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Clinical Protocol

Randomized Controlled Cross-Over Pilot Study of the Effectiveness of the Vector NIV Device in Hypercapnic COPD Patients with Expiratory Flow Limitation

Protocol # SRC-HRC-VectorEfficacy-2018-10377

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Sponsored by:

Philips RS North America LLC f/k/a Respironics, Inc.

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I. Document Control Page(s)

Protocol Title: Randomized Controlled Cross-Over Pilot Study of the Effectiveness of the Vector NIV Device in Hypercapnic COPD Patients with Expiratory Flow Limitation

Protocol Number: SRC-HRC-VectorEfficacy-2018-10377

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Investigator Agreement.

As Investigator of the study entitled "**Randomized Controlled Cross-Over Pilot Study of the Effectiveness of the Vector NIV Device in Hypercapnic COPD Patients with Expiratory Flow Limitation**." Protocol SRC-HRC-VectorEfficacy-2018-10377, 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 Declaration 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 Philips (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: [redacted] **Date**: [redacted]

Printed Name: [redacted]

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Protocol Revisions

Revision Level	Changes Made to Protocol	Date	By
0.0	Draft	13 Jul 2018	C. Cain, B. Fink, K. Davis, J. McKenzie
0.1	Incorporating changes after visit to site, formatting	15 May 2019	C. Cain, B. Fink, K. Davis
1.0	n/a	12 Jul 2019	C. Cain, B. Fink, K. Davis, J. McKenzie
2.0	Admin changes and clarifications based on site training visit	10 Jan 2020	B. Fink, M. Weiner, C. Cain
3.0	Inclusion of OSA, clarification of endpoints, update of Figure 1 , allowance for remote completion of questionnaires for visits 3 & 4, if needed, removal of visit 3a and added standard of care titration to visit 1 and 2-week acclimation period for Cohort 2, added adherence criteria for cohort 2 during acclimation period, administrative changes	10 Sep 2020	C. Cain, J. McKenzie, M. Weiner, K. Seese
4.0	Update medical monitor, revisions to inclusion/exclusion criteria, clarification of SAE reporting language, update to participant payment, addition of COVID-19 risk and precautions, update to Philips name/address/logo, administrative changes	09 Apr 2021	C. Cain, M. Weiner, K. Seese

II. Glossary

Apnea: The cessation of airflow at the nostrils and mouth for at least 10 seconds.

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.

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

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

COPD: Chronic Obstructive Pulmonary Disease

CPAP Pressure: Pressure needed to maintain an open airway in a sleep apnea patient treated with CPAP, expressed in centimeters of water (cm H_2O). The positive pressure can range from 4 - 25 cm H_2O. Different patients require different pressures. The value is determined in a CPAP titration study.

CPAP Therapy: Continuous Positive Airway Pressure: Delivers a constant pressure during inspiration and expiration

Hypersomnolence: Excessive daytime sleepiness

ODI: 4% Oxygen Desaturation Index

EFL: Expiratory Flow Limitation: A physiological phenomenon in which an increase in driving pressure fails to result in increased expiratory flow. In patients with COPD this occurs when the external pressure driving expiration exceeds the recoil pressure holding the airways open

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

FEV_1: Forced Expiratory Volume in one second: The volume of air exhaled in the first second of the FVC maneuver and is the most reproducible measurement of airway obstruction

FOT: Forced Oscillation Technique: A method to detect the presence of expiratory flow limitation

FVC: Forced Vital Capacity: Spirometry measurement in which the patient inhales maximally and then exhales as rapidly and completely as possible

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

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

Positive End Expiratory Pressure (PEEP): Pressure in the lungs (alveolar pressure) above atmospheric pressure (the pressure outside of the body) that exists at the end of expiration

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

S Mode: Spontaneous Ventilation: Provides ventilation in synchrony with a person's spontaneous breathing efforts; triggering of a breath cycle is only by the patient

