compared to outcome measures at the 4 month mark. Pre-treatment and post-treatment objective improvements on sleep studies will also be compared including sleep breathing indices, sleep consolidation indices, and objective data download information.

This study will be funded by ResMed Corporation, San Diego, CA. Research will be conducted by the non-profit Sleep & Human Health Institute (SHHI) at Maimonides Sleep Arts & Sciences (MSAS) and SHHI in Albuquerque, NM. This project will take 1-2 years to complete.

ABBREVIATIONS LIST

AASM – American Academy of Sleep Medicine
ABPAP – Auto-Bilevel Positive Airway Pressure
ADE – Adverse Device Effect
AEC – Adverse Effects Checklist
AHI – Apnea Hypopnea Index
APAP - Automatic Positive Airway Pressure
ASV – Adaptive Servo-Ventilation
BMI – Body Mass Index
BT – Bed Time
CAI – Central Apnea Index
CBT-I – Cognitive Behavioral Therapy for Insomnia
CHF – Congestive Heart Failure
COPD – Chronic Obstructive Pulmonary Disease
CPAP – Continuous Positive Airway Pressure
CRF – Case-Report Form
DME – Durable Medical Equipment
EIQ – Exit Interview Questionnaire
EPI – Expiratory Pressure Intolerance
ESS – Epworth Sleepiness Scale
FDA – Food and Drug Administration
FOSQ-10 – Functional Outcomes of Sleep Questionniare
FSS – Fatigue Severity Scale
HSCL – Hopkins Symptom Checklist
III – Insomnia Impairment Index
ISI – Insomnia Severity Index
ITT – Intent to Treat
MRD – Mandibular Repositioning Device
MSAS – Maimonides Sleep Arts & Sciences, Ltd.
NAR – Nonallergic Rhinitis
NDS – Nasal Dilator Strips
OOB – Out of Bed
OSA – Obstructive Sleep Apnea
OTC – Over-The-Counter
PAP – Positive Airway Pressure
PAP-T – Positive Airway Pressure Therapy
PGA – Patient Global Assessment of Sleep Questionnaire
PHI – Private Health Information
PLMD – Periodic Limb Movement Disorder
PSG - Polysomnogram
PUDS – PAP Units of Distress Survey

QLESQ – Quality of Life Enjoyment and Satisfaction Questionnaire
RCT – Randomized Controlled Trial
RDI – Respiratory Disturbance Index
RLS – Restless Leg Syndrome
SDB – Sleep-Disordered Breathing
SE – Sleep Efficiency
SHHI – Sleep & Human Health Institute
SOL – Sleep Onset Latency
SUDS – Subjective Units of Distress Scale
TIB – Time in Bed
TST – Total Sleep Time
UARS – Upper Airway Resistance Syndrome
VAS-F – Visual Analog Scale- Fatigue
VAS-S – Visual Analog Scale- Sleepiness
WASO – Wake After Sleep Onset

Background

Insomnia is the most common sleep disorder in the general population affecting millions, and difficulty staying asleep (sleep maintenance insomnia) is the most common presentation.(1-5) Chronic insomnia is linked to daytime impairment,(6) disability,(7) motor vehicle crashes,(8) workplace absenteeism(9) and errors,(8) and excess medical service utilization.(7) It also aggravates or increases risk for alcoholism,(10) depression,(11) diabetes,(12) obesity,(13) and stroke.(14) The economic burden of insomnia has been calculated in the tens of billions of dollars.(15;16)

Though insomnia is encountered routinely in primary care,(6;17;18) it often goes undiagnosed or untreated for years.(19;20) Disregard for insomnia complaints may be a function of physician training or knowledge;(21-23) conversely, patients may avoid discussing insomnia with their doctors or may not envision useful treatments for this sleep disorder.(24;25) The apparent lack of attention to insomnia care may occur as a result of a vast medical literature that defines insomnia as a symptom, secondary to a primary disorder (e.g. cancer or depression). When the primary condition is treated, insomnia presumably resolves.(26)

Treatment offered for insomnia usually consists of three approaches: basic sleep hygiene education,(27) over-the-counter (OTC) sleep aids, or sedative/hypnotics and other sedating medications by prescription.(5;6;18;28) For mild insomnia cases, sleep hygiene may prove cost effective and often yields satisfying results with minimal external coaching. Though no definitive epidemiologic studies on the application of sleep education or prescription of sleep aids by primary care physicians are available,(19) CDC and NHANES studies report sedative prescriptions are on the rise.(29;30) Notwithstanding, protracted use of prescription sedating medications (both indicated and off-label use) is a controversial subject.(31) Unquestionably, prescription sedatives help some insomnia patients in the primary care setting,(32;33) including some who use these medications nightly for several months(34) or potentially longer.(35;36) Clinical trials often report minimal complications(35;37) among a large proportion of sedative users, including long-term users, although it is not always as clear whether these patients are achieving optimal outcomes.(33) Counter to these observations, some reviews report sedatives are of limited(38) or no efficacy(39) for most chronic insomnia patients. Conventional wisdom suggests sedatives may be used frequently for short periods and then discontinued for myriad reasons. Last, emerging research has raised questions about increased risks for mortality,(40;41) suicidality(42) and other side-effects(43) associated with sedatives. Still, prescription sedatives for chronic insomnia represent only one form of treatment—a symptomatic therapy that may not lead to remission or cure when drug use ceases—thus, if this form of therapy fails to resolve episodes of sleeplessness, it is unclear how primary care physicians proceed with these patients.(21;44)

Newer perspectives and guidelines from the fields of sleep medicine(45) and psychiatry(42) view insomnia as a co-morbid disorder rather than a symptom, which then warrants independent clinical assessment and treatment. This point is key to the specialty of sleep medicine, whose main imperative seeks to determine whether or not the chronic insomnia patient is receiving an efficacious treatment,(5) which often leads to an assessment of whether pharmacotherapy is yielding optimal results. When pharmacotherapy is failing, it requires a more thorough sleep medical evaluation and usually a broader

array of therapeutic options.(5;21) In particular, pharmacotherapy failure raises suspicions for additional complex physiological etiologies for sleeplessness,(5) a direct indication for polysomnography (PSG) per American Academy of Sleep Medicine (AASM) guidelines.(5;46) Of potential clinical import, recent research focusing on PSG diagnostics revealed surprisingly high rates of the physiological disorder sleep-disordered breathing among insomnia patients(47-52)—referred to as "complex insomnia."(53) Two studies revealed very high rates of obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS)(54;55) in hypnotic-dependent insomniacs seeking treatment at a sleep medical center specifically for the chief complaint of persistent insomnia symptoms despite sedating medication use.

The manifestation and recognition of complex insomnia should be relatively straightforward, especially in light of newer research. In a recent study(56) we found that of 1,035 patients with an insomnia disorder (insomnia severity index score >7 and daytime impairment attributed to insomnia) who sought insomnia treatment at a sleep medical center, 42% ranked a sleep breathing disorder as one of their main reasons for seeking treatment, 13% reported a concern about sleep breathing problems, and another 26% reported awareness of sleep breathing symptoms. Only 19% of the total sample lacked awareness or concerns about a possible sleep breathing disorder. Although we found a high prevalence of sleep breathing awareness, it was only through multiple layers of questioning that these symptoms were uncovered, which suggests polysomnography may be underutilized in insomnia patients with sleep breathing complaints due to inadequate screening and thus fewer referrals to sleep centers.

Despite these obvious findings about insomnia, we presume most doctor-patient relationships currently steer clear of the discussion of sleep breathing symptoms, perhaps because so many insomniacs are more desperate about not sleeping. In our own clinic, we often hear people remark, "Sure I snore, but that's not why I came to your sleep center; I want to fix my insomnia. " Moreover, this combination of sleep disorders—Insomnia and SDB—creates clinical confusion, because each one causes sleep fragmentation effects, and both disorders present with overlapping symptoms such as non-restorative sleep, awakenings at night, and difficulty returning to sleep.(57;58) The complex insomnia co-morbidity may further complicate physicians' efforts to assess pharmacotherapy efficacy due to their lack of familiarity with the intricacies and assessments of either or both sleep disorders. In theory, confusion arises when primary care physicians face the challenge of prescribing different drugs or revising dosages to treat residual insomnia symptoms(21) instead of considering potential co-morbid SDB and referral to a sleep center.(28) Identifying pharmacotherapy failure may also be obscured if drug efficacy estimates are based on limited knowledge(27) or influenced by vested interests.(59) Making matters worse, no formal standards are published to define pharmacotherapy failure for insomnia drugs.(5)

When pharmacotherapy failure is suspected in primary care settings, many factors may dissuade physicians from referring insomnia patients to sleep medical centers for sleep specialist consultations or to sleep medical laboratories for overnight testing. However, when primary care physicians suspect sleep apnea in an insomnia patient, they may use screening tools designed to capture typical sleep apnea patients(60) but not validated to assess SDB risk among insomnia patients.(61) As a result, false negative screens may further confound care.

