RESPIRONICS®

Pilot study comparing the effectiveness of two different methods of acoustic stimulation to enhance Slow Wave Sleep.

Clinical Protocol

Protocol # AI-16052-PSCOMP-LO

Sponsored by

Respironics, Inc., a Philips Healthcare Company
1740 Golden Mile Highway
Monroeville, PA 15146
USA

Approved By:_____
David White, MD Date
Medical Director

Approved By:_____
Jeff Jasko Date
Clinical Data Manager, Q&R Reg. & Clin. Aff. - Biostatistics/DM

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DOCUMENT CONTROL PAGE

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Author(s):	Phyllis Zee, MD, PhD, Lynn Ostrowski, Barbara Miller, MS, CCRP, David White, MD, Kathryn Reid, PhD

Study Monitor(s):
Lynn Ostrowski
Clinical Project Manager
Phone: (724)387-7944
E-mail: lynn.ostrowski@philips.com

Barbara Miller MS, CCRP
Senior Clinical Research Associate
Phone: 724-387-4414
Email: barbara.miller_1@philips.com

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PROTOCOL APPROVALS

Protocol Title: Pilot study comparing the effectiveness of two different methods of acoustic stimulation to enhance sleep.

Protocol Number: # AI-16052-PSCOMP-LO

Protocol Version/Date: 4.0; November 13, 2018

Investigator Agreement.

As Investigator of the study entitled "Pilot study comparing the effectiveness of two different methods of acoustic stimulation to enhance slow wave sleep.", Protocol #AI-16052-PSCOMP-LO , I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the IRB (the "Protocol"); all applicable laws and regulations; Good Clinical Practice and the Declration of Helsinki; and any IRB or FDA conditions of approval;

(ii) await IRB approval for the Protocol before obtaining informed consents;

(iii) ensure that all requirements for informed consent are met and not let any subject participate in the Study before obtaining that subject's informed consent;

(iv) not make modifications to the Protocol as supplied to me by Respironics, Inc. (the "Sponsor"), without first obtaining the written approval of the Sponsor;

(v) provide the Sponsor with accurate financial information as required by FDA regulations;

(vi) supervise all testing of investigational devices that involves any Study subject;

(vii) maintain Study documentation for the period of time as required by FDA regulations;

(viii) will supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

Investigator Signature:_____**Date**:_____

Printed Name:_____

PROTOCOL REVISIONS

Revision Level	Changes Made to Protocol	Date	By
0.0	Original Release	09/16/2016	L. Ostrowski, L. P. Zee, B. Miller, D. White, K. Reid
1.0	Updates to include Philips Respironics Template and study design changes	01/10/2018	L. Ostrowski, L. P. Zee, B. Miller, D. White
2.0	Response to IRB comments	03/22/2018	B. Miller
3.0	Administrative changes in text box providing clarification to prototype to be used in overnight lab visit 2, revised the timing of morning assessments from 90 minutes to 60 minutes post wake for consistency with consent form, and PVT testing on pg. 18; deleted 3 times as it was intended to be completed once in the cognitive battery of tests	06/28/2018	L. Ostrowski, B. Miller
4.0	Updated PowerSleep Prototype 1 device description and risks per the most recent released version	11/13/2018	L. Ostrowski, B. Miller

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PHILIPS RESPIRONICS, INC. CONTACT INFORMATION

Technical Assistance

The following Philips Respironics employees are available for consultation, assistance, and/or problem solving during the course of this research study:

Josh Snyder
Software Engineer
Phone: (724) 387-4063
Email: joshua.snyder@philips.com

Reporting of Adverse Events or Adverse Device Effects

Report the occurrence of an adverse event or adverse device effect to Philips Respironics within 24 hours of the occurrence.

Lynn Ostrowski
Clinical Development Scientist
Phone: (724) 387-7944
E-mail: lynn.ostrowski@philips.com

Barbara Miller
Senior Clinical Research Associate
Phone: (724) 708-7048
E-mail: barbara.miller_1@philips.com

GLOSSARY

Actigraph: A wrist-watch-like device placed on the wrist to measure motor activity. The device continually records movements and ambient light intensity. Collected data are downloaded to a computer and analyzed offline. Analysis of activity/ inactivity can be further analyzed to estimate sleep patterns.

Digit Symbol Substitution Task (DSST): The Digit Symbol Substitution Task is a well-established psychometric test paradigm that is used to measure general cognitive performance. Participants must match symbols to digits and press the key that corresponds to the digit. The test is designed as a continuous performance task in which the participant must accomplish as many as possible correct matches within the 1.5 minute test period. The DSST results will be assessed for number of correct matches, and speed of completion for the entire set of a subset of the symbols.

Karolinska Sleepiness Scale (KSS): The Karolinska Sleepiness Scale measures subjective levels of fatigue. KSS queries subjects as to how sleepy they feel at that moment. The subjects answer is based on a 9-point scale where 1 = extremely awake and 9 = extremely sleepy/fighting to stay wake.

Matrix Reasoning Task (MRT): The MRT is a measure of abstract reasoning and consists of increasingly difficult pattern matching tasks. It is analogous to Raven's Progressive Matrices and recruits prefrontal, parietal, and temporal cortices. It is based on a well-known measure of the "g" factor. The test consists of a series of patterns, overlaid on a grid. One element from the grid is missing and the participant must select the element that fits the pattern from a set of alternative options. The current implementation uses 12 consecutive stimuli. MRT administration will stop automatically if three consecutive stimuli are answered incorrectly.