S/T Mode: Spontaneous Timed Ventilation: Provides ventilation in synchrony with a person's spontaneous breathing efforts; triggering of a breath cycle is by the patient or the ventilator, should the person fail to trigger the ventilator after a preset time. In Spontaneous/Timed mode a "backup" rate is set to ensure that the patient still receives a minimum number of breaths per minute if they fail to breathe spontaneously

Z_{rs}: Total impedance of the respiratory system as measured by the forced oscillation technique (FOT) at a forcing frequency of 5 Hz

X_{rs}: The reactance (i.e. the imaginary component of the impedance) of the respiratory system as measured by the forced oscillation technique (FOT) at a forcing frequency of 5 Hz.

ΔX_{rs}: The difference between the mean value of X_{rs} during expiration ($\overline{X}_{exp}$) and the mean value of X_{rs} during inspiration ($\overline{X}_{insp}$). A breath is classified as flow-limited if its ΔX_{rs} is greater than 2.8 $cmH_2O \cdot s \cdot L^{-1}$

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Protocol Synopsis

Title:	*Randomized Controlled Cross-Over Pilot Study of the Effectiveness of the Vector NIV Device in Hypercapnic COPD Patients with Expiratory Flow Limitation*
Study Design:	This will be a prospective randomized controlled cross-over pilot trial to investigate the clinical efficacy and safety of the Vector A-series NIV device to treat COPD patients with chronic hypercapnia.
Objectives:	Primary Objective: To compare treatment effect of providing NIV therapy with the Vector NIV Device vs current prescribed NIV in patients with hypercapnic COPD and evidence of expiratory flow limitation

Secondary Objectives:

- To evaluate treatment effect of Vector on overall quality of life
- To evaluate treatment effect of Vector on sleep quality
- To evaluate treatment effect of Vector on physical activity levels
- To Evaluate treatment effect of Vector on Ventilator collected parameters
- To Evaluate treatment effect differences on nocturnal SpO_2 and $PaCO_2$ or $TcCO_2$

Endpoints:

Primary Endpoint:

Daytime CO_2 levels at the end of 4-6 weeks of therapy as determined by Arterial Blood Gas ($PaCO_2$)

Secondary Endpoints:

- Average daily device usage
- Therapy Comfort and Preference
- Incidence of Unanticipated Serious Adverse Device Effects (USADEs) and Serious Adverse Events (SAEs) for the Vector vs. the control group.

Exploratory Endpoints:

- Changes in quality of life scores ((CAT) SGRQ, dyspnea ratings mMRC),
- Ventilator collected parameter differences after 6 weeks of use (Respiratory Rate (RR), Minute Ventilation (MV)
- Sleep Quality differences as measured by PSG and actigraphy
- Changes in activity levels (mean and max activity counts)

Study Population:	Approximately 30 COPD patients with chronic hypercapnia and evidence of expiratory flow limitation will be included.
Phase:	Pilot study
Sites/Facilities Enrolling Participants:	Temple University Hospital
Description of Study Intervention:	NIV with Auto Adjusting EPAP
Study Duration:	Approximately 12 months
Participant Duration:	Approximately 15 weeks

III. Background Information

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide.

Treatment options for COPD patients consist of medications, such as bronchodilators and anti-inflammatory drugs, pulmonary rehabilitation, long-term oxygen therapy (LTOT), and lung transplantation. Studies have shown that bronchodilators and anti-inflammatory drugs show minor or no benefit on long term outcomes but rather are used mainly for symptomatic relief.[1] Pulmonary rehabilitation has been demonstrated to improve functional status and symptoms but there is sparse evidence on long term outcomes of this therapy. [2] Lung transplantation is only appropriate for a small number of patients; therefore, there is no demonstration of improved long-term survival rate.[3, 4]

Of these available therapies, few have been shown to significantly improve long-term patient outcomes. For the severe COPD patient, LTOT is the only treatment that demonstrated prolonged survival in controlled studies. [5, 6] But, despite the effectiveness of LTOT, COPD is still characterized by a high morbidity and mortality rate.