In particular, primary care physicians as well as a fair number of sleep medicine specialists may never consider a sleep study evaluation, because it appears so expedient to simply address the number one complaint of the vast majority of insomnia patients: "Doctor, I wake up at night and can't go back to sleep." Prescribing a drug seems rational and logical, yet few physicians take the time to build a differential diagnosis to explain these nocturnal awakenings. Moreover, the vast majority of insomnia research implicates two primary and not mutually exclusive pathophysiological pathways: (1) innate hyperarousal; and (2) learned behavior. Both theories more or less assign the physiological aspects of insomnia to the somatized tension that may cause or be a result of learned behaviors or innate hyperarousal activity. Neither of these theories implicates sleep-disordered breathing as a major component to this process, despite the facts that sleep-disordered breathing creates hyperarousal activity all night long and has been reported to trigger awakenings in patients that lead to middle of the night insomnia.

Our center explored this problem by conducting a study on "What causes chronic insomnia patients to wake up at night?"(62) No one had ever looked at this issue in a prospective work, because most studies focus on the post-awakening problem of returning to sleep, which is usually attributed to hyperarousal.(7)

Hyperarousal theory posits insomnia patients suffer from a state of increased alertness or arousal during waking or sleeping periods.(63;64) As above, hyperarousal is innate or genetically predisposed (physiologically driven; e.g. increased somatic tension(65)) or learned through behavioral influences that promote excess alertness or arousal (psychologically driven; e.g. losing sleep over losing sleep(66)), both of which over-stimulate the mind with racing thoughts and ruminations that inhibit sleep. Hyperarousal creates vulnerability to nocturnal awakenings among individuals predisposed toward excess mental stimulation or conditioning influences, which then extends a brief awakening (e.g. 5 minutes) into a longer awakening (i.e. a period of insomnia). This theory explains the difficulty in returning to sleep (duration of an awakening), but no research explains how hyperarousal actually causes awakenings.(63;64)

Few researchers study or comment on subjective or objective causes of these awakenings. Ohayon's work is the most authoritative.(4) Among 8,937 adults surveyed from the general USA population, 35.5% reported frequent nocturnal awakenings. When queried on "motives for awakening," 75.5% reported needing to use the bathroom often or sometimes. Waking spontaneously, thirst or noise averaged 30 to 40%; children, bed-partner, or pain averaged 10 to 20%; and, hunger and breathing difficulties were about 5%.(4) While this research was detailed, no findings were objectively confirmed with polysomnography (PSG). However, it is intriguing that Ohayon found nocturia to be the most common factor in the sample in light of extensive research linking nocturia to sleep apnea via the pathophysiological mechanism of excessive release of atrial natriuretic peptide from the right atrium of the heart, which in turn overstimulates kidney production of urine through the night. (67)

In our prospective study,(62) we selected 20 chronic insomnia patients without previous sleep evaluations or testing who denied having symptoms of sleep disordered breathing. All patients completed an intake set of questionnaires as well as a qualitative interview to assess subjective reasons

for awakenings. The most common subjective reasons for nocturnal awakenings were unknown reason (50%), nightmares (45%), nocturia (35%), bedroom distractions (20%), and pain (15%). No patients identified sleep breathing problems as a cause. All patients underwent PSG to assess awakenings and their causes. Of 531 awakenings observed, 90% were preceded by a sleep breathing event (apnea, hypopnea, or respiratory effort-related arousal). Thus, in a sample of chronic insomnia patients with minimal or no risks for a sleep breathing disorder, based on conventional criteria 85% of the subjects suffered from co-morbid insomnia and sleep-disordered breathing. Although these findings in combination with the aforementioned findings of frequent sleep breathing complaints among insomnia patients presenting to a sleep center strongly suggest a critical role for sleep apnea among insomnia patients, there remains certain skepticism about the construct of complex insomnia as it relates to treatment.

In our work and that of Guilleminault and colleagues,(68-74) emerging research suggests complex insomnia represents a much more common condition than previously anticipated in contrast to the wealth of research that focuses on the psychophysiological basis of chronic insomnia. Some treatment research, while involving only small samples, points to the potential for sleep breathing to play a larger role in the etiology of chronic insomnia in a sizeable proportion of patients. Most of these studies have been anecdotal or cases series with a few randomized controlled studies.(68-74) Despite the weakness in many of these designs, particularly a lack of clarity in some protocols as to selection bias and diagnostic criteria for insomnia disorders, all the studies showed improvements in insomnia symptoms subsequent to treatment for sleep-disordered breathing regardless of the therapy mode (positive airway pressure therapy, oral appliance therapy, nasal/oral airway surgery, bariatric surgery, and nasal dilator strips).

Two of the more rigorous studies included our randomized controlled trial assessing the impact of nasal dilator strips (NDS) and SDB education on insomnia severity and SDB symptoms in chronic sleep maintenance insomniacs.(69) We found patients using NDS and receiving SDB education had significantly improved insomnia, sleep quality, and life satisfaction compared to a control group. The other study, a randomized crossover prospective study by Guilleminault et al. comparing CBT-I and surgical treatment for OSA in 30 complex insomnia patients,(74) showed surgical intervention was more successful in improving insomnia than CBT-I alone. Although patients receiving initial treatment with CBT-I also showed increased TST, once these patients completed the surgical arm of the study their TST was further increased and SOL was significantly decreased.

Missing from this body of work is a rigorously designed randomized controlled trial (RCT) of positive airway pressure therapy (PAP-T) for the treatment of chronic insomnia. Such a treatment approach must naturally be conducted if we are to learn how insomnia may or may not be influenced by sleep breathing events. In our own clinical and research experience, we have found that patients with insomnia and comorbid sleep-disordered breathing ("complex insomnia") often demonstrate greater difficulty in tolerating fixed CPAP devices due to the specific problem of expiratory pressure intolerance. Thus, we have progressed toward the use of advanced PAP technology such as auto-bilevel (ABPAP) or adaptive servo-ventilation (ASV) devices in the treatment of these patients, the latter device manifesting

the best results by eliminating expiratory pressure intolerance, central-like pauses or central apneas, any or all of which may arise in patients using fixed CPAP pressures.

Clinically, we have researched two different samples at our center for the value of using advanced devices to treat insomnia patients with sleep apnea. In the first study,(75) we looked at 56 patients who had failed standard PAP therapy and reported anxiety or psychiatric distress associated with use of PAP. While being titrated on standard PAP, all were diagnosed with complex sleep apnea and were subsequently switched to ASV, which resulted in significantly improved sleep efficiency, total REM sleep time, REM consolidation and decreased awakenings, arousals, and time awake during the night. Follow-up on 39 of the 56 patients showed significantly improved adherence indices of nights used and hours per night used compared to standard PAP. Germane to the current protocol, insomnia severity markedly decreased on the Insomnia Severity Index (ISI) (16.8 vs 9.7, $p = .001$, $d = 1.40$). In a more recent study,(76) we looked at follow-up data from 281 patients with moderate to severe insomnia (ISI>15) and diagnosed comorbid OSA or UARS who were using either ASV or ABPAP. We found that regular use (>20hrs per week) of ASV was associated with sizeable decreases in insomnia severity measured on the ISI (19.0 vs 11.9, $p = .001$, $d = 1.50$).

Finally, another and equally large barrier to any successful RCT with PAP-T for chronic insomnia patients involves the use of a PAP-T placebo device. By the nature of insomnia and by the expectation that a useful insomnia treatment should be demonstrated over a minimum of 3 to 6 months, in our opinion it is unreasonable that any insomnia patient, let alone any institutional review board would accept the notion of using sham PAP therapy for 3-4 months.

Thus, given the current standard of care in the field of sleep medicine, the most pragmatic initial PAP therapy RCT protocol would involve the use of fixed CPAP as the control in comparison to the experimental group with advanced PAP technology, which from our experience would be an ASV device.

We hypothesize the following:

(1) The use of ASV PAP therapy would prove superior to standard fixed CPAP in decreasing insomnia severity on a validated insomnia research scale, increasing sleep efficiency by self-report and objectively on PSG, and improving additional subjective and objective markers of sleep quality.

Patient Selection

All adult, chronic insomnia patients presenting at Maimonides Sleep Arts & Sciences, Ltd (MSAS) are potential candidates for this study. This sleep center serves the greater Albuquerque, NM area. The population consists of treatment seeking patients for a variety of sleep disorders. The estimated number of potential participants during any given month is 5 to 10; the recruitment and patient participation should be completed over a 12 to 18 month period.

Purpose & Clinical Impact

The purposes of this study are to: (1) determine the clinical relevance of different forms of positive airway pressure (PAP) therapy in treatment of sleep breathing events in chronic insomnia patients with co-morbid sleep-disordered breathing; (2) measure the impact of such treatment on insomnia severity; and (3) demonstrate a potential role for this new therapeutic pathway for chronic insomnia patients.

