A Double-Blind Placebo-Controlled Multi-Site Randomized Cross-Over Study of the Effectiveness and Efficacy of the PowerSleep device

Clinical Protocol

Protocol # AI-16128-PSPIV-LO

Ver : 2.0
September 18, 2017

Sponsored by

Respironics, Inc., a Philips company ("Philips Respironics")
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Monroeville, PA 15146
USA

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PROTOCOL APPROVALS

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Investigator Agreement.
As Investigator of the study entitled "A Double-Blind Placebo-Controlled Multi-Site Randomized Cross-Over Study of the Effectiveness and Efficacy of the PowerSleep Device" , Protocol # AI-16128-PSPIV-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	02/28/2017	*L. Ostrowski, D. White, A. Mahadevan, B. Miller, N. Papas, G. Lotz, J. Jasko*
1.0	Amendment 1: Update to aims, statistical section, study procedures, and inclusion of international study interim analysis	03/16/2017	*B. Miller, L. Ostrowski, N. Papas J. Jasko*
2.0	Amendment 2: Increase study enrollment	9/18/17	*B. Miller, L. Ostrowski*

RESPIRONICS, INC. CONTACT INFORMATION

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

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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.

Apnea: The cessation of airflow at the nostrils and mouth for at least 10 seconds as determined using nasal-oral thermistor, nasal pressure or device flow

Apnea/Hypopnea Index (AHI): The number of apneas and hypopneas per hour of sleep.

Hypopnea: Shallow breathing in which the air flow in and out of the airway is significantly reduced as detected by nasal pressure or device flow - often associated with oxygen desaturation of 4% or EEG arousal.

Obstructive Sleep Apnea (OSA): a disorder in which the airway collapses, either completely or partially, repeatedly during the night and is associated with desaturation, sleep fragmentation, and daytime sleepiness.

Polysomnography (PSG): Continuous and simultaneous recording of physiological variables during sleep, including EEG, EOG (the basic stage scoring signals). EEG (FPz-M1, F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), EOG (E1-M2, E2-M2).

PowerSleep device: A wearable and non-invasive device, consisting of a silicone headband with 1 integrated electrode and headphones covered by speaker foam over each ear. The headband is connected via a tether cable to a user interface which houses the electronics of the device. The headband is adjustable via a Velcro strap. The device also includes a right mastoid electrode. EEG can be monitored and recorded by the PowerSleep device. Soft audio tones (below 65dB) can be administered via the speakers during deep sleep throughout the night.

Sleep deprivation: is defined by insufficient sleep to support adequate alertness, performance and health, either because of reduced total sleep time or fragmentation of sleep by brief arousals.

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: is slow high-amplitude EEG oscillations which occur during Slow Wave Sleep.

Slow Wave Sleep (SWS): is the deepest stage of non-rapid eye movement (nREM) sleep. It is one of the two core sleep stages in mammals. SWS alternates with rapid-eye-movement (REM) sleep in a cyclical pattern. SWS is predominant during the early part of sleep and decreases in intensity and duration across the sleep period. SWS is known as deep sleep.

I. BACKGROUND AND SIGNIFICANCE

Sleep is increasingly recognized as important to public health. Sleep insufficiency may be defined as a condition where sleep duration or/and sleep quality is insufficient to support adequate alertness, performance, and health [1]. Sleep insufficiency has been linked to motor vehicle crashes, industrial disasters, medical and other occupational errors, reduced quality of life and productivity and a higher risk of chronic diseases such as hypertension, diabetes, depression, and obesity, and cancer [2]. Sleep insufficiency may be caused by behavioral sleep restriction to meet the demands and opportunities of modern society, but may reflect non-restorative sleep due to shallow and/or fragmented sleep [2]. The Center for Disease Control examined the prevalence of "insufficient sleep or rest during the past month" among American adults [3]. After adjustment for age, the prevalence of "insufficient sleep or rest" ranged from 7.9% to 19.3% [4]. In 2009, an average of 35% of Americans within the age range of 35-<45yrs reported falling asleep unintentionally during the past month [4].

In individuals between the ages of 20-60 slow-wave sleep (SWS), the deepest stage of non-rapid-eye movement (NREM) sleep, comprises between 10 and 30% of total sleep time[5]. During SWS, high amplitude, low frequency oscillations, referred to as slow waves or delta waves, appear in the EEG [6]. Larger slow waves reflect deeper, more intense sleep that is less likely to be fragmented or interrupted[7]. When slow-wave activity (SWA) is acutely suppressed by arousal stimuli or total sleep deprivation, a rebound occurs during the recovery night.