Noninvasive positive pressure ventilation (NPPV) is one therapy that may prove beneficial to stable COPD patients. NPPV, also known as NIV, is the use of positive pressure ventilation administered via a nasal or full-face mask (that covers both the nose and mouth). This type of ventilation has become a well-established and increasingly used therapeutic option for patients with hypercapnic respiratory failure (HRF) due to COPD.[7]

NPPV, used nocturnally, may improve nighttime hypoventilation that is common with COPD patients. An improvement in nocturnal hypoventilation would reset the respiratory center sensitivity for CO_2.[8 9] This would result in an improvement in daytime gas exchange and sleep quality. It is also known that hyperinflation in patients with COPD increases their work of breathing, thus fatiguing the respiratory muscles.[10] It has been suggested that by applying nocturnal NPPV it would allow the respiratory muscles to rest, resulting in muscle function recovery, increased respiratory muscle strength, reduced the tendency for fatigue and improvement in pulmonary function and gas exchange.[11] Adverse effects of 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.

COPD is a disease that results in varying degrees of dyspnea, or shortness of breath. Spirometry is a method of diagnosing COPD with the diagnosis confirmed by presence

of a post bronchodilator FEV_1 <80% of the predicted value in combination with an FEV_1 / FVC <70%.

The presence of airflow obstruction has been identified as one of the main causes of dyspnea in patients with chronic obstructive pulmonary disease [1]. Expiratory Flow Limitation (EFL) occurs when the driving pressure outside the airways exceeds the recoil pressure holding the airway open. As airflow obstruction worsens, EFL appears at much lower flows for a given lung volume and it becomes present at rest or at least develops early during exercise [2].

Previously detection of EFL consisted of either invasive esophageal balloon or relatively complex plethysmographic techniques. An alternative approach, and one that will be used in this study, involves the Forced Oscillation Technique (FOT), which is now incorporated into the vector device.

In 2003, *Dellacà et al.* proposed a new method to detect EFL during quiet breathing non-invasively using the FOT. It was based on the observation that COPD patients with EFL developed large negative swings in the respiratory system input reactance measured at 5Hz during expiration. They used this observation to define a sensitive and specific method of determining the presence of EFL. Normally the reactance reflects the elastic and inertial properties of the respiratory system but when flow limitation is present, the oscillatory signal cannot pass through the choke points and reach the alveoli. This produces a marked reduction in the apparent compliance and, consequently, a fall in Xrs.

Although this X_{rs} reduction is present at all the frequencies, the greatest difference is seen at the lowest frequency. Since the quiet breathing signal can interfere with the estimation of Zrs at frequencies below 5 Hz, this frequency was used for the forcing signal. The difference between the mean value of X_{rs} during inspiration ($\overline{X}_{insp}$) and $\overline{X}_{exp}$ is called $\Delta\overline{X}_{rs}$. A breath is classified as flow-limited if it's $X_{exp,\ min}$ is greater than 2.8 $cmH_2O \cdot s \cdot L^{-1}$.

This technology has been evaluated in numerous clinical studies for both the detection, reduction and abolishment of expiratory flow limitation in patients with COPD. In 1956, Dubios et al, demonstrated the FOT method to be applicable to the measurement of airway resistance in patients, evaluation of therapeutic procedures designed to relieve airway obstruction, separation of airway resistance from tissue resistance, and study of the multiple factors that may affect airway resistance.[1] And in additional work in 2006,

Dellaca et al, suggested the forced oscillation technique may be useful in chronic obstructive pulmonary disease patients using nasal pressure support by identifying expiratory positive airway pressure levels that support breathing without increasing lung volume, as turn increase the work of breathing and reduce muscle effectiveness and efficiency.[6]

The Vector project has incorporated this method as a new feature into the Philips BiPAP Ventilator overall platform (K121623). The device has been designed to produce a 5 Hz sine wave with peak to peak amplitude of approximately 2 cm H_2O superimposed upon the pressure and flow generated by the device. The resultant feedback waveform is then filtered and analyzed to measure reactance (deltaX) and thus determine if EFL is present. Subsequently, in a bi-level ventilation mode the EPAP (and concurrently and proportionally the IPAP keeping pressure support unchanged) is increased until the EFL is essentially abolished (falls below the predetermined EFL threshold). Since this reactance is analyzed continuously (breath by breath) during both inspiration and expiration, it is relatively immune to external factors such as modest leaks or coughing / swallowing.