Protocol

Abstract:

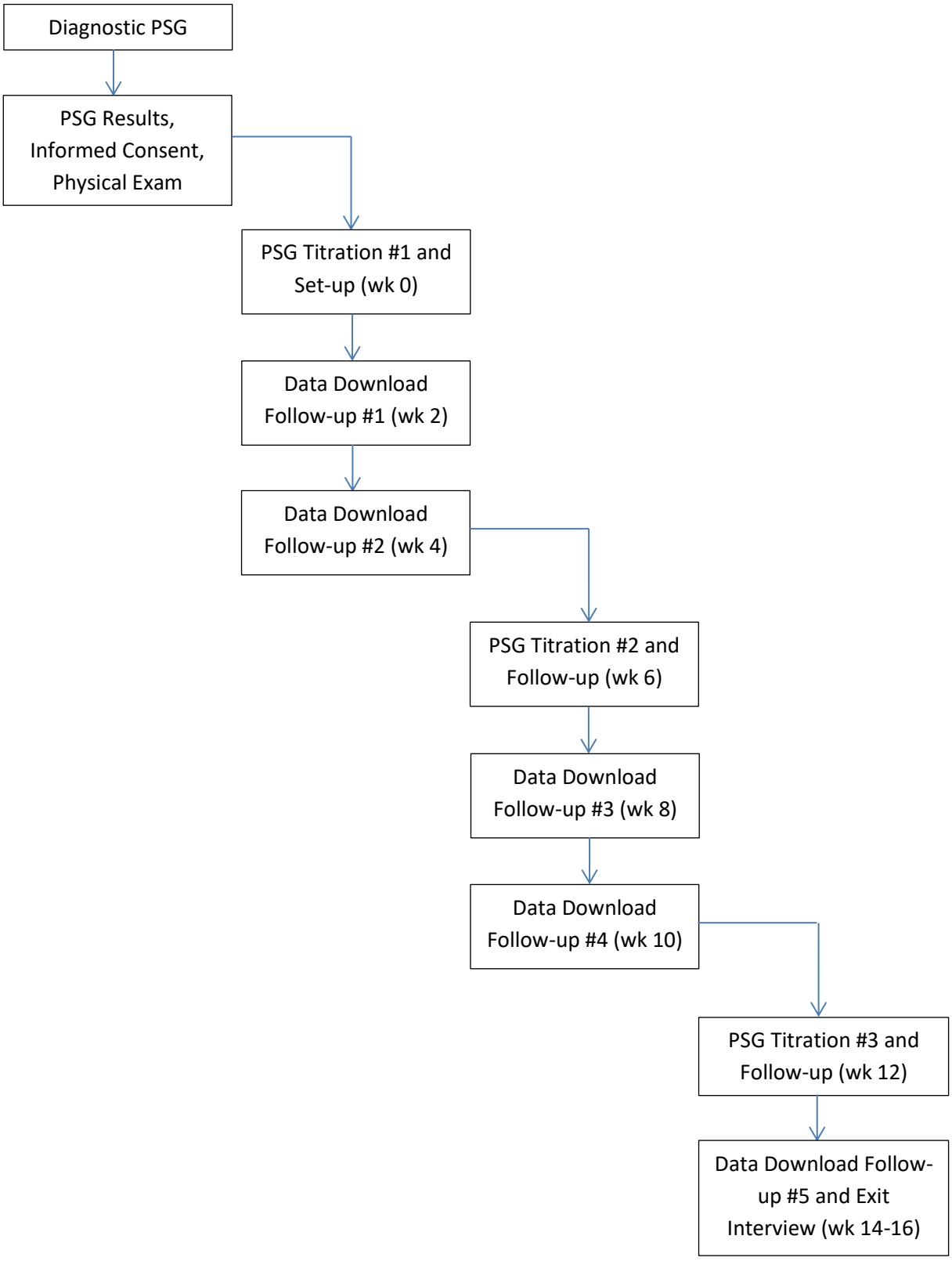
As presented in the in-depth Background material, emerging research strongly indicates the need for an RCT to evaluate the role of PAP therapy in the treatment of chronic insomnia. This study, succinctly summarized in the following two flow charts (A. Patient Encounters; B. Patient Timetable) proposes this project to test standard CPAP therapy versus a more advanced form of CPAP therapy known as adaptive servo-ventilation (ASV). During a 14-16 week period, two groups of approximately 25 patients each will use either CPAP or ASV, and their specific sleep outcomes and related variables will be tracked daily or every two weeks to provide data for a final comparative analysis between the two groups. The summary of endpoint objectives (page 10) following the two flow charts describes the primary and secondary outcomes for this study.

Flowchart A: Patient Encounters in Protocol Steps. This chart describes the entry of the patient into the study after confirmation of the diagnosis of SDB.

Flowchart B: Patient Timetable and Protocol Steps. This chart describes estimated time commitment for each participant once the diagnosis of SDB is confirmed.

Flow charts and timetables:

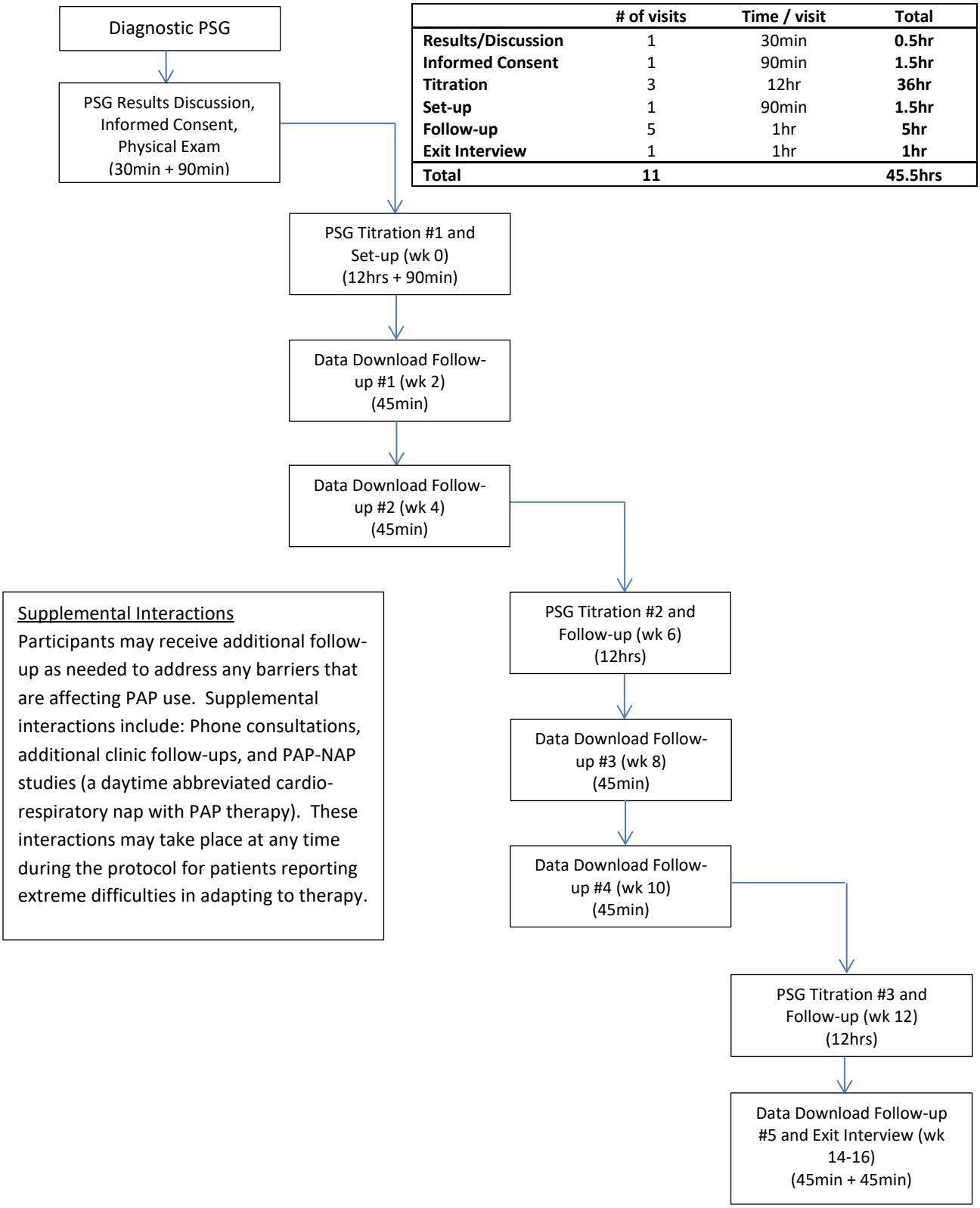
Flow chart A: Patient Encounters in Protocol Steps



Flow chart B: Patient Timetable and Protocol Steps

Patient Time Commitment Estimation

	# of visits	Time / visit	Total
Results/Discussion	1	30min	**0.5hr**
Informed Consent	1	90min	**1.5hr**
Titration	3	12hr	**36hr**
Set-up	1	90min	**1.5hr**
Follow-up	5	1hr	**5hr**
Exit Interview	1	1hr	**1hr**
Total	**11**		**45.5hrs**



Supplemental Interactions

Participants may receive additional follow-up as needed to address any barriers that are affecting PAP use. Supplemental interactions include: Phone consultations, additional clinic follow-ups, and PAP-NAP studies (a daytime abbreviated cardio-respiratory nap with PAP therapy). These interactions may take place at any time during the protocol for patients reporting extreme difficulties in adapting to therapy.