Paired Associates Learning task (PAL): The Paired Associates Learning Task is a well-established cognitive task used to assess declarative memory. Participants are presented with word pairs to learn. Immediately following and again in the morning after they wake up they are tested on the recall of the words. The recall testing involves showing participants one word and they are asked to state the paired word that they learned previously. Overnight memory retention is determined by the difference in the number of recalled words between morning retrieval testing after sleep and immediate recall performance at learning before sleep. The testing is scored by a technician and may also be recorded for scoring confirmation.

Polysomnography (PSG): Continuous and simultaneous recording of physiological variables during sleep, i.e., EEG, EOG, EMG (the three basic stage scoring parameters), EKG, respiratory air flow, respiratory excursion, lower limb movement, and other electrophysiological variables will be used to record sleep during all admissions for subjects. EEG as recorded by the Powersleep device or the standard PSG EEG channels

will also be analyzed for slow wave activity; a measure of the frequency and amplitude of slow waves.

PowerSleep Prototype 1: A wearable and non-invasive device, consisting of a headband with 2 electrodes (one forehead and one mastoid) and speakers located in the headband over each ear. The headband is adjusted via an adjustable slider. The device also includes a right mastoid reference electrode. EEG will be recorded by the PowerSleep device. Soft audio tones (below 65dB) will be administered via the speakers system during deep sleep as determined by the functionality of the device. This PowerSleep device has been extensively studied, and is a released product available for sale. The low risk PowerSleep device does not require a 510(k) and is considered a general wellness medical device.

Prototype 2*:* The PLL set up will function similarly to the PowerSleep prototype 1, but the stimulation will be provided using a standard PC setup at the bedside using standard PSG electrodes. EEG will be monitored and SWS identified using a standard PSG channels (international 10-20 system: Fpz, F3, F4, C3, C4, P3, P4, O1, O2) referenced to left mastoid. Electro-oculogram (EOG) will be recorded using 2 electrodes placed lateral to each eye and chin electromyogram (EMG) was recorded using 3 chin electrodes. The full EEG data set will be collected using Brain Vision Recorder software (Brain Products GmBH) and stored for off-line analysis and sleep scoring. A Matlab script (R2014b, MathWorks, Natick, MA) was developed for online detection of slow-waves and to control acoustic stimulation in a phase-locked manner (targeting the up phase of the slow wave) as described previously (Santostasi et al., 2016). Acoustic stimulation provided by headphones with an audible soft volume that do not result in arousals will be used. This device has been studied, however, is not a released product and therefore considered investigational.

Psychomotor Vigilance Testing – Brief (PVT-B): The Psychomotor Vigilance Task is a sustained-attention, reaction-time task that measures the speed with which participants respond to a visual stimulus. Sleep loss induces reliable changes in PVT performance, causing an overall slowing of response times, a steady increase in the number of errors of omission (i.e., lapses of attention, usually defined as response times ≥ 500 ms), and a more modest increase in the number of errors of commission (i.e., responses without a stimulus, or false starts) (Basner and Dinges, 2011; Van Dongen et al., 2003). Typically the PVT is a 10 minute assessment but a shorter 3 minute version (PVT-B) has recently been validated in controlled laboratory studies on total and partial sleep deprivation (Basner et al., 2011). The PVT results will be assessed for number of lapses, number of anticipations, average reaction time, average speed, average 10% fastest reaction time, and average 10% slowest reaction time.

Samn-Perelli 7-pt scale: The Samn-Perelli is a 7 point scale which measures subjective levels of alertness. This scale ranges from fully alert, wide awake to completed exhausted, unable to function effectively**.**

Sleep Quality: Sleep stage distribution will be scored from the standard sleep staging channels. It will also be assessed subjectively using a Visual Analog Scale (VAS) for sleep quality.

Sleep restriction: is also known as chronic sleep deprivation, and exists when the individual routinely sleeps less than required for optimal functioning.

Slow Wave Activity: EEG as recorded by the Powersleep device and the standard EEG channels will also be analyzed for slow wave activity; a measure of the frequency and size of slow waves.

I. BACKGROUND AND SIGNIFICANCE

Sleep disturbances are common in the general population and represent a major public health concern because of health care utilization, medical comorbidities impact on quality of life, and safety (Walsh 2004). In addition to sleep disorders such as insomnia, recent surveys suggest that a large percentage of the population is sleep restricted, and that the impairments in daytime functioning due to sleep restriction are responsible for decreased work productivity, morbidity and mortality related to automobile crashes and other adverse events (Banks and Dinges 2007).

Methods of sleep modification include pharmacological treatments, behavioral therapy, and homeopathic approaches. Pharmacological sleep aids are limited by side effects and drugs capable of affecting sleep maintenance, despite objective evidence of increased quantity or subjective reports of improved sleep, often have residual next-day effects that overlap with the disease symptoms (Rosenberg 2006). Behavioral and cognitive therapies have also been proven to be beneficial; however, they rely heavily on availability, patient motivation and practitioner skill. Homeopathic solutions are numerous and varied, but one example is the use of melatonin to augment sleep. There is limited evidence of their effectiveness or safety.

