A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) therapy on Re-hospitalization in Patients with Sleep-Disordered Breathing with co-morbid COPD.
Confidential

Protocol Title: A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) therapy on Re-hospitalization in Patients with Sleep-Disordered Breathing with co-morbid COPD. (STOP-BOUNCEBACK study)

Protocol Number: HRC-1426-BBACK-MS

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Confidential

A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) therapy on Re-hospitalization in Patients with Sleep-Disordered Breathing with co-morbid COPD.

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Investigator Agreement

As Investigator of the study titled "A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) therapy on Re-hospitalization in Patients with Sleep-Disordered Breathing with co-morbid COPD. (the "Study"), I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the Institutional Review Board (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 subject participate in the Study before obtaining that subject's informed consent;
(iv) not make modifications to the Protocol as supplied to me by Philips 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; and
(viii) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

INVESTIGATOR

Signature:_____

Printed Name: _____

Date:_____

Glossary of Definitions and Terms

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.

AVAPS-AE: A mode of therapy that automatically adjusts EPAP in response to patient events such as snores, leak, and apneas/hypopneas, provides an automatic back up rate, and automatically adjusts pressure support in order to maintain the target tidal volume.

Average Volume Assured Pressure Support (AVAPS): Positive airway pressure support that provides a gradual pressure change based on the average of the preceding several breaths to maintain the target tidal volume.

Bilevel 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.

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

COPD: Chronic Obstructive Pulmonary Disease

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

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

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.

Mode of Ventilation: Represents a combination of control, phase and conditional variables that establish a set pattern of spontaneous and/or mandatory breaths.

Noninvasive Positive Pressure Ventilation (NPPV): Mechanical ventilation provided noninvasively (by mask or similar interface) rather than through an endotracheal tube or tracheostomy.

OSA: Obstructive Sleep Apnea **-** a disorder in which complete or partial obstruction of the airway during sleep causes loud snoring, oxyhemoglobin desaturations and frequent arousals.

Polysomnography: 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.

Spirometry: Measurement by means of a spirometer of the air entering and leaving the lungs.

DOCUMENT CONTROL PAGE

Study Name
A Pilot, Multi-Center, Randomized, Open-Label, Parallel Group Study to Assess the Effects of a Novel Application of Averaged Volume Assured Pressure Support Ventilation (AVAPS-AE) therapy on Re-hospitalization in Patients with Sleep-Disordered Breathing with co-morbid COPD. (STOP-BOUNCEBACK study)

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PROTOCOL REVISIONS

Rev Level	Changes Made for HRC-1426-BBACK-MS	Date	Contributors
0.0	Initial Draft	01/08/2015	S. Parthasarathy, C. Cain, G. Lotz
1.0	Revisions	03/23/2015	C. Cain, L, Ostrowski, S. Parthasarathy
2.0	Revisions	1/15/2016	C. Cain L. Ostrowski, S. Parthasarathy
3.0	Updated Study Monitor Information. Updated Pap Wash-In Criteria. Removed "Acute Respiratory Failure" from Exclusionary Criteria; Removed "Alice PDX" verbiage. Add additional site Banner-University Medical Center South 2800 E. Ajo Way Tucson, AZ 85713	11/22/2016	T. Bowers
4.0	1.) Update Inclusion Criteria by removing " prior non-elective hospitalization (one in past 12 months) OR active smoker"	01/17/2017	S. Parthasarathy, C. Cain, A. Valentin
5.0	Updated Inclusionary content to state "a primary or secondary admission diagnosis of COPD", Removed Inclusionary Criteria section 2 part (b). Updates to the final table	03/08/2017	S. Parthasarathy, T. Bowers, C. Morton, C. Cain, G. Lotz

I. Background

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in America, claiming the lives of 133,965 Americans in 2009 [(1)]. In 2011, 12.7 million U.S. adults (aged 18 and over) were estimated to have COPD([2]). However, close to 24 million U.S. adults have evidence of impaired lung function, indicating an under diagnosis of COPD [(3)]. An estimated 715,000 hospital discharges were reported in 2010; a discharge rate of 23.2 per 100,000 population (3). COPD is an important cause of hospitalization in our aged population. Approximately 65% of discharges were in the 65 years and older population in 2010. In 2010, the cost to the nation for COPD was projected to be approximately $49.9 billion, including $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs [(3)]. Innovative improvements in care delivery, including novel device-based therapies, could potentially reduce re-hospitalizations, healthcare costs, and public health burden due to COPD.