Summary of Endpoint Objectives:

Primary Endpoint objectives:

- Change in insomnia severity from baseline to 4 months as measured by the Insomnia Severity Index (ISI)
- Sleep Diary sleep quality rating (8 point Likert scale)
- Global Morning Rating of Nightly Sleep (0-100% scale)
- Change in prospective sleep log data for insomnia parameters (SOL, WASO, SE)

Secondary Endpoint Objectives:

- Objective improvements on sleep studies
  - Sleep breathing indices (AHI, RDI)
  - Sleep consolidation indices (SE%, REM%, REM min)
  - Objective Data Download (% compliance; % use, AHI, flattening %)
- Subjective Validated Psychometric Instruments
  - Sleep related impairment (ESS, VAS-F, VAS-S, III, FSS, SDB-6)
  - Quality of Life/Impairment (FOSQ-10, QLESQ, HSCL)

Other Tracking Variables

- PAP Therapy Tracking Tools
  - PUDS, AEC, NOSE-8
- Change Tracking Tool
  - PGA (Insomnia, Sleep Quality, Fatigue, Sleepiness, Energy level)
  - Exit Interview

Subject Recruitment and Eligibility:

All adult insomnia patients presenting at MSAS are potential candidates for this study. Potential participants are pre-screened to identify likely candidates. Medications need to be clarified and a discussion regarding possible upcoming medication changes/adjustments is necessary. The patients' travel plans for the next 3-6 months need to be discussed: length of trip, time zone changes, and dates of trip. Does the patient have computer access and will they be able and willing to complete daily 5min online tasks? Evaluate the patient's transportation situation and ability to return to the facility for follow up visits. Certain medical conditions or lifestyle habits may exclude patients from the protocol, including but not limited to: asthma, COPD, RLS, PLMD, smoking, epilepsy. Query mental or medical health problems and any upcoming procedures that may interfere with research protocol including surgery or elaborate testing that may affect sleep and decide if it is possible to work around these dates. Besides talk therapy, determine whether there are any plans for shock therapy or other brain stimulation that may affect sleep physiology. Have they recently started or do they plan to start insomnia treatment within the next few months (aside from coming to our sleep center for insomnia help)?

Participants who are currently treating their insomnia are eligible for the protocol as long as they maintain (or decrease/cease) the same treatment program throughout participation. Example: a patient taking sleep aids may continue to take sleep aids or decrease their dose but may not increase the dose or add another treatment, such as cognitive therapy, during involvement with this protocol.

Inclusion and Exclusion Criteria:

Inclusion criteria:

1. ≥ 18 years old
2. Primary complaint of insomnia when presenting at clinic
3. Diagnosis of moderate to severe insomnia through the Insomnia Severity Index (ISI) with a score ≥ 15
4. Meet diagnostic criteria of Insomnia Disorder (per American Academy of Sleep Medicine)
5. Diagnosis of SDB, either OSA as determined by an AHI ≥ 5 events/hour or UARS with a RDI ≥ 15 events/hour and AHI < 5 events/hour
6. Naïve to treatment for sleep-disordered breathing (SDB), including CPAP, APAP, ASV; mandibular repositioning devices (MRDs), and any other nasal or oral therapy with a primary indication of treating SDB
7. Able to fully understand study information in English and sign informed consent

Exclusion criteria:

1. Primary complaint of sleep-disordered breathing or issues with apneas during sleep
2. Severe respiratory disorder or severe sleep disorder such as restless leg syndrome (RLS), idiopathic hypersomnia, or narcolepsy
3. BMI > 30 kg/m^2
4. Epworth Sleepiness Scale (ESS) score ≥ 10
5. Frequent napping behavior, such as a few times a week or more
6. Anticipated changes to start or stop sedative or psychotropic medications during the course of the trial.
7. Medical history of congestive heart failure (CHF) or other potentially unstable cardiac disease as well as chronic lung diseases or other debilitating medical conditions that manifest as more prominent in the patient's health compared to their sleep complaints.
8. Daily use of opiate medications
9. Known contraindications to PAP therapy as listed in the indication for use
10. Requires a CPAP (fixed) pressure > 20 cm H_2O
11. Inability to comply with study procedures

Informed Consent:

Patients will first be introduced to this research following completion of their New Patient Intake (a set of online questionnaires completed by all MSAS patients upon referral to our sleep center). They will be pre-screened for eligibility prior to their diagnostic PSG. Following MD review and interpretation of the diagnostic PSG, qualifying research candidates will be scheduled to meet with a research coordinator to discuss their results in detail (SDB, hypoxia, sleep fragmentation, sleep architecture, etc.). The research protocol will be introduced by discussing the relationship between SDB and sleep fragmentation as well as treatment credibility of PAP therapy. By reviewing his or her study and discussing the research protocol at the same time, we can illustrate how nighttime awakenings due to SDB are fragmenting sleep and discuss how this study will test whether or not treating these breathing events with different types of PAP may change their insomnia.

Study protocol is thoroughly discussed with patient and they are educated on insomnia as it relates to SDB. Patients will be informed that we are comparing two devices to find out which is more

effective in treating SDB events in patients with chronic insomnia and what impact this treatment has on decreasing insomnia. Once they have signed the informed consent form, they will be randomized into a treatment group but will have the option to try the other treatment at the end of the study.

Patients will meet with Dr. Krakow at this point to undergo a brief airway exam and are given the opportunity to ask Dr. Krakow any remaining questions. Candidates who do not qualify for the study following diagnostic PSG will continue to receive care in the sleep center as appropriate.

Study Procedure Summary (4 Phases)

Phase 1: Pre-Screening Steps and Enrollment in the Study

These steps may take place over the course of several days to complete all pre-screening and enrollment encounters.

First Encounter (by phone)

1. Patient seeks treatment at sleep center for chronic insomnia and completes Web Intake (full medical history and sleep history).
2. Physician reviews medical history, including concomitant medications, demographic information, and collects weight and height to assess BMI.
3. Dr. Krakow informs research coordinator of potential eligibility.
4. Research coordinator contacts patient to complete pre-screening survey.
    a. Patient informed whether they have potential eligibility based on pre-screen.
    b. Patient informed of Dr. Krakow's recommendation for proceeding according to standard of care, regardless of research interests.

Second Encounter (in person, at sleep lab)

1. Patients expressing interest in the protocol will be scheduled for and will complete the Diagnostic PSG.
    a. Dr. Krakow completes interpretation and recommendations per standard of care following a diagnostic study.
    b. If OSA or UARS positive (and confirmed by independent scorer), patient is scheduled for full explanation of research project and signing of informed consent form.
    c. If OSA or UARS negative, patient will be informed and will proceed with standard clinical care.

Third Encounter (in person, at sleep lab)

1. PSG results discussion with research coordinator
2. Confirmation that the patient meets I/E criteria
3. Patient reviews and signs informed consent form
4. Dr. Krakow conducts airway exam and answers patient questions.
5. Subject randomized to treatment arm
6. Completion of special baseline questionnaires
    a. One week Sleep Diary (see below) with Global Morning Rating of Nightly Sleep
    b. Insomnia Impairment Index

c. Fatigue Severity Scale
d. Intake Supplement

7. Schedule Titration #1

Phase 2: Treatment

Titration Procedure

1. Mask fit and mask evaluation.
2. Sleep technologist titrates the participant following AASM guidelines with his or her assigned mode to: eliminate all forms of abnormal SDB, consolidate sleep, and achieve REM sleep
3. MD will review study and determine starting pressures for each participant.
4. Study scored by an independent sleep technologist.
1. **Equipment Set-up Procedure at MSAS**VPAP Adapt set to patient's assigned mode (CPAP or ASV) and prescribed pressure settings.
2. Participants given their device, tubing, and mask at the clinic within 2 days of their titration.
3. A research coordinator spends time teaching the individual how to properly use device and mask at home. Patient must be able to demonstrate mastery of mask and machine.
4. Possible side-effect symptoms (soreness on pressure points, red marks, aerophagia, etc.) discussed at this time to expedite care if an issue arises.

Once the patient is set-up, he or she receives instructions for follow-up steps and procedures. Scheduling of all Follow-up appointments and titration studies will take place at this time.

Phase 3: Follow-up

Sleep Diary

Once patients are set-up with their PAP device, they are expected to complete the online Sleep Diary each morning. It should take no longer than 5min to complete this brief survey. The sleep diary measures:

1. Subjective sleep indices:
    a. Bed Time (BT)
    b. Sleep Onset Latency (SOL)
    c. Wake After Sleep Onset (WASO)
    d. Total Sleep Time (TST)
    e. Time in Bed (TIB)
    f. Time Out of Bed (OOB)
2. Subjective sleep quality:
    a. Sleep Quality rating: an 8-item Likert scale for sleep quality ratings in the morning
    b. Global Morning Rating of Nightly Sleep: patients rate their sleep on a 0-100% scale.
3. PAP Adaptation:
    a. PAP Units of Distress Scale (PUDS): a scale from 0-10 measuring current subjective distress as it relates to PAP therapy.