There is a need for new ways to improve sleep quality. Recently, researchers at the University of Wisconsin, Northwestern and other locations internationally have found that auditory stimulation can enhance slow wave activity during the night, relative to those times when there is no stimulation. An initial prototype, the PowerSleep System Prototype, was developed to monitor EEG and provide stimulation tones during slow wave sleep. In an initial feasibility trial, auditory stimulation provided by the PowerSleep System Prototype was shown to increase slow wave activity in sleep restricted adults.

A pilot study with 28 participants (average age 37.0 ± 7.3, 18 female/10 male), was conducted by Philips Respironics. The study showed that it is possible to enhance slow wave sleep by using non-pharmacological methods such as auditory stimulation (AS) and that coupled with closed-loop brain activity monitoring (EEG) provided by the device provides an increase in slow wave activity by 6.2% which may help improve vigilance,

cognitive functions, and memory, as well as subjective ratings of sleepiness, physical fatigue, and mental tiredness.

In addition, results (N=24) from an in-lab study conducted by the Cooperative Research Centre (CRC) for Alertness, Safety and Productivity with the PowerSleep device, showed positive results with SWA and executive function (verbal fluency task). An automated device based on the acoustic enhancement of slow wave sleep increased slow wave activity at the group level. In the majority of individuals, 18/24 75% (> 0% increase), 15/24 62.5% (> 5% increase). No change in cognitive outcomes was observed at the group level. At the individual level, the majority of individuals (75%) had increased slow wave activity. Magnitude of SWA increase was associated with the magnitude of improvement in executive function.

PowerSleep is a non-invasive portable light weight device designed to stimulate deep slow-wave sleep and thereby reduce daytime sleepiness associated with insufficient sleep. The concept is to stimulate deep sleep also known as Slow-Wave Sleep (SWS), to compensate for insufficient sleep duration by increasing sleep intensity. Sleep intensity can be objectively assessed by Slow-Wave Activity (SWA), defined as EEG spectral power in the frequency range 0.5-4 Hz. In normal individuals, a reduction in the amounts of SWA consistently results in reduced alertness with impaired performance due to cognitive and memory deficits.

The PowerSleep device delivers acoustic stimuli that are calibrated to stimulate SWA without awakening the user. The PowerSleep device is wearable and non-invasive, consisting of a headband with 1 integrated electrode, one mastoid reference electrode, and speakers located in the headband over each ear. The headband is adjusted via an adjustable slider. The device monitors and records EEG throughout the night, and is capable of on-line identification of sleep stages and continuous EEG analysis. EEG data collected by the PowerSleep device can be transferred to the computer by a technician after use and used to assess sleep quality. Soft audio tones (below 65dB to prevent arousals from sleep) will be administered via the speakers during deep sleep throughout the night.

As a second test condition of this protocol, we will also utilize a different system, Phase Locked Loop (Prototype 2) to provide acoustic stimulation during sleep. This Phase locked Loop (PLL) system was developed at Northwestern University and functions similarly to the PowerSleep Prototype 1, but the stimulation will be provided using a standard PC setup at the bedside using standard polysomnography (PSG) electrodes and acoustic stimuli will be delivered through earphones at specified times during sleep to increase slow wave activity.

II. SPECIFIC AIMS/HYPOTHESES

Primary Aim:

The primary aim of this study is to assess the effects of the auditory stimulation delivered by both the PowerSleep systems (Prototype 1) and a system developed

by Northwestern University (Prototype 2) in adults with mildly sleep restricted schedules.
We hypothesize that one night of in-lab use of a PowerSleep system (Prototype 1) or Prototype 2 under an active condition (tones played to increase slow-wave activity), as compared to one night of in-lab use of the same PowerSleep system (prototype 1) or Prototype 2 under a sham condition (no tones played) will result in a significant increase (≥ 5%) in cumulative or average slow-wave activity (SWA) in nonREM sleep across the whole night of sleep compared to sham. NOTE: We will also compare the relative ability of Prototype 1 versus Prototype 2 to increase the magnitude of SWA in sleep.

Secondary Aim:
The secondary aim of the study is to assess the impact of active versus sham PowerSleep Prototype 1 and Prototype 2 systems on measures of daytime function (PAL and PVT-B). The estimated effect of PowerSleep on specific measure(s) of daytime function will be used to help inform the choice of outcomes for future studies.

Exploratory endpoints:
Exploratory endpoints will include analysis of other daytime outcome assessments in relation to SWA.

III. STUDY DESIGN AND METHODS

A. Design: This study is a randomized, single-blind, sham-controlled pilot cross-over trial comparing the feasibility, and efficacy of 2 nights of in lab use with active versus sham conditions in adults with sleep restricted schedules. The expected duration of the study for each participant is up to 5 weeks.

B. Study Participants: We will enroll up to 60 individuals in order to complete a total of 10 participants using a cross over design. We will recruit male and female participants who satisfy the inclusion and exclusion criteria outlined in the following sections.

C. Study-wide recruitment methods: Potential participants will be recruited predominantly through media advertisements (ex. local newspapers, flyers, online advertisements), institutional postings, or existing online communities or site databases of patients who have previously indicated an interest in participating in research.

Dr. Phyllis Zee (Principal investigator) will not be involved in recruiting or consenting research participants, or in data collection. Dr. Kathryn Reid (Co-Principal Investigator) will be responsible for these aspects of the study.