A. Description of the Intervention Studied

Study Device Description:

The Vector ventilator (i.e. BiPAP A-40 EFL) with Vector Algorithm, Philips, Inc., Murrysville, PA) is intended to provide non-invasive ventilatory support to treat adult patients with Respiratory Insufficiency with the primary cause being COPD. It is intended to be used within the home, institutional/hospital, and diagnostic laboratory environments. This device is not intended for life support. It can be used to screen for the presence, and abolishment of Expiratory Flow Limitation. Study devices will be packaged and tracked according to lot number, serial number, and/or manufacturing number, as applicable.

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IV. Study Design Rationale

A. Study Objectives and Purpose

Primary Objective

To compare treatment effect of providing NIV therapy with the Vector NIV Device versus current prescribed NIV in patients with hypercapnic COPD and evidence of expiratory flow limitation

Secondary Objectives

- To evaluate treatment effect of Vector on Ventilator collected parameters
- To evaluate patient comfort and therapy preference
- Incidence of Unanticipated Serious Adverse Device Effects (USADEs) and Serious Adverse Events (SAEs) for the Vector vs. the control group.

Exploratory Objectives

- To evaluate treatment effect of Vector on overall quality of life
- To evaluate treatment effect of Vector on sleep quality
- To evaluate treatment effect of Vector on physical activity levels
- To evaluate treatment effect differences on nocturnal SpO_2 and $PaCO_2$ or $TcCO_2$

Study Hypothesis:

We hypothesize in patients with hypercapnic COPD, NIV therapy provided by the Vector device, with an optimized automatically adjusting EPAP to abolish expiratory flow

limitation, will maintain equal levels of gas exchange (PaCO2) will provide patients with improved therapy comfort and adherence when compared to standard NIV.

Primary Endpoint

1. Daytime CO_2 levels at the end of 4-6 weeks of therapy as determined by Arterial Blood Gas ($PaCO_2$)

Secondary Endpoints:

1. Average 30-day Ventilator Usage hours
2. Patient Comfort and Therapy Preference based questionnaire responses

Exploratory Endpoints:

1. Other Ventilator Parameters
    a. Respiratory Rate
    b. Minute Ventilation
    c. % flow limited breaths
    d. Patient ventilation synchrony
2. Total therapy Titration Time
3. Screening session parameters
    a. % flow limited breaths
    b. Delta Xrs final screening value
4. Quality of Life Questionnaire
5. Activity (measured via the Actiwatch)
6. Reported Adverse Events
7. Sleep Quality
    a. Total Sleep Time
    b. Sleep Efficiency
    c. Sleep Stage distribution
    d. Arousal and awakening indices
    e. Nocturnal TcO2 variability