Across a selection of 15 states in 2008, there were 190,700 index admissions with a principal diagnosis of COPD among patients 40 years old and older [(4)]. The 30-day readmission rate for a principal diagnosis of COPD was 7.1 percent and the rate of 30-day readmissions for any diagnosis of COPD was 17.3 percent [(4, 5)]. If all readmissions were counted regardless of diagnosis, one out of five index admissions for COPD (20.5 percent) were followed by a readmission within 30 days [(4, 5)]. Healthcare costs were consistently higher for readmissions than for initial stays [(5)]. On average, costs for a 30-day readmission with COPD as principal diagnosis were 18 percent higher than for the index stay. Costs were more than 50 percent higher for the readmission with COPD as any diagnosis or for all-cause readmissions. Healthcare costs due to COPD could be greatly reduced by innovative interventions aimed at reducing risk for readmission.

Currently, Medicare patients who are readmitted within 30-days could result in significant fines to healthcare providers and institutions. Innovations in healthcare delivery aided by device technology that expeditiously facilitates positive airway pressure therapy could mitigate such financial liabilities. Averaged Volume Assured Pressure Support –Auto EPAP (AVAPS-AE) device can not only prevent the nocturnal hypoventilation due to COPD, but also treat coexisted obstructive sleep apnea [(6)]. AVAPS-AE is a mode of therapy (Philips Respironics Inc, Monroeville, Pa) with potential advantages over the currently established modes of noninvasive positive pressure ventilation (CPAP and bi-level therapy). This mode of therapy incorporates AVAPS (automated adjustable IPAP setting to maintain target ventilation with a settable rate of change), Auto EPAP and Auto Back up Rate. It automatically adjusts EPAP in response to patient events such as snores, leaks, and apneas / hypopneas, provides an automatic back up rate and automatically adjusts pressure support in order to maintain the target tidal volume. In a prospective cohort study, Marin and colleagues have shown that positive airway pressure (PAP) therapy treatment for “COPD-OSA overlap syndrome” can reduce a composite index of hospitalizations and mortality [(7)]. A prospective multi-center study of PAP therapy aimed at reducing re-hospitalization due to COPD has not been performed.

II. Study Design

This is a multicenter, randomized, parallel-group, open label study of the efficacy of AVAPS-AE to prevent re-hospitalization in hospitalized patients with comorbid COPD. A wash-in period – aimed at assessing device tolerance – will be performed in order to exclude participants who are at high risk for discontinuing positive airway pressure (PAP) therapy. Similar to pharmaceutical studies, such a wash-in period for medication tolerance can help reduce attrition and missingness that can adversely affect study sample size estimations.

Hospitalized patients with comorbid COPD who are at high risk for readmission will be recruited. Specifically patients with comorbid COPD who are to be discharged with (a) admission diagnosis of COPD (GOLD stage II or greater); AND (b) either a prior non-elective hospitalization (one in the past 12 months) OR active smoker. Such participants will undergo questionnaire-based screening for sleep-disordered breathing (STOP-BANG questionnaire) and if they have a high risk for SDB ($\geq$ 3 points) will undergo an overnight portable sleep study for screening prior to hospital discharge (AHI $\geq$ 10 per hour; >3% oxygen desaturation for hypopneas). Sites may exercise the option of using the STOP-BANG questionnaire as a screening tool for the purposes of enriching the study population.

