Protocol Title: **Servo-Ventilation In-lab PSG Evaluation**

Protocol Number: # ST-1517-ALE-MS

Revision: Rev. 7.0

Principle Investigator:

PI: Dr. Sairam Parthasarathy
The University of Arizona
888 N. Euclid Avenue, Ste. 510,
Tucson, AZ 85719
Phone:520-626-8309
E-mail: sparthasarathy@deptofmed.arizona.edu

PI: Paul Wylie, MD
Arkansas Center for Sleep Medicine
11219 Financial Center Parkway
Suite 315 (clinical sleep practice),
Suite 320 (research office),
Suite 101 (PSG lab).
Little Rock, AR 72211
Phone: 501- 661-9191
Fax: 501- 661-1991
E-mail: pewyliemd1@gmail.com

Sponsor: Philips Respironics, Inc.
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-7500.
http://www.philips.com/

DOCUMENT CONTROL PAGE

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Sponsor: Respironics, Inc. doing business as Philips Healthcare (Philips Respironics")
1740 Golden Mile Highway
Monroeville, Pa 15146
1-(724)-733-0200
http://www.respironics.com/

Author(s)

Jeremy Powers
Clinical Project Manager

Sponsor

Respironics, Inc.
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-7500.
http://www.respironics.com

Study Monitor(s)
Allen Boone
Sr. Clinical Research Associate
1740 Golden Mile Highway
Monroeville, PA 15146
Phone: 724-387-4402
Email: allen.boone@philips.com

Protocol Revissions

Revision Level	Changes made to Protocol	Date	By
0.0	Original Release	October 26, 2015	A. Boone, D. 'Malley, G. Matthews, M. Kane, J. Powers
1.0	Updated based on IRB comments	November, 03, 2015	J. Powers
2.0	Updated exclusion and added an additional 30 day take home	January 7, 2016	J. Powers; M. Kane
3.0	Updated to include Randomization	January 19, 2016	J. Powers; M. Kane
4.0	Updated to include all PSG nights to be randomized	April 08, 2016	J. Powers; M. Kane
5.0	Updated based on Univercity of Arizona comments.	April 19, 2016	J. Powers; M. Kane, S. Parthasarathy
6.0	Added 20 days to complete the PSGs	June 27, 2016	J. Powers; S. Parthasarathy
7.0	Modified the Incl/Exc. Criteria	November 22, 2016	J. Powers; S. Parthasarathy

Investigator Statement

As Investigator of the study titled "Servo-Ventilation In-lab PSG Evaluation " (the "Study"), 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; 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 participant participate in the Study before obtaining that participant'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 appropriate regulations;
(vi) supervise all testing of investigational devices that involves any Study participant;
(vii) maintain Study documentation for the period of time as required by appropriate regulations; and
(viii) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

INVESTIGATOR

Signature: _____

Printed Name: _____

Date: _____

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Glossary of Definitions and Terms

For the purposes of this study, the following definitions will be used.

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

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

Auto Adjusting Continuous Positive Airway Pressure Device: A type of CPAP machine that monitors changes in breathing and compensates automatically by making appropriate therapeutic adjustments in pressure delivery.

Bi-Level PAP Therapy: Responds to both inspiration and expiration by the patient and delivers a set amount of pressure when the patient begins spontaneous inhalation and decreasing pressure when exhalation begins.

Central Apnea: The cessation of airflow at the nostrils and mouth for at least 10 seconds that is associated with the absence of inspiratory effort.

Central Apnea Index (CAI): The number of central apneas divided by the number of hours of sleep.

Complex Sleep Apnea Syndrome (Comp SAS): Presence of any of the following sleep disordered breathing conditions, independently or in any combination: Periodic Breathing including Central Sleep Apnea (CSA), Cheyne Stokes Respiration (CSR), and / or CPAP emergent central sleep apnea.

Compliance: Adhering to or conforming to a regimen of treatment such as CPAP or Bi-Level PAP.

CPAP Pressure: Prescribed therapeutic pressure needed to maintain an open airway in a sleep apnea patient treated with CPAP, expressed in centimeters of water (cm H_20). The positive pressure can range from 4 - 25 cm H_20. Different patients require different pressures. The needed therapeutic pressure is determined in a CPAP titration study.

CPAP Therapy: Continuous Positive Airway Pressure – delivers a constant pressure during inspiration and expiration.