A large body of evidence indicates that SWA is a pivotal component of the restorative effects of sleep for both the brain and the rest of the body [6, 8-24]. SWA has beneficial effects on memory and learning [25] as well as on hormonal function [26], glucose metabolism [9, 24, 27] and cardiovascular regulation [23, 28]. Experimental studies have shown that insufficient amounts of SWS lead to impaired alertness and cognitive performance [2, 29], obesity [30] and a higher risk of cardio and metabolic disease [11, 20, 31]. Low amounts of SWS are also typical of normal aging [5, 32-36], and of common sleep disorders such as obstructive sleep apnea [37] and insomnia [38]. Increasing the amount and intensity of SWS may have a wide range of beneficial effects on daytime function, quality of life and physical and mental health [2, 6, 33, 38-41].

Currently available sleeping medications, whether prescription or over the counter, have not been shown to increase SWA [42]. In fact, the most commonly used prescription sleep medications decrease SWA and are therefore often associated with residual daytime sleepiness despite increased sleep duration [43]. Nutritional supplements such as melatonin do not increase SWS or SWA and may decrease it [44]. Thus, there is a need for a new approach to increase the depth of NREM sleep.

Researchers at the University of Wisconsin have found that the timed delivery of auditory stimuli during sleep that are not consciously perceived can enhance SWA

throughout the night [6, 41]. The findings have led to the development of several prototype devices which have demonstrated increasingly higher performance. The goal of the present study is to test the most recent prototype, named PowerSleep, in active adults who have insufficient sleep.

PowerSleep is a non-invasive portable light weight device designed to stimulate slow-wave sleep and thereby reduce daytime sleepiness associated with insufficient sleep or poorly perceived sleep quality [45]. Auditory stimulation is provided during SWS, to compensate for insufficient sleep duration by increasing sleep intensity or to improve sleep quality by increasing sleep intensity. Sleep intensity can be objectively assessed by Slow-Wave Activity (SWA), defined as EEG spectral power in the frequency range 0.75-4 Hz. In normal individuals, a reduction in the amount of SWA consistently results in reduced alertness with impaired performance due to cognitive and memory deficits [41].

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 silicone headband with integrated electrodes and speakers over each ear. The headband is connected via a tether cable to a user interface which houses the EEG amplifier and electronics of the device. The headband is adjustable via a Velcro strap. The device also includes a right mastoid electrode. The device monitors and records EEG throughout the night, and is capable of on-line identification of sleep stages and continuous EEG analysis. The user interface contains the device electronics. EEG data collected by the PowerSleep device can be transferred to the computer by a technician after home 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.

A pilot study with 27 participants (average age 36.7 $\pm$ 7.3, 16 female/9 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 7% which helps improve vigilance, cognitive functions, and memory, as well as subjective ratings of sleepiness, physical fatigue, and mental tiredness[1].

In addition, interim results (N=9) from an in-lab study conducted with the PowerSleep device, 77.8 % showed an increase in SWA ranging from 5-33%. Participants showed an improvement in cognitive outcomes following acoustic stimulation during overnight sleep. Improvements were noted in executive function task (verbal fluency), vigilance

[1] Internal Philips Respironics Report- data on file

and alertness (PVT) and sleep dependent declarative memory task (Paired associates memory task).[2]

II. SPECIFIC AIMS/HYPOTHESIS

Primary Aim(s):
To assess the effects of the auditory stimulation delivered by the PowerSleep device in adults who are sleep restricted. Efficacy will be evaluated based on the average of two nights (2 night) use of active PowerSleep (delivering audio tones) compared to the average of two nights (2 nights) use of a sham device (delivering no audio tones).

It is hypothesized that the use of active PowerSleep, as compared to the sham device, will result in a significant increase (≥5%), in mean total slow-wave activity (SWA) over the 2 work nights of use.

Secondary Aims:
To evaluate the effect of 2 nights of PowerSleep use on MSLT (sleep latency), subjective sleepiness scales, and cognitive testing.

To evaluate the relationship between MSLT (sleep latency), subjective sleepiness scales, and cognitive testing changes and changes in SWA.

III. STUDY DESIGN and METHODS

A. Design:

This study is a randomized, double-blind, placebo-controlled cross-over study designed to evaluate the effectiveness and efficacy of 2 consecutive work days of nightly use of active versus sham PowerSleep devices in adults with self-imposed restricted sleep schedules. The primary analysis will be intent-to-treat with the secondary analysis as an as-treated analysis. The expected duration of the study for each participant is up to 4 weeks.