Participants who exhibit AHI $\geq$ 10 per hour; >3% oxygen desaturation for hypopneas based on the portable sleep test will undergo a PAP "wash in" daytime exposure for 30 minutes after adequate mask-fitting, on the therapy device (AVAPS- AE). Participants who fail to tolerate such therapy, or indicate that they would be unable to use such therapy at night, will not be randomized. Considering the "wash-in" is performed prior to randomization, such participants will not be included as part of the intention to treat (ITT) analysis.

After randomization and prior to discharge, participants will either be initiated on AVAPS-AE therapy (intervention arm) for 60 days or will be referred to the sleep center for further diagnostic testing and therapy initiation (standard of care arm). Participants will complete quality of life questionnaires (Functional outcomes of sleep questionnaire [FOSQ]) at baseline (in-person), and in 30 and 60 days (by mail) post discharge. If participants assigned to the intervention arm are discharged with home O_2 therapy, the O_2 will be entrained into the AVAPS-AE device for nighttime use. At time of hospital discharge, if participants in the intervention arm are not meeting conventional daytime and nighttime criteria for O2 therapy [(SpO2 <88% in room air –day) (> 5 continuous minutes SpO2 $\leq$ 88% - nighttime)], they will undergo AVAPS-AE therapy alone.

Over the first 30 days post discharge, participants in the intervention arm will receive 3 phone calls to promote PAP therapy and medication adherence. Participants in the standard of care (SOC) arm will also receive 3 phone calls to promote medication adherence over the first 30 days post discharge. On days 30 and 60, all participants will receive a phone call to determine if they had been admitted to the hospital, or had an unplanned visit to a physician's office or emergency room. Information regarding hospital

admission, diagnostic tests, medication changes, and procedures will be collected from all participants. Discharge summaries of re-hospitalizations and office or ER visits, as well as diagnostics tests and therapies received will be collected for measuring healthcare costs.

Participants who enrolled in a registry (optional) for a 3 year follow-up will also be queried on a yearly basis regarding hospitalizations, cardiovascular events, and assessment of vital statistics in the National Death Index registry. The study will conclude when all randomized participants have been followed for a minimum of 60 days. An independent Data Safety and Monitoring Committee (DSMC) will monitor safety data on an ongoing basis and may recommend that the study be stopped earlier in case of safety concerns. No Interim efficacy analyses is planned. Ongoing DSMB review is planned to assess device and/or safety related clinical events and adjudicate if applicable. This will be performed after 25%, 50% and 75% of target enrollment have been completed. Participants will be followed for occurrence of death or hospitalization throughout the duration of the study for a minimum of 24 months after randomization. All death and hospitalization reports will be collected on an ongoing basis during the study and will be adjudicated by an adjudication committee consisting of three site investigators.

AVAPS-AE is a mode of therapy (Philips Respironics Inc, Monroeville, Pa) with potential advantages over the currently established modes of non-invasive positive pressure ventilation (CPAP and bilevel therapy). This mode of therapy incorporates AVAPS (automated adjustable IPAP setting to maintain target ventilation with a settable rate of change), Auto EPAP and Auto Back up Rate. We believe that these automated parameters will allow better nocturnal ventilatory control to offset the differing elastic and resistive loads imposed by changes in body position during sleep. Furthermore, AVAPS-AE will counter the changing ventilatory requirements due to alterations in lung volumes and airway resistance during different stages of sleep. In summary, the AVAPS-AE mode will enable automatic adjustment in response to ventilatory changes throughout the night. The device platform used in this study with the AVAPS-AE feature is in the BiPAP A40 platform. This device uses existing modes of therapy, therapy features, and algorithms as that which have been previously cleared by the Food and Drug Administration (FDA) (K121623).

III. Study Objectives/Endpoints

Specific aim #1: Evaluate the effects of novel application of Averaged Volume Assured Pressure Support (AVAPS-AE) therapy on ***time to*** (# of days) emergent and non-emergent healthcare utilization in patients with sleep-disordered breathing who are hospitalized with co-morbid COPD.