4. Patients will be prompted to indicate if something has changed, such as medications, when they fill out this daily diary

Follow-up Visits

Participants will return every 2 weeks following their titration study for a follow-up clinic appointment conducted by sleep technologist with availability of Dr. Krakow for relevant Q&A with patient. The following will be completed at each follow-up appointment:

1. Outcomes: Subject completes the following questionnaires:
    a. Validated research instrument for tracking insomnia: ISI
    b. Sleep related impairment: ESS, VAS-F, VAS-S, III, FSS, SDB-6
    c. Quality of Life/Impairment: FOSQ-10, QLESQ, HSCL
    d. PAP Therapy Tracking Tools: AEC, NOSE-8
    e. Change Tracking Tool: PGA (Insomnia, Sleep Quality, Fatigue, Sleepiness, Energy level)
2. Data, download from the VPAP Adapt.
    a. Usage
    b. AHI, flattening %
3. Review device usage. Address concerns or questions including:
    a. Progress and experiences with PAP
    b. Benefits or lack thereof
4. Review sleep diary.
5. Determine if the subject has had any adverse events or adverse device effects.
    a. Troubleshoot as needed

Summary: Following initial titration, the following steps will reoccur for the remainder of the protocol (refer to initial flow chart to see repetition of steps):

- Patients return on weeks 2 and 4 for Follow-up visits
- On week 6 they repeat titration process and complete Follow-up visit surveys and downloads
- Return on weeks 8 and 10 for follow-up appointments
- Return on week 12 for a final titration

Phase 4: Exit Interview

The Exit Interview occurs 2-4 weeks after the final titration. The following will be completed during this visit:

1. Complete Follow-up Visits steps (Outcomes, Objective Data Download, review device usage and sleep diary, determine if there have been any adverse events)
2. Complete Exit Interview
3. Discuss next course of treatment such as:
    a. Transfer to clinical care at our sleep center or another sleep center of their choosing

b. Referral for alternative SDB treatment option
c. Clarifying any intent for switching PAP mode from that used during the protocol
d. Clarification of any insurance and DME questions going forward
e. Formal transfer of PAP device into patient ownership
f. Reimbursement of travel funds

Supplemental Follow-up Care

Pressure intolerance, mask problems, leak, and other adaptation issues will be addressed to maximize PAP use in all participants. Follow-up visits, PAP Naps, and phone calls will be available to help subjects acclimate to PAP and troubleshoot barriers. Clinical judgment will be used to determine the type of follow-up the subjects will need over the course of the trial. Subjects will be followed until the PAP concern or issue resolves. The type of follow-up (titration or PAP Nap or phone call or clinic visit), the PAP area of concern, how the concern was addressed will be recorded in study documents and case report forms (CRFs).

1. PAP-NAP
    a. Daytime abbreviated cardio respiratory desensitization study
        i. Used for patients having difficulty adapting to any aspect of PAP
    b. Individualized attention allows for gradual introduction to PAP with increased attention from a sleep technologist
    c. Can also be used to address mask and intolerance issues.
    d. Can occur at any time during the treatment, based solely on patient problems with compliance, and it often is an intervention that specifically can reduce drop-outs.
    e. The number of PAP-NAPs per each patient will be limited to one. In special circumstances, a patient may need an extended PAP-NAP conducted at night.
2. Phone Consult
    a. Participants have access to research assistants (and sleep technologists) to discuss or troubleshoot any issue that may come up during the course of the protocol, and as described on the Informed Consent Form, sleep technologists or Dr. Krakow can be contacted during the overnight hours for urgent issues.
3. Clinic Follow-up
    a. Follow-up to address any issues that need hands on attention (like mask issues) will be available to participants as needed.

Special Considerations

Due to the nature of this study and its short duration, it is necessary to expedite care of any issues that may be barriers to rapid acclimation of PAP. Without reasonably rapid acclimation, results will be skewed toward less than optimal outcomes for either treatment arm, therefore the items below will be addressed both prophylactically and as they arise.

1. Mask Issues
    a. Common mask issues discussed with the patient during Set-up as well as trouble shooting for each problem.

i. Mouth breathing or mouth leak
    - chinstrap will be demonstrated
ii. Mask leak
    - Proper mask fit
    - Tightening the mask
    - Chinstrap
    - Mask liners (mask liners will also be recommended for soreness, mask creases, and pressure spots)

2. Aerophagia (air swallowing)
    a. PAP therapy complication that can be very uncomfortable or even painful.
    b. We would like all participants to be aware of aerophagia and bring this symptom to our attention immediately.
    c. Leg jerks, mask issues, reflux, NAR, and pressure intolerance can all cause aerophagia and will require clinical attention.
3. Leg Jerks (sub-cohort potential)
    a. Patients who did not report restless leg or periodic limb movement symptoms on their intake, but had significant leg movements during their diagnostic PSG (not respiratory related) will be excluded from the study if the leg jerks persist on the titration.
    b. Patients who do not report leg movement symptoms on their intake and do not exhibit leg movements on their diagnostic PSG but do exhibit leg jerks on any titration study, will require careful re-evaluation of clinical care by Dr. Krakow to determine if leg jerks are a separate co-morbid medical issue requiring withdrawal from the study.

Research Rationale for Procedures

Titration #1 (Initial)

Participants return to MSAS sleep lab for a full night titration study during which only their assigned mode will be used. They will be fit with several masks and, with the help of a sleep technologist, will identify the best mask to start the PSG with and use during the study. The sleep technologist will titrate PAP pressure settings for each participant following AASM guidelines to eliminate all abnormal SDB wave forms, consolidate sleep, and achieve REM sleep with the assigned mode. All titrations will begin with low pressures, as recommended by the AASM, to help improve adaptation. Pressure settings will be determined to eliminate all SDB events (including RERAs). We anticipate that within the CPAP group the following trend will occur: aggressive treatment of RERAs will require increased pressure settings; these pressures will lead to expiratory pressure intolerance (EPI) or intolerance; and, “down” titration will be necessary for patient comfort. The highest pressures tolerated by the patient may not be equivalent to the pressures needed to effectively treat all SDB events. We would prefer to use pressures that treat all SDB events (including RERAs), but this may be an unrealistic goal for the CPAP group during the titration or the early adaptation period. Although we don’t anticipate as much of an issue of EPI or intolerance within the ASV group, we will follow the AASM procedure of “down” titration if it is needed. To avoid EPI and to help patients adapt to PAP, it may be

necessary to start CPAP patients on settings that do not treat all SDB events and increase settings over time. This approach may also occur with some ASV patients, but we expect the proportion of ASV patients with intolerance to be smaller than those using CPAP.

One other caveat to the above titration approach is the unlikelihood of finding the optimal pressures for any SDB patient upon first exposure to PAP therapy in the lab. Problems such as hysteresis, anxiety, psychophysiological discomfort, attention amplification, distress intolerance, and claustrophobia all weigh against an individual's ability to immediately adapt to PAP therapy. With this lack of immediate adaptation, certain pressure settings may prove intolerable. By way of an easier analogy, patients will be informed that learning to use PAP may be like learning to drive a car. In the beginning slower speeds (lower pressures) are more comfortable, and some training or experience may be needed before merging onto the highway to experience faster speeds (higher pressures). Returning to driving school (titrations in sleep lab) twice more during this protocol will enhance experience and expedite the capacity to adjust to higher pressures.

The studies will be scored by an independent sleep technologist to create consistency with baseline assessments and to prevent bias in the measurement of objective measures. Scoring technologist will be blinded to PAP mode. If discrepancy arises between independent scorer and MSAS technologist, the MD will review for final determination.

MD will review the study and prescribe PAP settings for each participant within 2 days of titration. It would be preferable to start all participants with their optimal pressure setting found during the titration, but as noted above lower pressures may be needed initially (preferably for no more than 1-2 weeks, leading up to first follow-up appointment) to help patients adapt to PAP therapy.

Set-up

At MSAS, the research coordinator will set VPAP Adapt to assigned mode and prescribed pressure settings. Patient will be introduced to device/humidifier and educated on use and proper maintenance. A prescription will be sent to a DME company for additional PAP mask and supplies. Interim equipment from MSAS will be used for initial set up. Common PAP and mask issues will be discussed with the participant as well as how we will be able to help them address these issues if needed, including the role of mask liners (e.g. REMzzz or padacheek) among those complaining of skin or other facial irritation, redness, or soreness

Common barriers that arise soon after set-up most likely involve mouth breathing, mask leak, and air swallowing (aerophagia). Patients will be informed prophylactically about these issues so they can address them as they arise during the titration or shortly thereafter. It is not uncommon for these factors to arise over time and will be dealt with through aggressive follow-up (see Special Considerations below).

Participants will be instructed on how to fill out the daily online sleep diary. All Follow-ups and titrations will be scheduled at this time. Research coordinator will document PAP setting, PAP pressure, mask type, and other relevant information from this encounter.

Follow-up Appointments

The goal is to achieve the maximum number of participants using the device. To reiterate, all participants are required to attend a total of seven follow-up appointments (2 full night studies after initial titration, 4 data download and progress appointments, and final data download and progress appointment with an exit interview). Additional follow-up appointment frequency will vary based on individual needs. All follow-up will be documented by research coordinator.

Online Follow-up

Sleep Diary

A sleep diary will be available online for patients to fill out daily. The sleep diary tracks subjective: bed time (BT), sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), out of bed time (OOB). They will also complete an 8-item Likert scale for sleep quality ratings in the morning as well as the Global Morning Rating of Nightly Sleep where patients rate their sleep on a 0-100% scale. The last question will be a rating on our PUDS scale to assess distress or lack thereof in using PAP therapy. Patients will be prompted to indicate if something has changed, such as medications, when they fill out this daily diary.

Clinic Follow-up

All participants are required to attend 5 clinic follow-up visits with a clinical research coordinator (refer to flowchart). The first is 10-14 days after set-up, the second is 10-14 days after their first follow-up, the third is 10-14 days after titration #2 (see below), fourth is 10-14 days after third follow-up, and final follow-up is 14-28 days after titration #3. These clinic follow-up visits will consist of: data download, outcomes, and qualitative measure of the participants progress.