EPAP: Expiratory Positive Airway Pressure **-** prescribed pressure for the expiratory (breathing out) phase of an individual on Bi-level PAP therapy.

Hyper somnolence: Excessive daytime sleepiness.

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.

IPAP: Inspiratory Positive Airway Pressure **-** Physician prescribed pressure for the inspiratory (breathing in) phase of an individual on Bi-level PAP therapy.

EEP: End Expiratory Pressure, the pressure applied at patient mask during end of expiration.

OSAHS: Obstructive Sleep Apnea Hypopnea Syndrome- a disorder in which complete or partial obstruction of the airway (apneas or hypopneas) during sleep causes loud snoring, oxyhemoglobin desaturations and frequent arousals.

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. [1]

I. Background and Significance

Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS) is a condition characterized by intermittent partial collapse and closure of the upper airway (UA). The partial collapse and closure of the airway leads to sleep fragmentation, oxygen desaturation, hypercarbia, and activation of the sympathetic nervous system. A result of disrupted sleep may be excessive daytime sleepiness. The syndrome is also associated with behavioral, functional, cardiovascular and cognitive dysfunction. (2, 3, 4)

Continuous Positive Airway Pressure (CPAP) is the most effective treatment for the OSAHS. CPAP stabilizes the airway and prevents instability and collapse. With a stable and patent airway, breathing continues in a normal manner, gas exchange is improved, and there is no disruption of sleep related to disturbed breathing. (5)

CPAP is applied to the upper airway via a mask that covers the nose or the nose and mouth and reduces or eliminates sleep disordered breathing. The period of maximum susceptibility to airway collapse is at the end of exhalation and during early inhalation. During inhalation, negative pressures are generated in the airway by the normal process of ventilation (increase of thoracic volume and reduction of intra-thoracic pressure). The constant pressure of CPAP supports the airway throughout the ventilatory cycle. (3)

In the sleep laboratory, manual titration of positive airway pressure is performed to determine effective CPAP pressures. During the in-lab procedure, the patient is instrumented for full polysomnography (PSG). Therapy is applied and pressure is adjusted during the course of the night to stabilize the upper airway and the breathing pattern. With conventional CPAP, a single pressure level is applied to the airway. While adequate for a majority of patients with obstructive sleep apnea, this static prescription will present challenges in certain patients and conditions. (6 7)

Other forms of positive airway pressure that are approved for the treatment of OSAHS include automatically adjusting CPAP, Bi-level Positive Airway Pressure (BiPAP), and automatically adjusting BiPAP. Automatically adjusting CPAP (Auto CPAP) evaluates the airflow pattern and adjusts pressure to optimize airflow. Pressure is increased or decreased at specific time intervals to adjust therapy in a proactive fashion. Auto CPAP accommodates patients presenting with highly variable pressure requirements (e.g., sleep stage or body position dependent sleep apnea). The automatic adjustment can be used in patients for whom in-laboratory therapy titration is either delayed or impossible. (8, 9, 10)

The REMStar Auto algorithm is a pro-active, flow-based algorithm. The basic algorithm evaluates the inspiratory flow and determines impending or actual flow limitation. This multi-dimensional flow evaluation occurs in concert with a program of pressure adjustments designed to evaluate the critical pressures (pressure at which the airway is susceptible to collapse) and maintains pressures slightly above the critical pressure. The patient is protected from “break-through” events with a full complement of intelligent responses to airflow events and snoring. (1)

BiPAP therapy is an alternative to CPAP therapy. With BiPAP therapy, the patient’s breathing pattern is monitored to identify the inspiratory and expiratory phases. Pressure is increased during inhalation and returned to a lower pressure during exhalation. Although titration procedures vary, the expiratory pressure (expiratory positive airway pressure or EPAP) is adjusted to prevent airway collapse (apnea) and the inspiratory pressure (inspiratory positive airway pressure or IPAP) is adjusted to prevent airflow limitation, hypopnea, snoring or arterial desaturation not associated with complete airway obstruction. BiPAP therapy differs from CPAP therapy, in that in addition to stabilizing the airway, inspiratory effort

is assisted by the difference between the inspiratory and expiratory pressure. This difference between EPAP and IPAP pressures is often referred to as "Pressure Support". (1, 3, 8, 10)

Patients with OSAHS may be prescribed BiPAP therapy if CPAP therapy is not tolerated. BiPAP therapy may also be prescribed for patients with other respiratory disorders or for patients with both sleep related airway instability and impaired lung function.