Specific aim #2: Evaluate the effects of novel application of Averaged Volume Assured Pressure Support (AVAPS-AE) therapy on the ***number of*** emergent and non–emergent healthcare utilization over 6 months;

costs related to re-hospitalization; number of visits to physician offices or emergency rooms, and health-related quality of life (disease-specific and general HR-QOL measures).

Primary Endpoints
Composite end-point of time to occurrence of emergent healthcare utilization (such as re-hospitalization, unscheduled physician office visits, urgent care visits or emergency room visits).

Secondary Endpoints:

1. Healthcare Costs
2. Change in quality of life (SF-36) at 30 and 60-days
3. Change in quality of life (FOSQ) at 30 and 60-days
4. Number of hospitalizations over 3 years (optional if enrolled in registry)
5. Time to re-hospitalization alone
6. Composite end-point of time to occurrence of non-emergent healthcare utilization (such as scheduled hospitalization, scheduled physician office, urgent care visits or emergency room visits).

IV. Subject Selection

Inclusion criteria:

1. Hospitalized patients who are at high risk for readmission who are at least 18 years of age.
2. Specifically patients with (a) a primary or secondary admission diagnosis of COPD who are ready for discharge AND (b) are also found to have sleep-disordered breathing (AHI ≥ 10 per hour; >3% oxygen desaturation for hypopneas) by overnight portable respiratory study prior to hospital discharge.
3. Bedside spirometry revealing evidence for obstructive lung disease (post-bronchodilator; GOLD stage II or greater (FEV1 <70% predicted post BD).
4. No previous home PAP or NIV use within the past year

Exclusion criteria:

1. Central sleep apnea (Central apnea index >5 per hour; and/or >50% are central apneas & hypopneas)
2. Clinically unstable, i.e., hypotensive shock, uncontrolled cardiac ischemia or arrhythmias, requiring life support ventilation or as otherwise determined by the investigator
3. Participants with Stage III & IV Chronic Heart Failure as defined by the New York Heart Association (NYHA) Classification
4. Known or expected contraindications for the use of non-invasive ventilation per the assessment of the investigator.

5. Lack of medical insurance

V. Study Enrollment

Participants who are screened for enrollment will be entered on a screening log which will be maintained at the clinical site. Participants referred for screening will be given a thorough explanation of the study and the requirements for participation by the study coordinator or other qualified medical professional. If the participant is interested in the study, the investigator or a member of his/her staff should approach the patient to obtain written informed consent. The background of the proposed study, the benefits and risks of the procedures and study should be thoroughly explained to the participant. The participant must sign the consent form prior to enrollment. This form or a modification of it must have prior approval of the study site's Institutional Review Board (IRB). Failure to provide informed consent renders the participant ineligible for the study.

Up to 10 sites will be recruiting for this study. Up to 80 participants will be enrolled across all sites with the goal of 60 participants (N=60) completing the study (25% attrition rate). One site should not enroll more than 25% of total N.

VI. Study Procedures

Screening Assessment

Hospitalized patients with comorbid COPD who are at high risk for readmission will be recruited. Specifically patients with comorbid COPD who are about to be discharged. with (a) prior hospitalization (within the past 12 months) Such participants will undergo questionnaire-based screening for sleep-disordered breathing (STOP-BANG questionnaire) and if they have a high risk for SDB ($\geq$ 3 points) will undergo an overnight screening portable sleep study the night prior to hospital discharge (AHI $\geq$ 10 per hour; >3% oxygen desaturation for hypopneas). Sites may exercise the option of using the STOP-BANG questionnaire as a screening tool for the purposes of enriching the study population.

Spirometry

Each participant will undergo a spirometric assessment, using a handheld Koko ^{TM} unit, to determine if they meet inclusion criteria.