Data Download

Objective data will be downloaded from the device.

Outcomes and Scales

ISI, III, ESS, FSS, QLESQ, FOSQ-10, VAS-F, VAS-S, HSCL, SDB-6

Patient Global Assessment scale, Adverse Effects Checklist, NOSE-8,

Qualitative Measure

This includes a discussion with patient regarding their progress and experiences with PAP. Are they receiving any benefits? Do they feel differently? We will also address anything noted on Outcomes and Scales that suggests a problem or barrier has arisen or remains unresolved.

Titration #2 (Repeat)

All participants will be required to undergo a full night retitration 6 weeks following set-up. In order to test this efficacy hypothesis accurately, retitrations are necessary every 6 weeks. In our clinical experience, we have found that pressures need to be adjusted frequently as patients adapt to PAP therapy. Physical changes in the airway during the adaptation process

require fine tuning of pressure settings of usually 1-2cmH_2O. The two retitration studies (at 6wks and 12wks) are key components to ensuring participants are using the most optimal pressure settings as they progress through the adaptation process. Data will be downloaded from each device at these studies and patients will complete all Follow-up outcomes and scales.

Titration #3 (Final)

The final titration study will not only serve as an opportunity to reevaluate pressure needs but also to measure sleep indices: sleep onset latency, wake after sleep onset, sleep as proportion of TIB, sleep efficiency, sleep architecture, AHI, RDI, CAI, etc. This comparison will serve as the main pre and post objective comparison of data, because we anticipate the patient's adaptation to the device to be approaching an optimal point, and therefore, the objective metrics would most likely show the most well consolidated sleep compared to baseline. However, in some cases, pressure tweaks may still be needed, which then permits opportunity for another minor adjustment of the device. The patient then will be permitted to use these new settings for the next two to four weeks before the exit interview. This two to four week period then is quite important for that proportion of patients where pressure settings were still not optimal until undergoing the third titration. For some, if the minor pressure tweaks approach optimal, we will see noticeable therapeutic gains in that final few weeks of use on the new settings.

Supplemental Follow-up/Care

PAP Nap

The PAP-Nap is our daytime abbreviated cardio respiratory desensitization study. Participants who are having difficulty adapting to any aspect of PAP may benefit from this procedure to help trouble shoot barriers. The individualized attention allows patients to be introduced to PAP in a gradual fashion with increased attention from a sleep technologist. PAP Naps can also be used to address mask and intolerance issues. This PAP Nap can occur at any time during the treatment, based solely on patient problems with compliance, and it often is an intervention that specifically can reduce drop-outs. The number of PAP Naps per each patient will be limited to one. In special circumstances, a patient may need an extended PAP Nap conducted at night.

Phone Consult

Participants will have access to research assistants (and sleep technologists) during the day to discuss or troubleshoot any issue that may come up during the course of the protocol, and as described on the Informed Consent Form, Dr. Krakow can be contacted during the overnight hours if needed. By having access to these resources, we hope to help patients adapt to PAP and use PAP nightly.

Clinic Follow-up

Extra daytime follow-up to address any issues that need hands on attention (like mask issues) will be available to participants as needed.

Special Considerations

Mask Issues

Common mask issues will be discussed with the patient during Set-up as well as first line trouble shooting for each problem. For mouth breathing or mouth leak, the chinstrap will be demonstrated. For mask leak, proper mask fit, tightening the mask, chinstrap, and mask liners will be discussed. Mask liners will also be recommended for soreness, mask creases, and pressure spots. Due to the nature of this study and its short duration, it is necessary to expedite care of these issues that may be barriers in rapid acclimation to PAP. A lack of reasonably rapid acclimation will skew the results toward less than optimal outcomes, therefore the above items will be addressed both prophylactically and as they arise.

Aerophagia

Aerophagia, or air swallowing, is a complication with PAP therapy that can be very uncomfortable or even painful. We would like all participants to be aware of aerophagia and bring this symptom to our attention immediately. Leg jerks, mask issues, reflux, NAR, and pressure intolerance can all cause aerophagia and will require clinical attention.

Leg Jerks (sub cohort potential)

Patients who did not report restless leg or periodic limb movement symptoms on their intake, but had significant leg movements during their PSG (not respiratory related) may be excluded from the study if they continue to show leg jerks on their titration study. Patients who do not report leg movement symptoms on their intake and do not exhibit leg movements on their diagnostic PSG but do exhibit leg jerks on any titration study, will require careful re-evaluation of clinical care by Dr. Krakow to determine if leg jerks are a medical issue requiring withdrawal from the study.

Final Datasets

Following the final titration, participants will return between weeks 14 and 16 to meet with a research coordinator to obtain a final data download and complete final outcomes questionnaires. This meeting also includes: follow-up care program, exit interview, scheduling into the clinical venue, opportunity to try other mode of PAP therapy, clarifications regarding the free equipment, and reimbursement for travel.

Follow up care program

Patients will be instructed to continue follow up as needed for treatment of their SDB and Insomnia. They will be transitioned into the patient population standard of care at MSAS or to another sleep center of their choosing. Patients may choose for referral for an alternative SDB treatment option.

Exit interview

Patients will undergo an Exit Interview and will be queried on five general topics: 1) general study overview; 2) PAP effectiveness; 3) PAP and sleep medication; 4) long-term treatment of sleep-disordered breathing; and 5) PAP devices and masks. Questions the

participant may have for us are addressed at this time. Any final measures and paperwork will be completed.

Final Dataset of RCT

The final dataset comprises those participants in 14 to 16 week window and will be used for the primary research paper for this study to address the comparison between CPAP and ASV in the treatment of SDB events among chronic insomnia patients as well as the resultant outcomes from these distinct therapies.

Six month follow-up

Outside of the research project, all participants will be scheduled for a 6 month follow up to track their progress with PAP therapy and their Insomnia. During this time, although there will be no formal cross over study, we will clarify which patients intend to continue to PAP use and in which mode, which means that some patients may have changed to a different mode after the completion of the RCT protocol. As such, patients originally assigned to CPAP may need to undergo a PSG titration study to find the most accurate pressures or to qualify for ASV therapy as it relates to their insurance coverage. We will strongly recommend this course of treatment to relevant patients. Then at the 6 month mark we will compile any available data from the cohort that continues using in preparation for a case series report, if such data offers scientific value. Otherwise, our main focus by the six month follow-up is to maintain continuity of care to insure a proper transition from the research venue to the clinical care model.

Equipment

There will be a discussion of free VPAP Adapt and H5i units and official transfer of PAP device into participant ownership. Masks and supplies need to be supplied through a DME company and any clarification of insurance can be addressed at this time.

Travel Reimbursement

Participants will be reimbursed $80.00 for travel costs during this study. This rate can be prorated for patients who did not complete the study.

Questionnaires:

Insomnia Severity Index (ISI): The seven-item questionnaire asks the individual to rate the level of insomnia and perceptions of sleep problems in the last two weeks. Answers must be provided using a scale from 0-4, with 0 reflecting no problem or being very satisfied to 4 indicating a very severe or very dissatisfied experience. Scores are divided into four tiers: 0-7 equates to no clinically significant insomnia, 8-14 equates to subthreshold insomnia, 15-21 indicates moderate severity insomnia, and 22-28 reflects severe insomnia.

Epworth Sleepiness Scale (ESS): The ESS is a simple, self-administered questionnaire which provides a measurement of an individual's general level of daytime sleepiness. The responder is asked on a scale of

0–3 to score the likelihood of falling asleep in eight various situations. A higher score indicates a higher level of sleepiness.

Functional Outcomes of Sleep (FOSQ-10): The FOSQ-10 is a shorter version of the FOSQ, an instrument used in both research and clinical practice to assess the impact daytime sleepiness has on daily living activities. Global scores range from 5 to 20; scores less than 15 indicative of severe impairment.

Visual Analog Scale for Fatigue (VAS-F): A single question on an 11 point Likert scale evaluating daytime fatigue. Higher scores are indicative of more fatigue.

Visual Analog Scale for Sleepiness (VAS-S): A single question on an 11 point Likert scale evaluating daytime sleepiness. Higher scores are indicative of more fatigue.

Insomnia Impairment Index (III): The III is an 11 item survey based on research diagnostic criteria for insomnia disorder, which measures forms of daytime impairment in relation to nighttime sleep difficulties. It uses a 5 –point Likert scale and is scored with an inter-item average (0 to 4), with higher scores denoting more impairment.

Fatigue Severity Scale (FSS): FSS is a 9 question survey on a 7 point Likert scale evaluating daytime fatigue. Higher scores are indicative of more fatigue.

Sleep Disorder Breathing (SDB-6): A 6 item survey assessing frequency (on a 4 point scale) and intensity (on a 4 point scale) of end organ symptoms of SDB including cognitive impairment, morning headache, dry mouth, and nocturia.

Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ)-Summary Sheet: QLESQ is a 17 question survey measuring current life satisfaction. It is an abbreviated version of the full QLESQ and is an expedient and satisfactory substitute for the full version.

Hopkins Symptom Checklist (HSCL): This well-known and widely used 25-item inventory measures symptoms of anxiety and depression. Part I of the HSCL has 10 items for anxiety symptoms and Part II of the HSCL has 15 items for depression symptoms. All questions are measured on a four point scale ranging from “Not at all” to “Extremely”.