B. Study Participants:

It is anticipated that the study will screen 100 individuals in order to complete a total of up to 75 participants. We will recruit male and female participants who satisfy the inclusion and exclusion criteria outlined in the following sections.

Potential participants will be recruited predominantly through media advertisements (ex. local newspapers, flyers), institutional postings, market research firms, word of mouth,

[2] Internal Philips Interim Report- Data on File

or existing site databases of individuals who may have previously indicated an interest in participating in research.

Inclusion Criteria

- Able to provide written informed consent prior to admission
- Able to read, write and speak English
- Adult volunteers aged 21-50 years
- Working full time with a regular work schedule; Full time is considered 4- 10 hour days or 5- 8 hour days with a start time of 7am or later
- Self-reported regular sleep schedule who are able to maintain their sleep schedule during the course of the study
- Self-reported sleep duration of > 5hrs. and ≤ 7 hrs. +/- 15 minutes (verified by 6 work days of ambulatory sleep monitoring with wrist actigraphy and daily logs)
- Self-reported sleep latency > 30 minutes no more than once / wk. (time to fall asleep)
- Self-reported wake time after sleep onset ≤ 30 minutes
- Participants who regularly use an alarm clock during the work week and who **self-report**:
    i. Regular time in bed (TIB) on work days of ≤7 hours
    ii. Regular increase in sleep duration by ≥ 1 hour during non-work days as compared to work days, either by nocturnal bedtime extension of via a daytime nap

Exclusion Criteria:

- Participation in another interventional study in the past 30 days.
- Previously enrolled in a PowerSleep study.
- 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.)
- Currently working night, swing, split or rotating shift.
- Current use or use of within the past month of a prescription or over-the-counter sleep medication or stimulant; use of psychoactive medication (based on self-report and review with a study clinician). Refer to table below for examples.
- Pregnant or currently breast feeding
- Current Smokers or using nicotine replacement therapy. Those that have been nicotine free for 30 days will be included.
- Body Mass Index > 40 kg/m^2
- Prior diagnosis of any sleep disorder including
    a. Obstructive Sleep Apnea (AHI ≥15 events/hour) – from ambulatory or in lab polysomnography
    b. Restless legs syndrome, or periodic limb movement disorder

    c. Insomnia
    d. Parasomnia
- High Risk of OSA based on STOP-BANG Questionnaire ("yes" on at least 4 of 8 questions)
- High Risk of Restless Legs Syndrome (RLS) based 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 $\geq$ 21 drinks / wk or binge alcohol consumption (>5 drinks per day)
- Excessive caffeine consumption (> 650mg/day combining all caffeinated drinks regularly absorbed during workdays.) Caffeine intake must be regular and maintained throughout study and on testing days
- Individuals who self-report a history of recurrent seizures or 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 silicone, nickel or silver.
- Individuals who self-report moderate hearing loss.
- Inability to achieve appropriate headband fit.
- Planned travel across more than one time zone one month prior to and or during the anticipated period of the study with PowerSleep device use
- Intentional naps during the work week.
- Alpha-Delta waveforms as determined by Baseline night PowerSleep Device data collection

*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.

Concomitant Medications:

The Investigator will make all final decisions regarding exclusion of participants on the basis of medication.

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,
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	

Psychoactive medications, medications associated with drowsiness/sedation and stimulants will not be allowed because they could interfere with study outcomes. These include prescription, over-the-counter and dietary/herbal supplements. The use of such medications must be discontinued for 2 weeks prior to Visit 1. Participants who develop a cold or flu during the work week use of the device should contact the study team immediately to discuss medication usage. The Investigator will make all final decisions regarding exclusion of participants on the basis of medication.

Before enrolling a woman of child-bearing potential in this clinical study, Investigators must review the following information with the participant:
• Risk of pregnancy;
• Contraceptives in current use;
• Drug interactions with hormonal contraceptives; and
• Pregnancy prevention during the study.

All women of child bearing potential, (defined as any woman, unless surgically sterile or postmenopausal for at least 1 year) must be instructed to contact the Investigator immediately if they suspect they might be pregnant while participating in this study. If a participant becomes pregnant, she will be discontinued from the study

C. Study Procedures and Measurements:

Participants may be pre-screened over the phone by the site or a market research firm to determine eligibility. A screening script will include a general review of key inclusion and exclusion criteria, the STOP-BANG questionnaire to assess the risk / possibility of an undiagnosed sleep disorder [46] and other questionnaires. Participants that meet all eligibility criteria will be asked to come into the office for a screening daytime visit (Visit 1) involving a detailed presentation of the study (informed consent) and an interview to verify eligibility and work schedules.