Spirometry will be performed based on the "Standardization of Spirometry – 2005". [11]Acceptability and reproducibility criteria are summarized in Table 8 of the ATS document. Spirometry equipment must be calibrated with a 3L syringe prior to the first use daily. The results will be printed and maintained in a calibration log, which will routinely be monitored for compliance during monitoring visits. Spirometry

values recorded on the CRF will be post bronchodilator. Participants will need to reveal evidence for obstructive lung disease Gold stage II or greater (FEV1 < 70%) in order to continue in the study.

Diagnostic Overnight Sleep Study

Site investigators will make appropriate documentation in the study participants chart that they will be undergoing an overnight sleep study. In addition, results of the sleep study will be communicated to the participant by the site investigator and documented appropriately.

Either an Alice Night One (Philips Respironics) will be used for the overnight diagnostic sleep study. The Alice devices are portable home sleep testing devices that records information about breathing. It is used to diagnose OSA. These devices may be used in a sleep lab or clinical setting by trained professionals, or it may be used at home by patients as directed by their health care provider. Participants who are found to have sleep disorder breathing (AHI ≥ 10 per hour) will qualify. It is known that supplemental oxygen that is titrated to maintain oxygen levels above 90% does not allow for easy differentiation of hypopneas. Therefore, for participants who require supplemental oxygen at night, oxygen will be titrated not to exceed 90% saturation at the start of the study on the night of the sleep test during calm wakefulness while lying in hospital bed at patient-determined head-elevation.

During the diagnostic sleep study, participants will be set-up with on with the portable device that includes the following sensors:

- An effort belt will be secured around the chest to measure movements associated with breathing effort
- Nasal cannula
- A flexible finger sensor placed on the finger to measure oxygen saturation (average signaling time of 3 seconds) and pulse

Scoring

- All sleep studies be scored by the automated Somnolyzer software program. Somnolyzer is a computer program intended for use as an aid for the diagnosis and treatment monitoring of sleep-related respiratory disorders. Somnolyzer scores sleep stages, arousals, respiratory events and periodic limb movements in sleep according to published standards based on polysomnographic (PSG) recordings. All sleep variables will be classified and scored using the 2007 AASM criteria. [9,

[10, 11] All sleep studies will be initially interpreted by trained research staff in order to determine participant qualification All studies will be centrally scored to verify enrollment criteria. Apneas will be scored according to AASM Scoring Manual rules VIII.3.A, B.

- Hypopneas will be scored according to the AASM Scoring Manual rule VIII.4.A for desaturations (SpO2 ≥3%) with a nadir below 90%

NOTE: If the portable sleep test yields less than 3 hours of total recording time, the participant will have the option of having the sleep test repeated. If the participant does not elect to repeat the sleep test or the repeat sleep test yields less than 3 hours of total recording time, the participant's data will not be included in the statistical analysis at the end of the study. Furthermore, a replacement participant will then be enrolled. An exception to when the minimum required recording time is < 3 hours is the following: when the total respiratory events (apneas and hypopneas) counted (in the actual recording time duration) is divided by 3 hours (rather than the actual recording time) results in an AHI of ≥ 10 per hour.

PAP Wash- in Titration PSG

Participants who exhibit AHI ≥ 10 per hour; >3% oxygen desaturation for hypopneas based on the portable sleep test will undergo exposure for 30 minutes after adequate mask-fitting on the therapy device (AVAPS- AE; see device settings under section below entitled, "Standard Procedures and measurements prior to discharge"). Participants who fail to tolerate such therapy, or indicate that they would be unable to use such therapy at night, will not be randomized. Considering the "wash-in" is performed prior to randomization, such participants will not be included as part of the intention to treat (ITT) analysis.

Participants that are placed on PAP therapy during admission and tolerate the therapy will not be subjected to this aspect of the trial. Their experience, during the hospital visit, with the therapy will count as the PAP Wash-In.