D. Setting: Subjects will be identified from the population of prior research subjects who have agreed to be contacted for additional research experiments. New

subjects will be recruited from the general population through use of flyers/posters and online advertisements.

E. Randomization: An EDC will be used to control the randomization schedule. This EDC will be set-up by Philips Respironics. The Philips Prototype will be double blind, as neither the study participants, nor study staff will know which is active or sham. The Northwestern Prototype will be single-blind, however scoring will be blinded. If any Serious Adverse Events or Unanticipated Device Effects occur the study staff will alert the sponsor and the sponsor will break the blind if necessary. The study staff will alert the sponsor prior to any unblinding.

IV. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Able to provide written informed consent prior to admission
- Able to read, write and speak English
- Adult volunteers aged 21-50
- Working full time (M-F) schedule [Note: Full time is considered a 32 hour work week start time at 7am or later] or full time student
- Self-reported regular sleep schedule who are able to maintain their sleep schedule during the course of the study
- Self-reported sleep latency ≤ 30 minutes
- Self-reported wake after sleep onset ≤ 30 minutes
- Participants who regularly (3 of 5 work/school nights) use an alarm clock during the work/school week and who self-report:
    - Regular sleep schedule of 5.5-7 hours +/- 15 minutes on work/school nights [confirmed by actigraphy at visit 2, at least 3 of 5 work/school nights between 5.5 to 7 hours total sleep time]
    - Regular increase in sleep duration by ≥ 1 hour during non-work/school days as compared to work days, either by nocturnal bedtime extension or via a daytime nap [confirmed by actigraphy with at least 1 hour of increased sleep duration during one non-work/school night]
- Participants who demonstrate successful performance of the Paired Associates Learning Task during the training session.

Exclusion Criteria:

- Participation in another interventional study in the past 30 days.
- Major controlled* or uncontrolled medical condition such as congestive heart failure, neuromuscular disease, renal failure, cancer, COPD, respiratory failure or insufficiency, or patients requiring oxygen therapy (as determined by self-report and reviewed by the study PI.)
- History of current or recent (e.g. within past 5 years) narcotic, or any other drug abuse.
- Daily caffeine intake > 650mg

- Current smoker (more than 6 cigarettes a week) or those using nicotine replacement therapy. Those that have been nicotine free for 30 days will be included.
- Currently working night shift, split shift or rotating shift (which includes night shifts).
- Current use, or use within the past month, of a prescription or over-the-counter sleep medication or stimulant; or use of psychoactive medication (based on self-report and review with a study clinician) Refer to table below for examples.
- Individuals who self-report a current severe or chronic medical condition that may affect sleep patterns (based on self-report and review with a study clinician).
- Pregnant or currently breast feeding
- Body Mass Index > 40 kg/m^2
- Prior diagnosis (via self report) of any sleep disorder including:
    - Obstructive Sleep Apnea (AHI ≥15 events/hour) – from ambulatory or in lab polysomnography
    - Restless legs syndrome, or periodic limb movement disorder
    - Insomnia
    - Parasomnia
    - Circadian Rhythm Sleep-Wake Disorders
- High Risk of OSA based on STOP-BANG Questionnaire (“yes” on at least 4 of 8 questions)
- High risk of Restless Legs syndrome (RLS) base on Cambridge-Hopkins Screening Questionnaire
- High Risk of Insomnia based on Insomnia Severity Index (score of 22 or higher)
- Self-reported history of excessive alcohol intake – self-report ≥ 21 drinks/week or binge alcohol consumption (>5 drinks per day)
- Individuals who self-report a history of recurrent seizures or epilepsy or family history of hereditary epilepsy or have a history of medical conditions that could increase the chance of seizures (e.g. stroke, aneurysm, brain surgery, structural brain lesion).
- Individuals who self-report severe contact dermatitis or allergy to silver.
- Individuals who self-report moderate hearing loss.
- Inability to achieve appropriate headband fit (for prototype 1).
- Planned air travel or travel across more than one time zone during the anticipated period of the study with PowerSleep or PLL device use.
- Alpha-delta sleep on the first night in the sleep lab.
- Intentional naps during the work week.

Classes of medications that will not be allowed include:

Class	**Examples**
Sedating Antihistamines	chlorpheniramine, brompheniramine, diphenhydramine, doxylamine
OTC Decongestants	phenylephrine, ephedrine,

	pseudoephedrine
Sedative/Hypnotics	zolpidem, eszopiclone, zaleplon, ramelteon, triazolam, gabitril, tiagabine, suvorexant, gamma-hydroxybutyrate, tasimelteon
Anxiolytics	alprazolam, clonazepam, diazepam, lorazepam
Sedating Antidepressants	amitriptyline, nortriptyline, duloxetine, venlafaxine, mirtazapine, nefazodone, buspirone, bupropion
Medications for Attention Deficit Hyperactivity Disorder	atomoxetine, methylphenidate, amphetamine
Stimulants	amphetamine, modafinil, armodafinil
Dopamine Agonists	ropinirole, pramipexole, rotigotine
Narcotic/Opioid Analgesics	Including tramadol
Dextromethorphan	Many OTC cough products
Dietary supplements and other preparations affecting sleep-wake regulation	Kava (Piper methysticum), Ashwagandha (Withania somnifera), Valerian (Valeriana officinalis), St. Johns Wort (Hypericum Perforatum)
OTC stimulants	
Diet aids	
Melatonin	