Participants who are interested and eligible will be consented. Participants will scheduled for a second daytime visit, 5 overnight lab visits, and provided with information on use of the actigraph. At Daytime Visit 2, participant qualification will be assessed based on the PowerSleep device data, actigraphy, and sleep logs. Qualifying participants will be randomized and scheduled for their sleep lab visits.

Participants will use the PowerSleep device within the active and sham study arm for two nights each week. After completing a baseline night in the lab, participants will sleep in the sleep lab two consecutive nights for two consecutive weeks. The first week participants will be randomized to active or sham and complete two consecutive nights. Participants will be asked to come in the same nights the following week to cross-over to the other arm of the study.

Daytime Visit 1 Procedures (Up to 2 hours):

Initial evaluation and anthropometric measurements:

Participants will be asked to report to the office for a daytime visit. After a full explanation of the consent and after all the participants' questions have been answered, they will be asked to sign the consent form. A detailed interview will be performed verifying eligibility criteria, and review of work and non-work schedules.

Participants will be asked to fill out the following baseline questionnaires:

- Medical History Questionnaire and Review of Systems
- Epworth Sleepiness Scale
- Insomnia Severity Questionnaire
- Cambridge-Hopkins Questionnaire (RLS screening)
- STOP-BANG Questionnaire
- Questions about sleep schedule and sleep quality.

Participants will have their height, weight, neck circumference, temperature, respiratory rate and blood pressure including heart rate (heart rate, systolic and diastolic after being seated for approximately 5 minutes) recorded.

Participants will be trained on the use of the sleep logs and actigraphy including instructions from the study staff on how to wear the actigraph. Participants will be asked to keep a sleep log and wear an actigraph during the entire course of the study. It is important participants keep to their regular sleep schedule throughout the study.

Baseline Night (Sleep-Lab night 1):

Participants will be asked to come into the sleep-lab for a baseline night. This visit should occur as close as possible to Daytime Visit 2, preferably the night before the visit. If this cannot occur at that date due to the sleep lab or participant schedule this visit should be conducted at least 6 work days after the participant starts wearing the actigraph. Participants will be asked to come into the lab up to 4 hours before bedtime. Participants will be fitted with the PowerSleep device and PSG electrodes and asked to go to bed and awaken at the same time as their regular work-night sleep schedule. Participants will then be able to leave to complete their day. See Appendix I for standardized rules and restrictions for participant activities for the in lab study.

Daytime Visit 2 Procedures (2 hours):

Participants will return to the office (within 2 weeks of daytime visit 1, ±2 days) with the actigraph and sleep diary for review by the study staff. Those participants who demonstrated alpha-delta waveforms as detected by the PowerSleep device during the baseline night will be excluded.

Actigraphy review:

The sleep log and actigraph data will be reviewed by trained study staff prior to randomization to ensure participants continued eligibility.

Eligible participants will be randomly assigned to active or sham treatment during this visit in a 1:1 ratio. Participants and study staff will be blinded to the treatment they are receiving during each work week.

> *Active treatment*: Participants will wear the PowerSleep device with soft audio tones (below 65dB to prevent arousals from sleep) administered via the speakers during deep sleep throughout the night.
>
> *Sham treatment:* Participants wear the same PowerSleep device as with the active treatment, however no audio tones will be administered via the speakers.

Those participants that state they have heard tones during the baseline night will be set to a sensitive setting.

Overnight in-lab visit 2 (Work Week 1)
Participants will be asked to come into the sleep lab during their work week on a Tuesday – Thursday night to complete their first study arm night. Participants will be asked to report to the lab up to 4 hours before bedtime with all study materials. Women of child-bearing potential will be asked to take a urine-pregnancy test. Prior to bedtime participants will go through a learning activity of the assessments they will complete the following night in order to have an understanding of the tasks. Participants will be fitted with the PowerSleep device, PSG electrodes and asked to go to bed and awaken at the same time as their regular work-night sleep schedule. Participants will complete the KSS, Samn Perelli, and VAS Sleep Quality 60 minutes of waking. After completing the questionnaires participants will be able to go to work, but will be instructed to not nap during the day. They will return to the sleep lab that evening 3 hours before bedtime.