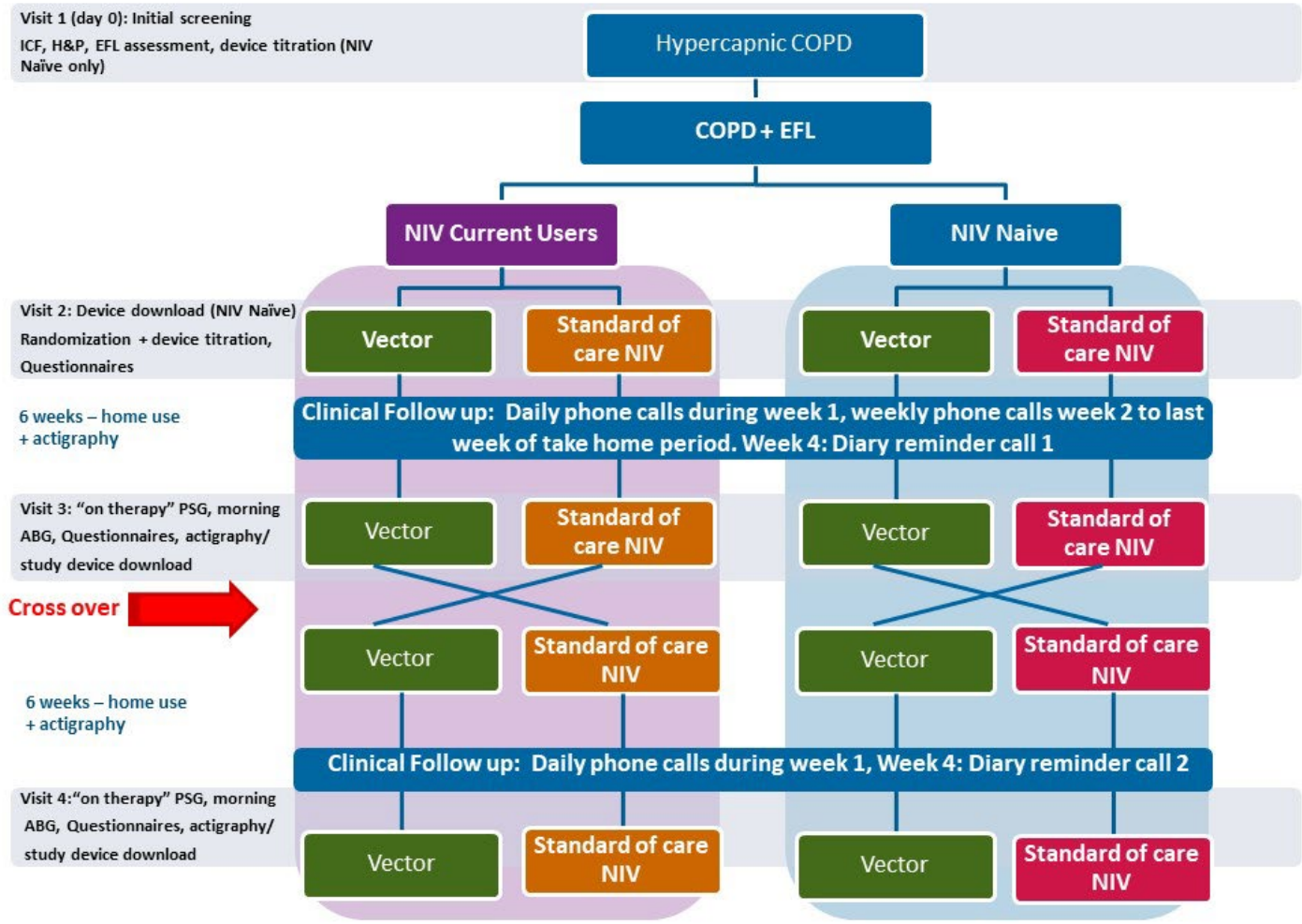
f. Nocturnal TcO2 averages

g. Nocturnal SpO2 Saturation

V. Study Design:

This will be a prospective, randomized, pilot study with cross-over design.
Patients who meet inclusion criteria will be randomized in a 1:1 ratio to receive either standard of care (SOC) NIV (control) or Vector (Active) for the first 4 to 6-week treatment period, followed by the other treatment during the second 4 to 6 weeks (see Figure 1). There will be two different patient cohort groups, patients that are current users of NIV and patients that are Naïve to NIV.

(Figure 1)



A. Schedule of Events:

Screening Procedures:

Study Participation Screening (Prior to Visit 1)

Participants will be contacted by designated study staff from Temple University Lung Center Research Team. Participants may be pre-screened through medical records over the phone to determine eligibility. A screening script will include a general review of key inclusion and exclusion criteria. Participants that are interested will be scheduled for the screening visit at the clinical office.