*Participants who are on a stable and well-tolerated pharmacological treatment for hypertension, dyslipidemia, or thyroid replacement will not be excluded as long as they continue to take their medication at the same dose and at the same time(s) of day

IV. STUDY PROCEDURES AND MEASUREMENTS

Each subject will undergo a baseline screening period with screening questionnaires, clinical history, and 1 week of actigraphy measurement to determine eligibility for inclusion in the study. Prior to the overnight study they will undergo an additional 1 week of actigraphy measurement. Each subject will have two 3 day/2 night stays, separated by one week. Including outpatient screening and the inpatient study periods, the duration of participation for each subject will be ~5 weeks. We anticipate 6 months to enroll and complete the 12 subjects. Primary data analysis should be completed within one year of starting this study.

Study Procedures:

Participants may be screened over the phone to determine eligibility. A screening script will include a general review of key inclusion and exclusion criteria, and the Stop-Bang Questionnaire to assess risk for undiagnosed obstructive sleep apnea. Participants that meet all eligibility criteria will be asked to come into the research lab for a brief daytime screening visit. Participants who are interested and eligible will be consented. Participants will be provided with information on use of the actigraph and sleep logs at

home. Participants will be asked to return their actigraph and sleep logs to the laboratory either in person or via pre-paid FedEx. Participant qualification will be assessed based on sleep logs and the actigraph results. Qualifying participants will wear the actigraph and fill out sleep logs again for the week prior to their first overnight visit.

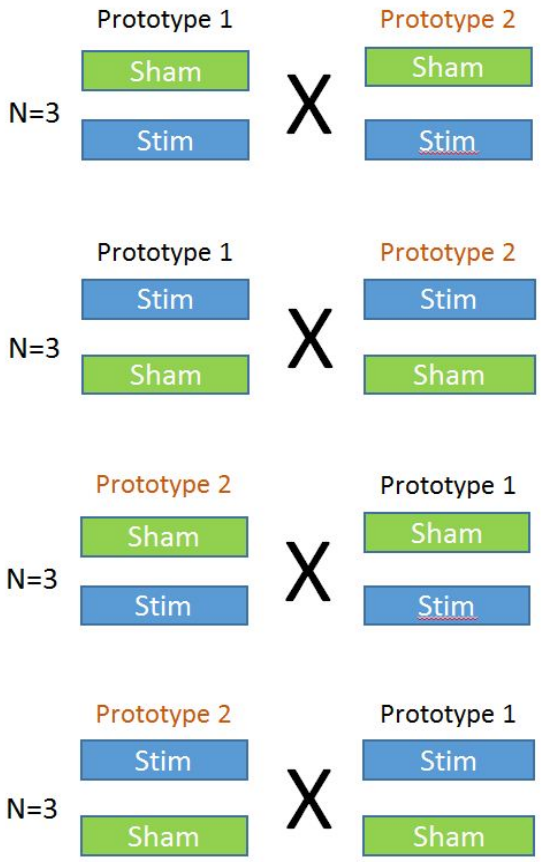

Figure 1. Overall Study Design. Qualifying participants will be randomized to receive either stimulation or sham condition. Then each group will be further randomized to receive PowerSleep Prototype 1 or Prototype 2 system at their first overnight visit, and will receive the other condition at their second overnight visit. Overnight visits will have a one night washout in between nights. The overnight visits (Visits 3 and 4) are scheduled as two sets of 3 day/2 night overnight studies and may be completed with a washout period of 5- 14 days between visits. In order to assess sleep quality, participants with an arousal index (AI) > 20 events/hour or alpha-delta sleep during an overnight visit will be excluded from further participation in the study. On the morning following each treatment, the participants will remain the lab to complete daytime function assessments and questionnaires.

Visit 1 (Screening) Procedures (up to 2 hours):

Participants will be asked to report to the Center for Circadian and Sleep Medicine at 710 N. Lake Shore Drive, Abbott Hall, 5th floor for a daytime visit. A detailed interview will be performed verifying eligibility criteria, as well as a review of work and non-work schedules. After a full explanation of the protocol and after all the participants questions have been answered, they will be asked to sign the consent form, following the SOP: Informed Consent Process for Research. Written documentation of consent will be obtained for all subjects.

Participants will complete the following baseline questions:

- Demographics
- Medical History Questionnaire

Collection of Current Medications
Epworth Sleepiness Scale (ESS)
Insomnia Severity Index Questionnaire (ISI) (if not completed during telephone screen)
Stop-Bang (if not completed during telephone screen)
Cambridge Hopkins (Restless Leg Syndrome) Questionnaire (if not completed during phone screen)

Participants will have their height, weight, neck circumference, temperature, heart rate and blood pressure recorded. Women of child bearing potential will have a urine pregnancy test.

Participants will be trained in the use of the sleep logs and actigraphy.

Actigraphy screening:
Participants will be asked to wear an actigraph and complete a daily sleep diary for 7 days +2 days to monitor their sleep schedule. Participants will receive instructions from the study staff on how to wear the actigraph and will be asked to keep to their regular sleep schedule.

Assessment training:
Participants will also be trained on daytime assessments which will be completed during the overnight visits. Only participants that are able to perform the task will be asked to remain in the study and through completion.