Automatically adjusted Bi-Level Positive Airway Pressure (Auto BiPAP®) is currently marketed for the treatment of OSAHS. Auto BiPAP adjusts EPAP levels based upon the detection of an apnea or evidence of airway instability. IPAP is adjusted to overcome hypopnea and airflow limitation.

Patients experiencing reduced ventilation from lung disease, neuromuscular disorders, or problems with the control of the breathing can experience nocturnal hypoventilation that is worse during sleep than it is during wakefulness. These patients are typically more complex and require more extensive evaluation and follow-up than patients suffering only from OSAHS. Patients may also be more vulnerable to loss or interruptions in treatment and often require more advanced modes and features such as alarms and timed back-up breaths.

OSAHS patients may respond to increases in CPAP or BiPAP therapy by demonstrating a shift in the nature of the apnea from obstructive to central. In these cases, patients may not receive adequate treatment with CPAP since lower pressure levels do not manage the instability of the airway leaving residual airway obstruction, while higher pressure levels are associated with CPAP emergent events. This condition is referred to as CPAP Emergent Complex Apnea.

Auto SV (Auto Servo Ventilation) is a mode of positive airway pressure used to treat obstructive and complex central sleep apnea. The main features of the Auto SV mode include:

- Normalization of ventilation by automatically adjusting IPAP pressure to achieve a target ventilation. IPAP is increased or decreased to help stabilize the ventilation.
- Provision of timed, back-up breaths during central apneas. The optimal back-up rate is automatically determined by the device based on the patient's breathing.
- Automatic control of EPAP pressure to treat obstructive events.

Several manufacturers produce these types of devices. The algorithms used to determine the IPAP, EPAP and minimum respiratory rate are different. The largest number of these devices currently in use are the BiPAP AutoSV Advanced System One (Philips Respironics, Murrysville PA) and the VPAP Adapt (ResMed Corp., San Diego CA).

I. Purpose and Scope

This study is to better understand the performance and features of the BiPAP autoSV Advanced System One. Philips Respironics will evaluate the PSG and Encore data from each night. The aim of the study is to characterize the acute outcomes of treatment provided by the device and evaluate any modifications made to the Philips Respironics device's algorithm

The participants for this study will be experienced in having used servo ventilation therapy at their home because it is only such patients who are already using servo ventilation as part of routine clinical care that are eligible for participation.

Participants will receive four (4) randomized PSG's during which they will receive treatment from the following devices in a randomized manner:

- FDA released Philips BiPAP AutoSV Advanced System One
- A Modified Philips BiPAP ASV
- FDA released ResMed S7 VPAP Adapt
- FDA released ResMed S9 VPAP Adapt

Target Patient Population

The participants sought for this effort will be previously prescribed a servo-ventilation device as part of routine clinical care.

II. Study Objective

The objective of this study is to compare the performance of servo ventilation devices.

III. Participant Selection

Participants will be recruited from the sleep center laboratory, clinics, through recruitment flyers as well as through IRB approved PHI waiver aimed at soliciting potential participants to enroll in the study. Eligible participants will be required to provide informed consent prior to beginning their participation in this study.

The inclusion and exclusion criteria for this study are listed below. All participants are required to demonstrate Sleep Disordered Breathing conditions requiring treatment with a servo-ventilation device.

Inclusion Criteria

- Ability to provide consent
- Age ≥ 21
- Currently prescribed servo ventilation therapy at home
- Current device compliance report demonstrating residual AHI of 4 or more

Exclusion Criteria

- Participants who are acutely ill, medically complicated or who are medically unstable
- Participants in whom PAP therapy is otherwise medically contraindicated
- Participants who are claustrophobic
- Symptomatic ("Symptomatic" defined as hospitalized for heart failure or a change in cardiac medications, within the last two months) chronic heart failure (NYHA 2-4) and reduced LVEF≤45%, AND moderate to severe predominant central sleep apnea
- Participants with previously diagnosed respiratory failure or respiratory insufficiency and who are known to have elevated arterial carbon dioxide levels while awake ($PaCO_2$ ≥ 55mmHg).
- Participants requiring any kind of oxygen therapy
- Participants who have had surgery of the upper airway, nose, sinus, eyes, or middle ear within the previous 90 days
- Participants with untreated, non-OSA sleep disorders, including but not limited to; insomnia, periodic limb movement syndrome, or restless legs syndrome (PLMI > 15).