Overnight in-lab visit 3 (Work Week 1) followed by Daytime in-lab testing (8 hours): On the next evening participants will be asked to return to the sleep lab for the second study arm night. Participants will be asked to report to the lab up to 4 hours before bedtime. Participant will be asked to complete the PAL learning activity prior to bedtime (120 to 30 minutes before lights out). Participants will be asked to go to bed and awaken at the same time as their regular work-night sleep schedule. Participants will be asked to wear the PowerSleep device and PSG electrodes during this overnight visit.
On the morning of the day following the overnight in lab visit work week 1, participants will remain in the lab and undergo the following assessments:

After Wake-Up

- Collect and download PowerSleep device data

Anytime after wake-up

- Review of any reported changes in medical condition since last visit
- Collect sleep logs
- Data download from actigraph
- Questionnaire identifying whether participant believes they had undergone active versus sham treatment
- Breakfast- participants can have one (1) 6 ounce cup of coffee or caffeine equivalent. Coffee or equivalent is only for those who routinely drink caffeine in the morning.
- Lunch

1 hour after wake up:

- Complete morning recall of PAL task
- Complete 3 minute PVT
- VAS for sleep quality
- Verbal fluency

- Karolinska Sleepiness Scale
- Samn-Perelli Fatigue Scale

2 hours after wake up:

- 4- Research Multiple Sleep Latency Test (see Appendix II for standardized MSLT procedures) each nap is followed by the following assessments:
  - Complete a 3 minute PVT
  - VAS for mood and vigor
  - Karolinska Sleepiness Scale
  - Samn-Perelli Fatigue Scale

Participants will continue to wear the actigraph and complete sleep logs until the next set of overnight visits.

Overnight in-lab visit 4 (Work Week 2)

Participants will be asked to come into the sleep lab during their second work week on a Tuesday – Thursday night to complete the cross-over week portion of the study. Participants will be asked to report to the lab up to 4 hours before bedtime with all study materials. Women of child-bearing potential will be asked to take a urine-pregnancy test. Participants will be fitted with the PowerSleep device, PSG electrodes and asked to go to bed and awaken at the same time as their regular work-night sleep schedule. Participants will complete the KSS, Samn Perelli, and VAS Sleep Quality 60 minutes of waking. After completing the questionnaires participants will be able to go to work, but will be instructed to not nap during the day. They will return to the sleep lab that evening 3 hours before bedtime.

Overnight in-lab visit 5 (Work Week 2) followed by Daytime in-lab testing (8 hours)

On the next evening participants will be asked to return to the sleep lab for the second study arm night. Participants will be asked to report to the lab up to 4 hours before bedtime. Participant will be asked to complete the PAL learning activity prior to bedtime (120 to 30 minutes before lights out). Participants will be asked to go to bed and awaken at the same time as their regular work-night sleep schedule. Participants will be asked to wear the PowerSleep device and PSG electrodes during this overnight visit.

After Wake-Up

- Collect and download PowerSleep device data

Anytime after wake-up

- Review of any reported changes in medical condition since last visit
- Collect sleep logs

- Data download from actigraph
- Questionnaire identifying whether participant believes they had undergone active versus sham treatment
- Breakfast- participants can have one (1) 6 ounce cup of coffee or caffeine equivalent. Coffee or equivalent is only for those who routinely drink caffeine in the morning.
- Lunch

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- 4- Research Multiple Sleep Latency Test (see Appendix II for standardized MSLT procedures) each nap is followed by the following assessments:
  - Complete a 3 minute PVT
  - VAS for mood and vigor
  - Karolinska Sleepiness Scale
  - Samn-Perelli Fatigue Scale

Exit Interview

Participants may be asked to complete an exit interview. During the interview, the participant will be asked to answer a set of questions about their opinions related to future iterations of the device, device functions, and technology preferences. This interview will be conducted by a member of the study staff or study sponsor. The interview may occur at the end of the study or as a phone interview. The interview will require up to an hour of the participant's time. Participants will be asked to indicate their approval to have the interview audio recorded and the potential to be contacted for future discussions.

D. **Temporary Discontinuation Criteria**

If a participant develops a cold, flu or upper respiratory infection during the course of the work week, they may be asked to temporarily discontinue the study for one week. Participants will be instructed as part of the Informed Consent to call the study team if they develop a cold, flu or upper respiratory infection. The study team will let the participant know whether or not they can temporarily exit the study and restart at a later date or if they will need will need to discontinue the study.

E. **Outcome Measurements**

Performance of PowerSleep device components:

- EEG signal quality as measured by impedance and ability to detect sleep-specific activity and/or events.
- Sleep staging algorithm performance as measured by sensitivity and specificity, PPV compared to the gold standard scoring.
- Audio stimulation algorithm performance as measured by the number and timing of tones provided.

Slow Wave Activity: EEG as recorded by the PowerSleep device and overnight PSGs will be analyzed for slow wave activity.

Sleep Quality: EEG from device downloads will be scored by an experienced registered polysomnographic technologist following current guidelines to determine sleep stage distribution. Sleep quality will also be measured via the Samn-Perelli Fatigue Checklist, the Karolinska Sleepiness Scale (KSS), and the visual analog scales.