Patient Global Assessment of Sleep (PGA): The PGSA consists of 5 question subjectively assessing daytime and nighttime insomnia symptom improvement (or worsening) on a percent scale in comparison to the intake assessment.

PAP Units of Distress Survey (PUDS): The PUDS is a scale of 0-10 measuring current subjective distress as it relates to PAP therapy. This survey is based on the Subjective Units of Distress Scale (SUDS) typically used in a clinical desensitization-based therapy setting to evaluate treatment progress.

Adverse Effects Checklist (AEC): This checklist consists of common side effects or adverse experiences common to new PAP users. Symptoms are categorized into three groups: mask problems, pressure problems, or other problems. The checklist will facilitate discussion with the patient at follow-up.

NOSE-8: This 8 question survey queries patients on congestion, stuffiness, or runny nose symptoms as they relate to sleep and PAP use on a 5 point Likert scale. This questionnaire also measures subjective treatment efficacy of these symptoms.

Intake Supplement: This questionnaire is a baseline assessment of the patient's understanding of the treatment rationale and their views on PAP and sleep medication, so that we can compare any changes in views at the exit interview.

Exit Interview Questionnaire (EIQ): This questionnaire is an assessment of the patient's perception of the study including: general overview, treatment rationale, effectiveness of PAP therapy, PAP and sleep medication, long-term treatment of SDB, and PAP devices and masks.

Sleep Diary: A sleep diary will be available online for patients to fill out daily. The sleep diary tracks subjective: bed time (BT), sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), and out of bed time (OOB). They will also complete an 8-item Likert scale for sleep quality ratings in the morning and rate their sleep on a 0-100% scale. The last question will be a rating on our PUDS scale to assess distress or lack thereof in using PAP therapy. Patients will be prompted to indicate if something has changed, such as medications, when they fill out this daily diary.

> **Sleep Diary Sleep Quality Rating (8 point Likert scale):** This is a single question on an 8-point Likert Scale (0= extremely good sleep to 7=extremely poor sleep) assessing subjective sleep quality.
>
> **Global Morning Rating of Nightly Sleep:** This is an experimental variable using a global rating system to help us track nightly changes in the sleep experience. In this daily subjective rating scale, 0-100%, 0% reflects an awful night of sleep and 100% reflects a great night of sleep.
>
> **PAP Units of Distress Survey (PUDS):** The PUDS is a scale of 0-10 measuring current subjective distress as it relates to PAP therapy. This survey is based on the Subjective Units of Distress Scale (SUDS) typically used in a clinical desensitization-based therapy setting to evaluate treatment progress.

Polysomnography:

Polysomnography will be completed at three different time points during the protocol: a diagnostic PSG study is completed during screening (not part of protocol) and three titration PSG studies are completed during the protocol (including a final study completed after four months of treatment with either CPAP or ASV).

PSGs will be conducted by registered sleep technologists at the investigative site. Titration protocols will be followed based on the subject's treatment arm. Scoring criteria will be applied using version 2.0 of the AASM Scoring Manual. PSGs will be scored by the sleep technologist on the night of the study as well as a third party sleep technologist who will be blinded to the treatment mode so as to preserve data integrity.

PSG parameters to be collected include:

- Total sleep time (minutes)
- Total recording time (minutes)
- Sleep efficiency (total sleep time/total recording time)
- Sleep stages (% and minutes of total sleep time): Stage 1, Stage 2, Stage 3, REM
- Awakenings index (arousals/hour)
- Arousal index (arousals/hour)
- Wake after sleep onset (minutes)
- REM consolidation index (total REM time in min/total # of discrete REM periods)
- Apnea-hypopnea index (events/hour)
- Obstructive apnea index (events/hour)
- Central apnea index (events/hour)
- Oxygen desaturation index (events/hour)
- Respiratory effort related arousal (RERA)
- Respiratory disturbance index (RDI)

Power Analysis, Sample Size Data Analysis

Power Analysis and Sample Size:

Based on our description in the background (see page 6), our work with ASV anticipates an effect size of at least 1.40 to 1.50 change in insomnia severity with ASV PAP therapy. Whereas, based on our clinical experience we presume that the effect of CPAP on insomnia would yield an effect size range between 0.50 and 0.70. Thus, the average net effect between ASV and CPAP use would be ~0.80 effect size. Using a resource specific to clinical research(77)in order to calculate power and sample size estimates, we used a beta of .90 for two tailed significance testing at .05 which arrived at 26 patients per group, or a total sample of 52. Therefore, using the less stringent criteria of beta .80, we believe our sample size allotments of 25 per group or 50 total should prove more than sufficient for this protocol.

Data Analysis:

Primary analysis is a repeated measures ANOVA to test for a group by time interaction with calculated effect sizes (Cohen's d or Hedges g). The initial analysis will be with a single ISI score. Both study completers and intent-to-treat (ITT) analyses will be conducted, albeit this is an efficacy study therefore the ITT is not necessarily germane to the focus of the work.

Several other variables will be analyzed in similar fashion (breathing event indices, sleep consolidation indices, sleep diary metrics, addition secondary variable measurements). As indicated by post-hoc factor analyses, we may also conduct more advanced multi-variate analyses.

Risks/Benefits:

Risks:

The study is considered to be of low risk to subjects in that PAP Therapy will be used as indicated according to the instructions for use, and study devices will be dispensed by trained clinic staff, who will also oversee the subjects throughout the course of their study participation. Safety events

reported by subjects and observed by the investigator and study staff will be carefully reviewed and treated as required by the Patient Safety Advocate.

Adverse Events and Adverse Device Effects

An Adverse Event (AE)/Adverse Device Effect (ADE) is any untoward occurrence in a subject or clinical investigation where the subject has been administered an investigational product and which does not necessarily have a causal relationship with this product. An AE/ADE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product or clinical investigation procedure, whether or not related. At each evaluation, the investigator will determine whether any adverse events (AEs) or adverse device effects (ADEs) have occurred. For the purpose of this protocol, an adverse event and adverse device effect is any undesirable clinical occurrence in a subject that can be attributed to the device or procedure required by this protocol.

Certain adverse effects are anticipated with the use of PAP therapy. Expected adverse effects are usually mild in intensity and resolve within 24 hours after discontinuing the use of the device. The following adverse effects may occur:

- Drying of the nose, mouth or throat
- Nosebleed
- Ear or sinus discomfort
- Eye irritation
- Skin rashes

Anticipated adverse effects that are mild in intensity and resolve within 24 hours do not need to be recorded in the case report forms (CRFs).

Benefits:

All participants will receive extensive free clinical care in this protocol. At the completion of this study, when participants have completed all the steps in the protocol, they will receive free of charge the same PAP device they used during the study.

Data Collection and Storage:

All data will be stored at SHHI. Patients will enter data directly into our database, thereby eliminating hard copy records.

Current SHHI computers are operated through the SHHI facility, which have appropriate firewall protection to prevent unauthorized access from anyone outside SHHI. Access to the database will be limited to appropriate SHHI staff and clinical caregivers. All HIPAA regulations will be followed to protect private health information (PHI).

Reference List

(1) Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. *Sleep* 1999; 22 Suppl 2:S347-S353.

(2) Ohayon MM, Zulley J. Correlates of global sleep dissatisfaction in the German population. *Sleep* 2001; 24(7):780-787.

(3) Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002; 6(2):97-111.

(4) Ohayon MM. Nocturnal awakenings and comorbid disorders in the American general population. *J Psychiatr Res* 2008; 43(1):48-54.

(5) Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008; 4(5):487-504.

(6) Buysse DJ. Insomnia. *JAMA* 2013; 309(7):706-716.

(7) Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry* 1997; 154(10):1417-1423.

(8) Leger D, Massuel MA, Metlaine A. Professional correlates of insomnia. *Sleep* 2006; 29(2):171-178.

(9) Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Med* 2009; 10(4):427-438.

(10) Crum RM, Storr CL, Chan YF, Ford DE. Sleep disturbance and risk for alcohol-related problems. *Am J Psychiatry* 2004; 161(7):1197-1203.

(11) Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. *Sleep* 2005; 28(11):1457-1464.

(12) Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010; 33(2):414-420.

(13) Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analyses of the NHANES. *Sleep* 2005; 28(10):1289-1296.

(14) Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. *J Epidemiol Community Health* 2006; 60(1):69-73.

(15) Stoller MK. Economic effects of insomnia. *Clin Ther* 1994; 16(5):873-897.

(16) Walsh JK, Engelhardt CL. The direct economic costs of insomnia in the United States for 1995. *Sleep* 1999; 22 Suppl 2:S386-S393.

(17) American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic & Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.

(18) Wilson JF. In the clinic. Insomnia. *Ann Intern Med* 2008; 148(1):ITC13.

(19) Benca RM. Diagnosis and treatment of chronic insomnia: a review. *Psychiatr Serv* 2005; 56(3):332-343.

(20) Hamblin JE. Insomnia: an ignored health problem. *Prim Care* 2007; 34(3):659-74, viii.

(21) Lande RG, Gragnani C. Nonpharmacologic approaches to the management of insomnia. *J Am Osteopath Assoc* 2010; 110(12):695-701.

(22) Papp KK, Penrod CE, Strohl KP. Knowledge and attitudes of primary care physicians toward sleep and sleep disorders. *Sleep Breath* 2002; 6(3):103-109.