Actigraphy review:
Participants will drop off or mail their actigraph and sleep log to the Center for Circadian and Sleep Medicine for review by the study staff. The actigraph data will be reviewed by a trained technologist. Only participants that demonstrate a regular sleep schedule and an average sleep duration of 6-7 hours during the work week will be asked to return to the lab for the study. A regular sleep schedule will be defined as a bedtime between 9pm and midnight with no more than 1 hour of variability across the 7 nights. Qualifying participants will be asked to continue wearing the actiwatch and completing the sleep diary throughout the remainder of the study.

<u>Visit 2 Procedures (3 days/2 nights with washout in between nights):</u>
Participants will be randomly assigned to the sham or active stimulation condition during the first night of the overnight visits, and the other condition (sham or active stimulation) during the second night of the overnight visits. Participants may also be asked to undergo additional night study testing if data collected is unable to be analyzed due to unforeseen technical or environmental reasons. Participants and study staff will be blinded to the condition they are receiving during each overnight study for prototype 1. However, study staff will not be blinded during each overnight for prototype 2.

Active condition: Participants will be set-up with one of the PowerSleep Prototypes. Soft audio tones (below 65dB to prevent arousals from sleep) will be administered via the headphones during deep sleep throughout the night.

Sham condition: Participants will be set up with the same PowerSleep prototype as with the active arm, however no audio tones will be played.

Participants will typically be asked to arrive at the Sleep Disorders Center on the 7th Floor of Arkes or Galter Pavilion ~3 hours before their usual bedtime.

Upon arriving at the Sleep Disorders Center for the first overnight study, the actigraph data will be downloaded for review by a trained technologist. Only participants that demonstrate a regular sleep schedule and a sleep duration of 6-7 hours per night will be asked to remain in the study and through completion.

The PAL learning set will be completed before the participant goes to bed.

Overnight monitoring:
Participants will complete an attended overnight polysomnogram (PSG). During all PSGs, the electroencephalogram (EEG), electrooculogram (EOG) and sub-mental electromyogram (EMG) will be recorded with surface electrodes according to American Academy of Sleep Medicine (AASM) standards. In addition, surface ECG electrodes (standard lead II) will be applied to the participant. All PSG signals will be recorded and monitored continuously by a trained sleep technologist throughout the night.

After the baseline recordings while awake, the PSG channels indicated above will be recorded for the participants' entire night of sleep. Participants will be in a private room with the door closed and lights off. During the overnight recordings, participants will be directly observed via video camera. The participant can contact the trained technologist present at any time via an intercom.

During overnight studies under the active condition, soft auditory tones will be provided via the speakers during N3 sleep for prototype 1 and N2 or N3 sleep for prototype 2.

Morning:
The participant will be awakened at their usual wake time according to sleep logs and actigraphy
Participants will be asked to complete daytime assessments each morning of the visit (60 minutes post awakening) including:

- Karolinska Sleepiness Scale (KSS)
- Samn & Perelli Fatigue Scale
- VAS sleep quality
- MRT (to be completed on iPad)
- DSST (to be completed on iPad)
- Psychomotor Vigilance Test (PVT-B – 3min) - to be completed on iPad

Paired Associates Learning (PAL)

The DSST, MRT, PVT-B and PAL assessments will be completed electronically and the other assessments will be completed in paper form.

The actigraph data will be downloaded and the re-configured actigraphy device will be returned to the participant to be worn for the period before Visit 4. Sleep logs will be given for the participant to fill out during any time at home.

The subject will be allowed to go home or to work during the day and will be instructed not to nap during the day. This will be monitored with the actigraph. The subject will return to the lab the following evening 3 hours before the usual bedtime and will be instrumented and studied as described for night 1. For example, participants that spent the night Monday and completed Tuesday morning testing will come into the lab Wednesday night for Thursday morning testing or if participants sent Tuesday night and completed Wednesday morning testing they will come into the lab Thursday night for Friday morning testing.

Visit 4 Procedures (3 days/2 nights):
Participants will return to the Sleep Disorders Center to complete the second set of overnight studies one or two weeks after the first set of overnight studies. If participants spent Monday and Wednesday night in the lab for the first set of overnight studies, they will complete the second set of overnight visits Monday and Wednesday. The actigraph data will be similarly downloaded and reviewed for further participation upon arriving at the Sleep Disorders Center. This visit will be identical to Visit 3 except that the subjects will receive the prototype system that was not used in Visit 3 (Prototype 1 or 2).

V. STATISTICAL ANALYSIS

Determination of Sample Size

Twelve participants will be enrolled in order to ensure ten completed data sets. Since this is a pilot study, no sample-size calculation was performed.

General Considerations

The primary analysis will be performed including all completed participants. Subjects who complete all 4 in lab study nights with functional devices will be included in data analysis. If the sleep data are not usable for one or more of the participants' treatment conditions, those participants will be excluded from the primary analysis, and site(s) may over-enroll to compensate for these missing data. The analysis of safety will include all randomized subjects.

All variables will be summarized by descriptive statistics. The statistics for continuous variables includes mean, median, standard deviation, minimum, maximum, 95% confidence interval (CI) for the mean, and number of observations. For categorical variables, number and percentage of subjects with the event will be presented. Continuous variables will be summarized using the number of non-missing observations,

mean, standard deviation (SD), 95% confidence interval (CI) for the mean, median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category. All analyses will be conducted using either SPSS® or SAS® software.