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) [47, 48]. 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 [47]. The PVT results will be assessed for average reaction time, average speed, number of omission errors, number of commission errors, and total number of errors.

Verbal Fluency: Participants are required to generate as many words directly related to the instructions as they can. This task has three conditions, the letter fluency condition (that has 3 trials), the category fluency condition and the switching condition. For each trial within each condition, the trial lasts for 60 seconds. This task is expected to take 6 minutes and will be audio recorded for scoring purposes.

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.

Karolinska Sleepiness Scale: The Karolinska Sleepiness Scale (KSS) 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. The KSS will be administered.[49, 50]

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. [51]

Visual analog scales for mood & vigor: Subjective alertness will be assessed using the Visual Analog Scale for Global Vigor and Mood, which combines the scores on four 10-cm scales (alert, sleepy, weary, and effort) to obtain a Global Vigor score between 0 and 40 cm and the scores on four 10-cm scales (happy, sad, calm, tense) to obtain a Global Mood score between 0 and 40 cm. Data are then divided by 4 to obtain a rating between 0-10. [52]

Visual analog scale for sleep quality: Sleep quality will be assess using the Visual Analog Scale for Sleep Quality, which combines the scores on four 10-cm scales (refreshed, alert, sleep quality, and deep sleep) to obtain a Global Sleep Quality score between 0 and 40 cm. Data are then divided by 4 to obtain a rating between 0-10. [53]

Multiple Sleep Latency Test (MSLT)
The MSLT is the gold standard to evaluate physiological sleepiness and consists of a series of five nap opportunities presented at 2-h intervals beginning approximately 2 hours after initial (morning) awakening. We will use a modified version of the test, with four instead of five naps. [54, 55] The MSLT will be scored by an experienced registered polysomnographic technologist following the study protocol design.

Polysomnography: Both the active and sham PowerSleep devices perform online polysomnography. For each night of each treatment period, the recordings will be visually scored in 30-second epochs as wake, rapid eye movement (REM) sleep, or non-REM sleep stages N1, N2, and N3 according to standardized criteria. The following summary variables will be calculated: sleep period time (i.e. time interval separating sleep onset from morning awakening), total sleep time (i.e. SP – duration of intrasleep wake periods), sleep efficiency (i.e. total sleep time / time in bed *100), duration of REM sleep, duration of light non-REM sleep (i.e. stages N1+N2), and duration of deep non-REM sleep (i.e. stage N3).

F. **Other Measurements**

STOP-BANG Questionnaire
This is an 8 item questionnaire which determines the risk for sleep apnea. These are a series of yes no questions. [46]

Cambridge-Hopkins Screening questionnaire (for RLS)
This is a 2 to 13 question questionnaire. If participants answer yes to one or both of the first two questions then they answer a series of questions about sensations in their lower body. Depending on the responses participants may be found to be ineligible to continue.

Epworth Sleepiness Scale (ESS)
This is an 8 item questionnaire that measures the general level of daytime sleepiness. Participants will be asked what the chance is they would doze off or fall asleep during different routine daytime situations.[56]

Insomnia Severity Questionnaire
The Insomnia Severity Index has seven questions about sleep problems. The answers are scored 0 to 4 and added to obtain a total score which indicates the clinical significance of the insomnia complaint. Total score can range from 0 (no clinically significant) to 28 (clinical insomnia, severe). [57]

IV. ADVERSE EVENTS

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study device, whether or not considered related to study device.

AEs will include:
- Changes in the general condition of the participant
- Subjective symptoms offered by or elicited from the participant;
- Signs observed by the investigator or study personnel;

All concurrent disease including any change in severity or frequency of pre-existing disease.

A serious AE is one that:
- Results in death
- Is an immediate threat to life
- Results in permanent disability

In addition, a serious AE is one that is judged by the investigator to be an important or medically significant event. Causality assessments of AEs: For all AEs, the investigator will provide an assessment of causal relationship to study device. Appropriate forms will be used for this purpose and filed in the case report forms and submitted to the IRB for review. They will be classified as related, possibly related, and not related. The severity will be adjudged as being mild, moderate, or severe.

Adverse Event Follow-up
Participants with non-serious adverse events that are ongoing at the participant's last study visit must be followed until resolution or for 30 days after the participant's last study visit, whichever comes first. Non-serious adverse events that are reported during the 7 days following the participant's last study visit need to be recorded on the Adverse Events Case Report Form provided by the Sponsor and followed until resolution or for up to the 30 days after the participant's last study visit, whichever comes first. Serious adverse events will be followed until the event resolves or the event or sequelae stabilize. Serious adverse events that are reported within 30 days of the participant's last study visit should be reported on the Adverse Events Case Report Form provided by the Sponsor.