(23) Rosen RC, Rosekind M, Rosevear C, Cole WE, Dement WC. Physician education in sleep and sleep disorders: a national survey of U.S. medical schools. *Sleep* 1993; 16(3):249-254.

(24) Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989; 262(11):1479-1484.

(25) Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. *Sleep* 1999; 22 Suppl 2:S359-S365.

(26) McCrae CS, Lichstein KL. Secondary insomnia: diagnostic challenges and intervention opportunities. *Sleep Med Rev* 2001; 5(1):47-61.

(27) Sivertsen B, Nordhus IH, Bjorvatn B, Pallesen S. Sleep problems in general practice: a national survey of assessment and treatment routines of general practitioners in Norway. *J Sleep Res* 2010; 19(1 Pt 1):36-41.

(28) Hilty D, Young JS, Bourgeois JA, Klein S, Hardin KA. Algorithms for the assessment and management of insomnia in primary care. *Patient Prefer Adherence* 2009; 3:9-20.

(29) Bertisch SM, Herzig SJ, Winkelman JW, Buettner C. National use of prescription medications for insomnia: NHANES 1999-2010. *Sleep* 2014; 37(2):343-349.

(30) Chong Y, Fryer CD, Gu Q. Prescription sleep aid use among adults: United States, 2005-2010. *NCHS Data Brief* 2013;(127):1-8.

(31) Brandt NJ, Piechocki JM. Treatment of insomnia in older adults: re-evaluating the benefits and risks of sedative hypnotic agents. *J Gerontol Nurs* 2013; 39(4):48-54.

(32) Hajak G, Geisler P. Experience with zolpidem 'as needed' in primary care settings. *CNS Drugs* 2004; 18 Suppl 1:35-40.

(33) Omvik S, Pallesen S, Bjorvatn B, Sivertsen B, Havik OE, Nordhus IH. Patient characteristics and predictors of sleep medication use. *Int Clin Psychopharmacol* 2010; 25(2):91-100.

(34) Randall S, Roehrs TA, Roth T. Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. *Sleep* 2012; 35(11):1551-1557.

(35) Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 2003; 26(7):793-799.

(36) Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep* 2008; 31(1):79-90.

(37) Ancoli-Israel S, Richardson GS, Mangano RM, Jenkins L, Hall P, Jones WS. Long-term use of sedative hypnotics in older patients with insomnia. *Sleep Med* 2005; 6(2):107-113.

(38) Mattila T, Stoyanova V, Elferink A, Gispen-de Wied C, de Boer A, Wohlfarth T. Insomnia medication: do published studies reflect the complete picture of efficacy and safety? *Eur Neuropsychopharmacol* 2011; 21(7):500-507.

(39) Kripke DF. Chronic hypnotic use: deadly risks, doubtful benefit. REVIEW ARTICLE. *Sleep Med Rev* 2000; 4(1):5-20.

(40) Chen HC, Su TP, Chou P. A nine-year follow-up study of sleep patterns and mortality in community-dwelling older adults in Taiwan. *Sleep* 2013; 36(8):1187-1198.

(41) Kripke DF, Klauber MR, Wingard DL, Fell RL, Assmus JD, Garfinkel L. Mortality hazard associated with prescription hypnotics. *Biol Psychiatry* 1998; 43(9):687-693.

(42) Brower KJ, McCammon RJ, Wojnar M, Ilgen MA, Wojnar J, Valenstein M. Prescription sleeping pills, insomnia, and suicidality in the National Comorbidity Survey Replication. *J Clin Psychiatry* 2011; 72(4):515-521.

(43) Zammit G. Comparative tolerability of newer agents for insomnia. *Drug Saf* 2009; 32(9):735-748.

(44) Davy Z, Middlemass J, Siriwardena AN. Patients' and clinicians' experiences and perceptions of the primary care management of insomnia: qualitative study. *Health Expect* 2013.

(45) Lichstein KL. Secondary insomnia: a myth dismissed. *Sleep Med Rev* 2006; 10(1):3-5.

(46) Littner M, Hirshkowitz M, Kramer M, Kapen S, Anderson WM, Bailey D et al. Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep* 2003; 26(6):754-760.

(47) Beneto A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. *Sleep Med Rev* 2009; 13(4):287-293.

(48) Fung CH, Martin JL, Dzierzewski JM, Jouldjian S, Josephson K, Park M et al. Prevalence and symptoms of occult sleep disordered breathing among older veterans with insomnia. *J Clin Sleep Med* 2013; 9(11):1173-1178.

(49) Krakow B, Ulibarri VA, Romero EA, McIver ND. A two-year prospective study on the frequency and co-occurrence of insomnia and sleep-disordered breathing symptoms in a primary care population. *Sleep Med* 2013; 14(9):814-823.

(50) Lichstein KL, Riedel BW, Lester KW, Aguillard RN. Occult sleep apnea in a recruited sample of older adults with insomnia. *J Consult Clin Psychol* 1999; 67(3):405-410.

(51) Luyster FS, Buysse DJ, Strollo PJ, Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med* 2010; 6(2):196-204.

(52) Wickwire EM, Collop NA. Insomnia and sleep-related breathing disorders. *Chest* 2010; 137(6):1449-1463.

(53) Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. *Biol Psychiatry* 2001; 49(11):948-953.

(54) Krakow B, Ulibarri VA, Romero EA. Patients with treatment-resistant insomnia taking nightly prescription medications for sleep: a retrospective assessment of diagnostic and treatment variables. *Prim Care Companion J Clin Psychiatry* 2010; 12(4).

(55) Krakow B, Ulibarri VA, Romero E. Persistent insomnia in chronic hypnotic users presenting to a sleep medical center: a retrospective chart review of 137 consecutive patients. *J Nerv Ment Dis* 2010; 198(10):734-741.

(56) Krakow B, Ulibarri VA. Prevalence of sleep breathing complaints reported by treatment-seeking chronic insomnia disorder patients on presentation to a sleep medical center: a preliminary report. *Sleep Breath* 2013; 17(1):317-322.

(57) Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep* 2000; 23(2):243-308.

(58) Stone KC, Taylor DJ, McCrae CS, Kalsekar A, Lichstein KL. Nonrestorative sleep. *Sleep Med Rev* 2008; 12(4):275-288.

(59) Kripke DF. Who should sponsor sleep disorders pharmaceutical trials? *J Clin Sleep Med* 2007; 3(7):671-673.

(60) Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999; 131(7):485-491.

(61) Chung KF. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. *Respiration* 2005; 72(5):460-465.

(62) Krakow B, Romero E, Ulibarri VA, Kikta S. Prospective assessment of nocturnal awakenings in a case series of treatment-seeking chronic insomnia patients: a pilot study of subjective and objective causes. *Sleep* 2012; 35(12):1685-1692.

(63) Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. *Sleep Med Rev* 2010; 14(1):9-15.

(64) Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010; 14(1):19-31.

(65) Hauri P, Fisher J. Persistent psychophysiologic (learned) insomnia. *Sleep* 1986; 9(1):38-53.

(66) Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry* 2002; 159(1):5-11.

(67) Romero E, Krakow B, Haynes P, Ulibarri V. Nocturia and snoring: predictive symptoms for obstructive sleep apnea. *Sleep Breath* 2010; 14(4):337-343.

(68) Bjornsdottir E, Janson C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S et al. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. *Sleep* 2013; 36(12):1901-1909.

(69) Krakow B, Melendrez D, Sisley B, Warner TD, Krakow J, Leahigh L et al. Nasal dilator strip therapy for chronic sleep-maintenance insomnia and symptoms of sleep-disordered breathing: a randomized controlled trial. *Sleep Breath* 2006; 10(1):16-28.

(70) Krakow B, Melendrez D, Lee SA, Warner TD, Clark JO, Sklar D. Refractory insomnia and sleep-disordered breathing: a pilot study. *Sleep Breath* 2004; 8(1):15-29.

(71) Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. *J Psychosom Res* 2000; 49(5):291-298.

(72) Guilleminault C, Stoohs R, Shiomi T, Kushida C, Schnittger I. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. *Chest* 1996; 109(4):901-908.

(73) Guilleminault C, Palombini L, Poyares D, Chowdhuri S. Chronic insomnia, premenopausal women and sleep disordered breathing: part 2. Comparison of nondrug treatment trials in normal breathing and UARS post menopausal women complaining of chronic insomnia. *J Psychosom Res* 2002; 53(1):617-623.

(74) Guilleminault C, Davis K, Huynh NT. Prospective randomized study of patients with insomnia and mild sleep disordered breathing. *Sleep* 2008; 31(11):1527-1533.

(75) Krakow B, Ulibarri VA, Romero EA, Thomas RJ, McIver ND. Adaptive servo-ventilation therapy in a case series of patients with co-morbid insomnia and sleep apnea. *Journal of Sleep Disorders: Treatment and Care* 2013; 2(1).

(76) Ornelas J, McIver ND, Krakow B, Ulibarri V. Change in self-reported insomnia severity following advanced forms of PAP therapy (Adaptive Servo-Ventilation and Auto-Bilevel) in patients with CompSA and OSA. Sleep 35[Abstract]. 2014.

(77) Hulley SB, Cummings SR. Sample size required per group when using the t test to compare means of continuous variables. Designing Clinical Research. Baltimore: Williams & Wilkins, 1988: 215.