There are no statistical criteria for terminating the study. No sensitivity analysis will be completed, and any deviations to the original statistical plan will be noted in the analysis report.

Philips Respironics will complete the data analysis on Prototype 1. In addition Philips Respironics will analyze the Prototype 2 data in the same manner.

Subject Disposition

Subject disposition, including the total number of participants enrolled, randomized, completed, early terminations and withdrawals, will be presented by treatment group, and overall. In addition, a listing will be provided with the reasons for discontinuation by treatment group.

Demographics and Baseline Characteristics

Standard subject demographics (e.g., age and gender) and baseline characteristics will be summarized for all participants enrolled and for evaluable subjects.

Treatment Compliance

It is expected that the drop-out rate will be low as the study is of short duration and will be completed in a controlled, in-lab setting.

Primary Efficacy Analysis

The primary efficacy measure for this study is the cumulative or average slow-wave activity (SWA).

The primary analysis will be done on completed participants with SWA data collected during the four conditions: Prototype 1 active and sham, Prototype 2 active and sham. A 2-way repeated measures Analysis of Variance (RMANOVA) will examine the SWA data with the repeated measures factors of therapy (active and sham) and prototype (1 and 2). An interaction factor will also be included to determine whether the active / sham effect differs between prototypes. The significance level will be $p<0.05$.

If the required assumptions for the RMANOVA model are violated, transformation of the data or non-parametric procedures may be used.

Secondary Efficacy Analysis

The daytime outcomes will be analyzed using the same statistical model as the SWA data.

Safety Analysis
Safety evaluations will be performed by recording clinical adverse events at the time originally reported and at each visit thereafter. Adverse events will be provided in data listings.

A complete medical history will be obtained at screening, and subjects having any of the outlined exclusion criteria will be immediately discontinued.

Interim Analysis
Interim analysis will occur after 5 to 6 participants have successfully completed the study.

VI. PROTECTION FOR HUMAN PARTICIPANTS

Potential risks and discomforts: Overall, risks in this study are minimal. However, the potential risks are detailed below, and they will be described in detail in the informed consent and will be repeated verbally to the participants prior to the studies.

Sleep studies are routinely conducted on a variety of patients and pose no untoward risks. A trained sleep technologist will always be present monitoring the participant during the study, and all standard laboratory procedures will be followed. The application of sensors and electrodes may include slight discomfort caused by skin abrasions, tape or adhesive irritation or irritation from sensitivity to the conductive material (typically silver) used in some electrodes. Red marks or pressure marks should dissipate within one hour. Some discomfort may occur due to the pressure of the headband on the ears. If the participant experiences discomfort, the headband will be adjusted to reduce pressure. None of the materials tested contain latex.

The use of sensory stimuli during sleep does not pose unique risks. However, although it is contrary to the intent of the current study, stimulation during sleep can result in fragmented sleep. The effect may be similar to partial sleep deprivation, when participants are prevented from sleeping during a portion of the night. The stimulation of audio tones will be halted if the participant complains of any pain (including headaches), tinnitus, significant sleep disturbance, or if there are any unusual EEG activity noted.

In addition, participants may also find it hard to sleep in the laboratory. They will be educated on the risks of drowsy driving and will be provided with a pamphlet on the risk of drowsy driving that they will be asked to read. Participants may also be provided with a cab voucher or voucher for public transportation if requested. A trained sleep technician / technologist will always be present monitoring the participant during the study, and all standard laboratory protocols will be followed.

Potential benefits: There are no direct benefits to participants in this study. It is hoped that the results of this study will lead to new treatment strategies to improve sleep quality in sleep-restricted patients.

Confidentiality: Privacy rules and requirements according to governing regulations will be implemented. All the information collected as part of this study will be kept confidential by all parties involved in the study at all times. All information collected for this study will be kept in a secured area or stored in a password protected computer if digital. Except when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records. For records disclosed outside of Philips Respironics, participants will be assigned a unique code number. The key to the code will be kept by the investigators. Data will be managed by study number and analyzed anonymously.

Subject identity will be protected by identifying all data used for statistical analysis only by code number, and maintain names and addresses used for mailings in separate databases on secure servers, with password protection. Paper records and other identifying information are maintained separately in locked files, and all project personnel are thoroughly indoctrinated in maintaining confidentiality of data. All data collected in this study will be kept strictly confidential.

Provisions to Protect the Privacy Interests of Participants: Subjects will only interact with approved members of the research staff, and will have the option to decline to provide any information that they are uncomfortable revealing. Subject's medical records will only be accessed after obtaining written consent from the subject, and will only be reviewed by members of the research staff for whom review of this information is necessary for continued participation in the study (e.g. coordinator obtaining information, and study physician reviewing the information prior to admission).

Compensation for Research-Related Injury: There is no compensation available for research-related injury.

Vulnerable Populations: N/A

Community-Based Participatory Research: N/A

Sharing of Results with Participants: Study results will not be shared with the subject.

Economic Burden to Participants: There will be no cost to the subject to participate in the study.