Standard Procedures and measurements prior to discharge

Room Air SpO_2 assessment/Supplemental Oxygen

A room air SpO_2 measurement will be used to make a determination if supplemental oxygen is required prior to hospital discharge. SpO_2 should be collected with the participant breathing room air for at least 15 minutes prior. If participants cannot maintain a SpO_2 of at least 90% on room air, supplemental oxygen will be prescribed. If the participant requires supplemental oxygen (according to the guidelines stated

below), but was not previously prescribed supplemental oxygen, the study investigator will prescribe it for the participant.

Data collection will consist of key demographic characteristics including gender, age, height, and weight. In addition, a medical history, physical exam, vital signs, medication assessment and Charlson co-morbidity index will all be collected/obtained.

Quality of Life Questionnaires

Two different quality of life questionnaires will be used in this study. Quality of life questionnaires are important tools for measuring health status changes in participants receiving an intervention. The general health questionnaire that measures functional health, well – being, and physical and mental health (SF-36) will be used in this study. The disease specific quality of life questionnaire (Functional Outcome of Sleep Questionnaire, FOSQ) will also be used in this study. Participants will be asked to complete these questionnaires prior to discharge.

Randomization

Following the completion of the screening procedures to determine study eligibility, participants will be randomly assigned to one of two study arms: 1) Intervention Group (AVAPS-AE), or 2) Standard of Care (SOC). A randomization website will balance the therapy assignments within each of the three classifications of COPD severity: Gold Stage 2, 3, and 4. The research sites will attempt to balance recruitment between stage-3 and stage-4 patients; however, enrollment of stage-2 patients will be capped at 10, as this severity comprises a small proportion of the hospitalized patients with COPD.

Intervention Group:

AVAPS settings:

- Target Tidal Volume 8 ml/kg of ideal body weight
- Pressure Support Min / Max 4 / 26 cmH_2O
- Max Pressure 30 cmH_2O
- EPAP Min / EPAP Max 4 / 20 cmH_2O
- Rate Auto

Participants in the intervention group will be sent home the AVAPS-AE therapy device. They will receive one on one training on the device as well as a user manual

SOC Group:

Standard of care: Portable sleep test results will be communicated to the participant and their health care provider. Timing and determination of further evaluation and treatment of the participant's sleep disordered breathing will be per their participant's health care provider's usual care pathway. Sites with change in usual care pathways that involve immediate initiation of PAP therapy as a standard practice will remain in the study. Such data will be analyzed in "per-protocol analysis". Participants in the SOC arm will receive phone calls to promote medication adherence.

Post Discharge Study period (60 days)

- One week Device Adherence Assessment (Intervention Group)

During the first 2-7 business days post discharge, research staff will evaluate participant's device adherence via remote download. Participants with poor adherence to AVAPS-AE at home (adequate adherence defined as ≥ 4 hours of use on at least 5 of the first 7 nights) will not be included in the "per-protocol analysis" (Such participants will, however, be considered in the intention to treat analysis). Per the investigators discretion, the device setting parameters may be adjusted at this time.

- Weekly Phone Follow-ups (Initial 30 days only):

Phone calls will be made weekly (± 2 business days) by the study coordinator to assess mask interface issues (Intervention group) and encourage adherence to AVAPS-AE (Intervention group) and medications (both intervention and SOC group). If participants require an additional visit related to issues noted above, this visit may occur either in the home or as an office to the study site.

- Day 30

At 30 days (± 2 business days) post discharge, participants in both Intervention and SOC groups will receive a phone call to determine if they had been admitted to this hospital, or had an unplanned visit to a physician's office or emergency room. Participants will be asked to complete FOSQ and SF-36 questionnaires. Participants will be given the option of completing the questionnaires verbally via phone call or completing handwritten copies and returned via direct mail. Postage paid return envelopes will be provided to participants who elect to complete and return the surveys by mail.