Adverse Event Reporting Period
Adverse events, both serious and non-serious, are to be recorded on the Adverse Events Case Report Form provided by the Sponsor from the time of the participant's informed consent signature until the end of the participant's study participation. If the participant reports or the Investigator learns of a new AE(s) up to 7 days after the participant's last study visit or a new SAE(s) up to 30 days after the participant's last study visit, the event needs to be recorded on the form provided by the Sponsor. All SAEs should be reported to the Sponsor within 24 hours of occurrence.
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. Philips Respironics Engineering team will be notified to troubleshoot any issues associated with the PowerSleep Device.

V. STATISTICAL ANALYSIS

Data quality will be assessed by the blinded personnel scoring the PSGs and device data. Criteria will be defined regarding whether the data sets are scorable and of sufficient duration to be included in the statistical analysis. These criteria will be consistently applied across all participant records and described in any study publications or reports.

Determination of Sample Size

100 participants may be screened, up to 75 participants will be enrolled (randomized) in order to ensure at least 50 complete data sets. An interim analysis (N=9) from an international study of similar design suggests that between 24-47 participants would be required to reach statistical significance for the primary endpoint of slow-wave activity (SWA).

General Considerations

The primary analysis will include all completed participants who contributed at least one night of usable PSG data for each therapy condition. If there are participants whose therapy order is switched from their randomized assignment, then the results will be analyzed according to both the as-randomized and the as-treated assignments. If the sleep data are not usable for both nights in a given therapy, those participants will be excluded from the primary analysis, and site(s) may over-enroll to compensate for these missing data. The safety analysis will include all randomized subjects.

All variables will be summarized by descriptive statistics. The statistics for continuous variables include mean, median, standard deviation, minimum, maximum, 95% confidence interval (CI) for the mean, and number of observations. For categorical variables, frequencies and percentages will be presented. All analyses will be conducted using either SAS® or SPSS® software.

Subject Disposition

Subject disposition, including the total number of participant's enrolled, randomized, completed, early terminations and withdrawals, will be presented. In addition, a listing will be provided with the reasons for discontinuation.

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. Any discontinued participants or protocol deviations will be documented.

Primary Efficacy Analysis

The primary efficacy measure for this study will be the cumulative or average slow-wave activity (SWA), which will be measured at multiple EEG electrode locations (channels). As stated in the study procedures, two PSG nights will be collected for each therapy.

The primary SWA endpoint will be the average of the two nights, but secondary analyses will include separate assessments of the first and second nights within each therapy. The data will be evaluated to determine whether they meet the assumptions of parametric methods. SWA will be compared between the Active and Sham conditions, using either a paired t-test or the nonparametric Wilcoxon Signed Ranks test, depending on the distribution of the paired differences. The comparisons will be performed within and between EEG channels. The significance level will be a two-sided alpha of 0.05, and if necessary, this will be adjusted for multiple comparisons.

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

An interim analysis is planned when approximately 50% of the enrolled population completes the study. If the effect size observed at the interim is less than originally expected, the sample size may be increased.

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 informed consent and will be repeated verbally to the participants prior to the studies.

The application of electrodes from the PowerSleep device or PSG may include minor skin irritation and redness from abrasive scrub used to prepare the skin for the PSG electrodes and the tape used to attach the PSG electrodes. Therefore, you may have some discomfort with the application or removal of the electrodes from your scalp including skin abrasions, blisters, tape irritation and unpleasant odor. Additionally, you may experience red/pressure marks that should dissipate within one hour. You may also experience some discomfort due to pressure of the headband on your ears. If this is the case, the headband will be adjusted to reduce the pressure. The headband used

for this study contains silicone. Participants allergic to silicone will not be able to participate in this study. 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 application 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.

Participants will be informed that biocompatibility testing related to skin contact of the cable tether has not been completed. Participants will be instructed to wear a shirt when wearing the device to minimize skin contact and any potential irritation.

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. All information collected for this study will be kept in a secured area or stored in a password protected computer if digital. Audio recordings will be stored without identifiers and only include participant ID. 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 the 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.

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.

VII. MONITORING AND QUALITY ASSURANCE

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).

VIII. Registration on ClinicalTrials.gov

This study will be registered on ClinicalTrials.gov.