Withdrawal Criteria:
The term "discontinuation "refers to the participant's premature withdrawal from the study prior to completing all procedures. Participants may be discontinued from the study for any of the following reasons:

- If in the investigator's judgement, continuation in the study may prove harmful to the participant. Such a decision may be precipitated by adverse events, including fever, nausea, rash, changes in vital signs, or the development of a new medical condition. The investigator will be solely responsible for making medical/safety decisions regarding the participant's continued participation in the study.
- Noncompliance.
- At the request of the participant.

The study coordinator will document whether or not each participant completed the study. If, for any participant, study treatment or assessments were discontinued, the reason will be recorded.

The study goal is to have 10 participants complete the entire study. Participants that withdrawal from the study will be replaced in order to obtain the necessary 10 completed data sets.

Early Stopping Criteria: The sponsor reserves the right to stop the study at any time.

VII. MONITORING AND QUALITY ASSURANCE

All adverse events, serious and non-serious, occurring during the course of the study will be collected, fully documented, and reported to the Northwestern University Internal Review Board (IRB) and to the Sponsor by the Principal Investigator, Dr. Zee or designee. Serious adverse events will be reported to the Sponsor within 24 hours of the study team being aware of the event. For each adverse event, the investigator will provide the onset, duration, intensity and treatment required, outcome and action taken. We anticipate that adverse events during this study would be related skin irritation from PSG or sleep deprivation from acoustic stimulation. All reasonable care will be taken to avoid these complications. In addition to adverse event reporting, the investigators will report a summary of the protocol findings, subject recruitment, drop-outs, and events to the IRB annually. The physiological studies will be conducted in the Sleep Disorders Center on the 7th Floor of Arkes Pavilion. All data will be kept confidential and in a locked cabinet. Only approved study personnel will have access to study related documents.

All device deficiencies, use or user errors, and equipment failures will be documented. Use or User errors will be captured as part of the source documentation. Device deficiencies and equipment failures will be kept on a separate log. The serial numbers and type of deficiency/failure will be captured. If the deficiency/failure is related to Prototype 1, Philips Respironics Engineering team will be notified to troubleshoot the issue.

This clinical study will be monitored by Philips Respironics Inc. (Sponsor) in compliance with the Code of Federal Regulations (CFR) for clinical research; namely, 21 CFR Parts 50, 54, 56 and 812 and others as applicable. The purpose of such monitoring is to assure that the study remains in compliance with the approved protocol, investigator agreement and regulatory requirements, to verify the completeness and accuracy of study data and

to resolve any issues that arise during the conduction of the study. The Sponsor will scheduled monitoring visits periodically as specified by the monitoring plan that will be conduct by trained clinical research professionals. A unique source record will be created for each study participant. This record will include documentation of the informed consent form review process, HIPAA competition according to site policies, concomitant medications and applicable medical history. The Sponsor will have access to these source records. An electronic data capture (EDC) will be used for this trial. Only those members of the study team that have completed training and have been delegated by the Principal Investigator will be able to access the EDC to enter data or make changes to the data. It has been determined that this study does not require a Data Safety Monitoring Board (DSMB).

VIIl. RESOURCES AVAILABLE:

- Research Staff: Teams of experienced, qualified, CITI certified personnel are already assembled to undertake this research project. Any new study personnel will be paired with senior researchers for training. All research staff will be trained by Philips Respironics in regards to this study and Prototype 1.
- Recruitment: Participants will be recruited from the general public.
- All equipment required to conduct this research is already owned by the PI or has been provided to the PI by Philips Respironics according to the contract. A sleep laboratory is already in place.

VIII. Registration on ClinicalTrials.gov or other applicable registry

This study is a comparison study between two algorithms. This study will include sham treatment, and compare the performance of both algorithms.

PRIOR APPROVALS:

N/A

IX. REFERENCES

Banks, S. and D. F. Dinges (2007). "Behavioral and physiological consequences of sleep restriction." J Clin Sleep Med 3(5): 519-28.

Basner, M, and D.F. Dinges (2011). “Maximizing the sensitivity of the psychomotor vigilance test (PVT) to sleep loss.” Sleep 34(5). 581-591.

Basner, M, D. Mollicone, and D.F. Dinges (2011). “Validity and sensitivity of a brief psychomotor vigilance test (PVT-B) to total and partial sleep deprivation.” Acta Astronaut. 69. 949-959.

Drummond SP, Brown GG, Gillin JC, Stricker JL, Wong EC, Buxton RB (2000). “Altered brain response to verbal learning following sleep deprivation.” Nature. 10;403(6770):655-7.

Nicassio P., D.R. Mendlowitz, et al. (1985). “The phenomology of the pre-sleep state: the development of the pre-sleep arousal scale.” Behav Res Ther 23(3): 263-71.

Parrott A.C. and I. Hindmarch (1980). “The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations – a review.” Psychopharmacology: 71: 173-79.

Rosenberg R.P. (2006). Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. Ann Clin Psychiatry 18:49-56.

Sunwoo, B.Y., N. Jackson, et al. (2011). “Reliability of a single objective measure in assessing sleepiness.” Sleep 35(1): 149-158.

Van Dongen, H.P.A, G. Maislin, et al. (2003). “The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology.” Sleep 26(2): 117-126.

Walsh J.K. (2004). “Clinical and socioeconomic correlates of insomnia.” J Clin Psychiatry 65 (suppl 8):13-19.

Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP (2007). “A deficit in the ability to form new human memories without sleep. Nat Neurosci.” 10(3):385-92.