- Day 60

On day 60 (± 2 business days), participants in both Intervention and SOC groups will receive a phone call to determine if they had been admitted to this hospital, or had an unplanned visit to a physician's office or emergency room. Participants will be asked to complete a final FOSQ and SF-36 questionnaire. Participants will be given the option of completing the questionnaires verbally via phone call or completing handwritten copies and returned via direct mail. Postage paid return envelopes will be provided to participants who elect to complete and return the surveys by mail. Participants in both

intervention and SOC groups will receive $150.00 as compensation for participating in the study. Compensation will be pro-rated based on completion of study milestones.

Information regarding admission, diagnostic tests, medication changes, and procedures will be collected from all participants. Discharge summaries of re-hospitalizations and office or ER visits and diagnostics tests and therapies received will be collected for measuring healthcare costs.

Participants will be asked if they would be interested enrolling in a registry for a 3 year follow-up. This will involve participants being contacted on a yearly basis inquiring about any hospitalizations, cardiovascular events, and assessment of vital statistics in the National Death Index registry. Participants who elect to enroll the registry will receive an additional $25 in compensation.

Transition Plan:
Upon completion of the study or earlier termination, site investigators will cooperate with the study participants' primary health care providers regarding continuity of care to assure that participants receive appropriate follow-up care after the conclusion of the study. Study participants who are randomized to the treatment group, where a therapeutic benefit is evident, will be allowed to keep the provided AVAPS device until a similar replacement device can be provided to the participant through usual care pathways as part of this transition plan. Study participants who are randomized to the SOC group will have the option of receiving an AVAPS unit at the end of the 60 day period if prescribed and provided through the usual care pathway of their healthcare provider as part of this transition plan. The risk of additional and on-going device supplies not being covered by insurance or involving co-pays will be explained to the participant within the consent. Philips will not be responsible for providing device maintenance or study supplies after the 60 day study period.

Study Process Flow:

Study Procedures	Hospital Procedures (Pre-Discharge)	Post Discharge Study Procedures	Post 60 Day Study Procedures
Informed consent	X		
Inclusion/Exclusion Review	X		
Medical History Assessment	X		
Vitals	X		

Physical Exam	X		
Medication Assessment	X		
Bedside Spirometry	X		
Room Air SpO2 assesment	X		
Anthropometric measurements	X		
Stop –Bang Questionnaire	X		
20 minute PAP Wash-in	X		
QOL questionnaires (FOSQ and SF-36)	X	X	X
Charleston Co-Morbidity Index	X		
Overnight Portable Sleep Test	X		
Randomization	X		
Device Set up training/Mask fitting	X		
1 week PAP adherence assessment (Treatment Group only)		X	
Weekly phone calls to promote PAP and medication adherence		X	
30 day Healthcare utilization assessment and questionnaire Phone Call		X	
60 day Healthcare utilization assessment and questionnaire Phone call		X	
Transition Plan			X
Optional Registry			X

VII. Statistical Analysis

The method described by Cook and Lawless will be used to handle repeated hospitalizations, physician office visits, or emergency room visits in patients who may or may not also have a terminal event. All repeated hospitalizations that occur in patients will be counted. We will use the count-approach and the gap-time approach, described by Cook and Lawless because we are interested in studying event occurrence rates in the two groups as well as the time to occurrence of events. Analysis will be performed for both 30- and 60-days. Actuarial costs will be assessed in patients belonging to both the intervention and usual care arm. Unadjusted comparisons of these costs will be made by independent t-tests or non-parametric equivalent. Differences will be adjusted for potential confounders and other covariates in

multivariate regression models, to include age, gender, race, body mass index, baseline severity of COPD, AVAPS-AE and medication adherence. Biologically plausible effect modification will be evaluated before significant confounders are selected by inspection of significance levels as well as impact of estimated coefficient for hypothesis variable.