V. Participant Enrollment

Sample Size: This is a pilot study and no formal sample size calculation has been performed. Up to fifty (50) participants may be screened for this study with the intent on collecting data from forty (40) participants.

Table 1. Study Procedures

Baseline with PSG • Informed Consent • Inclusion/Exclusion Criteria Review • Demographics • Anthropometric Measurements • PAP Prescription information (if available; from Device or from Medical records). This is the pressure settings of the device that was prescribed by the patient's clinical sleep medicine provider. • Medical History and physical examination • Sleep History- Including that past 30 day detailed report • Diagnostic PSG history (copies of sleep studies that were performed as part of routine clinical care in the past that qualified the patient for the servo-ventilation device) • Current Medications • Vital Signs (at beginning of PSG night) • Research Trial PSG- Randomized to a device
Procedures for Each PSG after Baseline • Current Medications • Vital Signs (at beginning of PSG night) • Research Trial PSG- Randomized to one of the four devices (4 research PSGs will be performed for each subject over a 20 day period).
30 day Take Home with Modified Philips BiPAP ASV device After the last PSG participants will be sent home on Modified Philips ASV study device. A wireless modem will be connected to the Modified Philips ASV study device. The wireless modem is for device data collection/transmission purposes only that monitors the usage and performance of the device in the home-setting. The device setting should be set to the following: P max: 30 EPAP min: 4 EPAPmax:15 PS min: 0 PS max: 15 BiFlex: 2 Rate: Auto
After 30 day Take Home Participants Will • Return to the Sleep Lab • Complete the end of study questionnaire • Return all of the study equipment

Additional Take Home with the Modified Philips BiPAP ASV device: • Participants may be asked to use the Modified Philips ASV study device for an additional 30 days if more data is needed for analysis. Participants will complete the same end of day questionnaire noted above.
After trial completion: • When the Participant is done with the trial they will go back to using their own prescribed device.

Polysomnography

For each PSG, participants will be asked to report to the sleep center and/or research site at a predetermined time agreeable to the participant and the sleep center. The participant may be asked to return for up to four sleep studies, as described above.

During the PSG, participants will use their own mask and accessories from their home treatment in order to maximize their comfort. Should the participant need a mask or should the sleep technologist feel the mask is not appropriate for the PSG, the participant will be provided a new mask as part of this study by the research site.

Participants will be instrumented for PSG via sleep acquisition system. The PSG will be configured per standard operating procedures at the research site.

- Two belts secured around the chest and abdomen to measure movements associated with breathing effort
- A small sensor which attaches to the chest belt to measure body position
- Electroencephalographic (EEG) leads attached to the scalp and face to measure sleep stages (F4-M1/A1, C4-M1/A1, O2-M1/A1, F3-M2/A2, C3-M2/A2, O1-M2/A2), left and right electro-oculograms, submental and frontal electromyogram, respiratory effort, oximetry, and right and left anterior tibialis electromyogram (11).
- A flexible finger sensor placed on the finger to measure arterial saturation (SpO2)
- Surface electrodes attached to the skin bilaterally over the anterior tibialis muscle, to measure leg movements
- A microphone attached to the skin at the base of the neck to measure snoring sounds. The microphone is no bigger than a nickel.
- A plethysmography signal from the pulse oximetry device may be added to the montage
- Lead II ECG Electrode derivation
- Several channels of data (flow, pressure, and other device generated information) from each therapy device will be included as part of the PSG montage:

Participants will be monitored closely by a trained sleep technologist during each PSG.

Randomized PSG Device Set Up:

Philips BiPAP ASV PSG Set Up

The following device settings will be set up for the PSG night:

- FDA released Philips BiPAP AutoSV Advanced System One
- The modified Philips BiPAP ASV

P max: 30
EPAP min: 4
EPAPmax: 15
PS min: 0
PS max: 15
BiFlex: 2
Rate: Auto

ResMed BiPAP ASV PSG Set Up

The ResMed devices noted below will be configured to operate on the following device settings for the PSG night:

- FDA released ResMed S7 (VPAP Adapt SV)

  EEP: 4
  PSmin: 3
  PSMax: 16

- FDA released ResMed S9 (S9 VPAP Adapt)

  EPAP min: 4
  EPAPmax: 15
  PS min: 0
  PS max: 20
  Max Ramp: Off

If the device is not adequately treating the participant, the device may be adjusted during the night. If available, device data normally stored on internal memory or written on to a data card in the device will be collected and reviewed for each PSG.