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APPENDIX I

The sleep center environment is important to the conduct of this study. It is the trial be conducted under highly controlled conditions for the polysomnography recording and PowerSleep device. The participant rooms of the sleep center should operate with the same or similar controls for sound and lighting conditions as required by the American Academy of Sleep Medicine Accreditation Standards. The sleep recording bedrooms should be quiet and guarded from of disturbing noise in the surrounding area. Lighting control in bedrooms should be available for the attending technologists and/or coordinators. A single “night-light” is permissible; the light should not be in direct line of sight for the participant, and should not exceed 7 Lux. Audio and video monitoring of the participants during the sleep periods is recommended, however, recording the audio/visual is not allowed. Staff should conduct the testing procedures in the same manner as those requirements during clinical recordings. Room entry and operationally-related disruptions should be minimized, and should occur on a last-available-option basis.

Participants should wear comfortable loose bed clothing while in the sleep center. They should arrive to the sleep center with sufficient time to complete all required documents, change clothing, and generally acclimate to their assigned room for the night. 30 minutes prior to Lights Out the technologist will help the participant put on the PowerSleep Device. Once the device is on the head the technologist will connect it to the provided study laptop for an impedance check. If the software detects any issues electrodes may need to be repositioned or replaced. If the software detects no issues the participant will be able to continue with their bedtime routine before lights out. If during the course of the overnight stay, a software alert is generated regarding the PowerSleep device impedance, the technologist should follow the instructions in the prompt, which may include adjusting the electrodes.

If the participant should need to use the restroom during the night, they should be instructed to speak up and wait for the technologist to assist them in getting out of the bed. They may also need to assist the participant with getting back into the bed so as to avoid removing the PowerSleep device. If the PowerSleep device does come off or becomes disconnected from the user interface, the technologist will provide new electrodes if necessary and will reconnect the user interface.

APPENDIX II

The MSLT will consist of four trials conducted at approximately two-hour intervals beginning 2 hours after wake time +/- 5 minutes.

The research version of the MSLT will be performed.

- Each trial will be terminated after 2 to 3 consecutive minutes of sleep have occurred **OR** after 20 minutes, whichever occurs first.
- Sleep latency is defined as the time from the start of the trial ("Lights Off") to the first of three consecutive epochs (30-second epochs) of unambiguous stage N1 **OR** one epoch of N2, N3, or REM. (If three consecutive epochs consist of N1-N1-N2, sleep latency is the first epoch of N1. If three consecutive epochs consist of N1-N2-W, sleep latency is the N2 epoch). If sleep latency criteria is not met within 20 minutes, the sleep latency is defined as 20 minutes.
- IMPORTANT: Trials should not be terminated until the technologist is absolutely certain that sleep onset has occurred. Continue the trial to collect an additional 2-3 consecutive minutes of sleep if unsure.

MSLT protocol

1. The MSLT should be conducted by an experienced technologist.
2. Conventional recording montage including EEG (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), EOG (E1-M2, E2-M2), submental EMG, and ECG should be used.
3. Subjects should wear comfortable clothing and remove shoes/slippers prior to each trial.
4. Subjects should be instructed to use the restroom prior to each trial.
5. Subjects should be instructed to turn off electronics prior to each trial.
6. Perform bio-calibration before each trial to ensure the integrity of the recording signals. Leads should be replaced, if necessary, prior to the start of the trial.
7. Standard instructions for bio-calibrations:

   "Lie awake with your eyes open until my next instruction." (30 seconds)
   "Close your eyes but remain awake until my next instruction." (30 seconds)
   "Open your eyes and look straight ahead."
   "Without moving your head, look to the right", <pause>, "look to the left" <pause>, "look to the right", <pause>, "look to the left". <pause> "look up", <pause>, "look down", <pause>, "look up", <pause>, "look down".
   "Blink slowly 5 times."
   "Grit your teeth" (or "Stick out your tongue.")
8. Just prior to start of trial: "Please lie quietly, keep your eyes closed and try to fall asleep."
9. Stop the trial after 2-3 consecutive minutes of sleep have occurred OR after 20 minutes, whichever occurs first.

10. An experienced technologist or individual designated by the principal investigator should review and score sleep latency.
11. Record on source document: Trial number, start time (“lights off”), stop time (“lights on”), site scored sleep latency.

What to do if:

- If a trial is interrupted (e.g. emergency bathroom break, fire alarm, patient safety issue, no readable EEG tracing) re-start the test, and document the issue and timing. Interrupting a trial can cause invalid data and should be avoided if at all possible.
- If the subject moves more than 50% of two consecutive epochs, the technologist should instruct the subject to “Please lie still.”
- If the subject persistently opens eyes, the technologist should instruct the subject to “Please keep your eyes closed.”