Data and Safety Monitoring Plan:

Each subject will be assigned an identifying number to maintain confidentiality. Records will be stored in a database format that can be read by a standard statistical package. The examination forms will be formatted to facilitate accurate data entry and editing, and programs will be written to allow range checks at entry with illegal values not accepted. Specific missing codes will identify non-obtainable data due to missed visits or skipped questions. The research coordinator will enter the data into the case report forms and the PI will proof read the forms. Data will be entered weekly and cross-checked with the original data forms at the end of the week. The data manager and the study coordinator will perform weekly data verification and protocol compliance checks. Case Report Forms will minimize data entry error.

Safety monitoring plan: Adverse event reporting will be monitored in accordance with the guidelines and regulations of the governing IRB. Any serious and/or unanticipated problems will be reported immediately to the Institutional Review Board (IRB) and Philips-Respironics, Inc. as required. The site-PI and coordinator will monitor adherence to the protocol and data quality standards, and monitor for patient safety and evidence for adverse or beneficial effects. The site-PI will prepare annual report for review by the IRB. The reports will include: screening and baseline data, efficacy data, safety and adverse data, subject enrollment data, and dropout data (number, reason, and at what study phase).

VII. Risks and Discomforts

We believe that there are minimal risks to participating in this study. Adverse effects of Non-Invasive (NPPV) are usually minor and manageable. The masks may cause some discomfort and air pressure and flow have adverse effects. All adverse effects encountered, including mask discomfort, nasal or mouth congestion or dryness, eye irritation, gastric insufflation, and nasal bridge ulceration will be recorded on data sheets that are part of the case report form. NPPV has not been shown to cause sinusitis or bronchitis, but these will be recorded if they occur, as well. Other more serious adverse effects, such as pneumothorax or aspiration pneumonia, are distinctly unusual in the outpatient setting, but will be recorded if they occur. The risk of pneumothorax is rare, occurring in less than 1% of the participants. All adverse events will be reported the IRB annually and at the time of study closure. All significant adverse events will be reported to the Institutional Review Board within 24 hours.

Discomfort is unusual during the lung function testing (spirometry); however, some participants can experience shortness of breath, lightheadedness, fainting, increased blood pressure or heart rate, coughing, wheezing or chest tightness after performing the test. All testing will be conducted by a trained study staff

The study equipment that will be used by the participant has been tested to ensure safety. Should the AVAPS-AE device not perform as designed, ventilation could increase or decrease more than desired. This effect could be uncomfortable or awaken the participant. Additionally, there will be weekly-up phone calls to ensure there are no issues with the therapy. In the event there is an issue with either therapy, the participant can easily remove their interface device should it become uncomfortable or make breathing difficult.

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

AEs will include:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient;
- 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. Due to the complicated medical conditions of the patient population being recruited into the study, SAEs including hospitalizations are to be expected. The expected 30 day Re-admission rate for the patient population enrolled in this study is 20.5 percent [4, 5].

Discomfort is unusual during the lung function testing (spirometry); however, participants can experience shortness of breath, lightheadedness, fainting, increased blood pressure or heart rate, coughing, wheezing or chest tightness after performing the test. All testing will be conducted by a trained study staff.

Given the risks outlined, we believe that although there may be discomforts associated with the use of this device and study related procedures, the risks are minimal.

VIII. Potential Benefits

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

IX. 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, and to resolve any issues that arise during the conduct of the study. The monitoring process includes initial site qualification, periodic visits to the site, and a final visit to the site once the study is complete. Monitoring visits are scheduled periodically throughout the conduct of the study to assure compliance with the investigational plan, and to verify the completeness and accuracy of study data. Monitoring also aids in identifying any research-related problems for the sponsor and/or investigator to correct. The Sponsor will conduct monitoring visits with appropriately trained clinical research professionals.

X. Confidentiality

Confidentiality of participant 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 participants and clinical information will be used. A unique identification number designed to protect the identity of participants will be used to identify the participant on report forms, recruitment logs, data forms or other reports containing information or referring to a participant.

X. References

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