All PSG's will be scored using Somnolyzer automated scoring software to determine all sleep and respiratory parameters. Results of the PSG's will not be used to make any decisions or recommendations on the participant's usual treatment.

VI. Statistical Analysis

Baseline data will be presented with descriptive statistics. Endpoints will be compared between therapy nights, and between device and PSG scores. Data that are not normally distributed may undergo appropriate transformation to fit the assumptions of a paired t-test. Otherwise, the nonparametric

Wilcoxon Signed Rank test will be used. All tests will be conducted at a significance level of $p < 0.05$, and confidence intervals will be presented.

VII. Risks and Discomforts

Risks associated with polysomnography are minor and transient. Adhesive materials used to hold the various sensors in place may cause skin irritation. The sensors may feel uncomfortable. Some patient may find it difficult to sleep in the sleep laboratory setting. If participants feel tired after the research study, the research staff can give the participant extra sleep time, or contact a family or friend to be the designated driver.

The currently released AutoSV devices being used in this study have been cleared for marketing by the US Food and Drug Administration, being used within the intended use. The modified AutoSV Philips Respironics device used in this study has undergone standard verification and validation testing and other reviews to assure patient safety.

For each PSG, the positive airway pressure may feel different than the participant is accustomed to and breathing may feel different than normal. The pressure delivered by the device may be higher or lower than the patient is used to. These factors may cause discomfort or anxiety or may negatively impact sleep.

The use of positive airway pressure through a mask may cause dryness or irritation of the upper airway, discomfort in the ears or eyes or a runny nose. The mask may create red marks on the face.

None of the risks or discomforts are more than those seen in normal clinical practice. Any irritation usually self resolves in hours after the PSG is completed. Heated humidification will be available to address issues with the upper airway. Participants will be using the mask they use for home treatment so mask side effects should be minimal.

VIII. Potential Benefits

Although participation in this trial will not result in any direct benefit to the subject, they will be contributing to generalizable data that will help improve the device design and function.

IX. Monitoring and Quality Assurance

The clinical trial site will be monitored in accordance with policies at Respironics Inc. and those federal regulations that pertain to clinical research; namely, 21 CFR Parts 50, 54, 56 and 812; and others as applicable. Monitoring will occur on a regular frequency, such to allow ongoing review of data collected, site qualifications and compliance with the protocol. All monitors will be appropriately trained to ensure compliance with the protocol.

X. PROTECTION FOR HUMAN SUBJECTS

Medical information produced by this study may become part of the participant's medical record. Information that does not become part of the medical record will be stored in the investigator's file and identified by a code only. The code key connecting the participant's name to specific information about participation will be kept in a separate, secure location. Information contained in the records may not be given to any person unaffiliated with this institution in a form that could identify the participant without written consent, except as described in the consent form or as required by law.

It is possible that the participant's medical and research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the FDA, the Institutional Review Board, federal or state government agencies, or accrediting agencies, in the course of carrying out their duties. If the participant's record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, this institution will use reasonable efforts to protect participant privacy and the confidentiality of the medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, participant names or other identifiers will not be used in any publication or teaching materials without specific permission.

XI. Confidentiality

Confidentiality of subject identification and test-related information is very important. The privacy rules and requirements according to governing regulations will be implemented. Methods to protect the privacy of subjects and clinical information will be used. A unique identification number designed to protect the identity of subjects will be used to identify the subject on report forms, recruitment logs, data forms or other report containing information or referring to a subject. This unique identification number will be generated using a password protected online data numbering system and subjects will be assigned a number based on the screening order.

This unique identification number, if needed, can be linked to identifiable data. The Respironics clinical research associate managing the study will be the only person to have access to the link between the unique identifiable number and the participant. All other Respironics representatives involved in this study will only have access to the subjects' unique identification number. The linked data will be stored within the study binder in the Clinical Research department for two years or until the end of the study. After that point, the de-identified data will be stored indefinitely within the Clinical Research department Electronic Data Capture (EDC) system.

XII. References

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