Upon screening, study participants will be divided into 2 different cohorts – current NIV users and participants that are Naïve to NIV therapy.

COVID-19 Screening Procedure (All visits)

Due to the COVID-19 pandemic, participants may be screened for COVID-19 symptoms over the phone prior to each scheduled study visit. During each study visit, participants may be asked to complete a self-declaration form, which asks about COVID-19 exposure, current symptoms, and confirms that participants have been briefed on safety measures. The form will be used for safety purposes and is not intended for data collection. Site COVID-19 safety procedures and documentation will also be followed. Study products and materials will either be single use or will be cleaned and disinfected per the multi-patient use guidelines in the Instructions for Use.

Study Visit 1 (screening)

Once the participants arrive, the study will be explained in full detail. If the participant agrees, he/she will be consented into the study and the participant will be given a copy of the informed consent.

Once consent is obtained, and eligibility is confirmed, the following study related procedures will be conducted:

- Demographics: sex, age, ethnicity, and race will be collected
- Anthropometeric Measurements: height, weight, neck circumference will be collected.
- Current Medications: all current medications will be collected.
- Medical History Assessment: information will be collected regarding historical spirometry data, $PaCO_2$ level at the time of NIV initiation, COPD history questionnaire, smoking history and other relevant medical history including the diagnosis of Sleep disordered breathing.
- Physical examination with vital signs to include HR, BP, RR, and SPO_2 maintained at least 88%, and chest auscultation.
- Administration of CAT and STOP-BANG questionnaires.
- Urine pregnancy test for women of childbearing potential
- Mask Fitting: Participants may have up to two mask fittings in order to determine the best possible provided mask while using the Vector NIV device.

EFL Screening/Determination and EPAP Titration

- For the EFL Screening/Determination and EPAP Titration procedure, the following device settings will be applied:

  - Pressure Support 6 cmH_2O
  - Max Pressure 26 cmH_2O
  - EPAP Min / EPAP Max 4 / 20 cmH_2O
  - EPAP setting Auto

- EFL Determination: The participant will be asked to lie supine or semi-recumbently while breathing into the Vector NIV device using the selected mask initially for 5 minutes. This device has a screening test that has the capability of detecting and estimating the severity of EFL. If it is determined that the participant does not have EFL after 5 minutes by the device screening indicator, the participant will not continue in the study. After the screening is complete, participants will be asked a couple of questions about their experience.

- EPAP Titration: If it is determined by the Vector NIV device that the participant has EFL, the Vector NIV device will be changed from screening mode to therapy mode to delivery BiPAP therapy. The participants will then breathe on the Vector NIV device in the supine position for an additional 20 minutes approximately. During the additional 20 minutes of breathing, the device will automatically increase the EPAP (and concurrently and proportionally the IPAP) until the EFL is abolished (falls below the predetermined EFL threshold). After the titration is complete, participants will be asked a few questions about their experience

- While the automatic EPAP Titration is being performed all participants' SpO2 will be monitored via finger pulse oximetry. Oxygen will be provided to patients at the clinician's discretion.

- Patient must stay awake during the EPAP Titration. If the patient falls asleep, they will be awoken by study staff.

- The Final EPAP that is determined to abolish the participants EFL will be recorded. If the determined EPAP pressure is 6cmH_2O or higher, the participant may continue to study visit 2. If the determined EPAP is below 6cmH_2O then the participant will not be scheduled for study visit 2.

- Participants that are determined to have EFL and a titrated EPAP $\geq$ 6cmH_2O will be eligible to continue in the study.

• Current NIV users who also have a clinical diagnosis of OSA must have a calculated final titrated EFL EPAP that is higher than their EPAP settings of their current NIV device in order to continue in the study and to be scheduled for study visit 2.

NIV SOC Titration (NIV Naïve Cohort only)

Participants who are NIV naïve and determined to have EFL with a titrated EPAP >6cmH_2O will then undergo standard SOC titration (Appendix A) in order complete a 2 week NIV acclimation period. Initiation of SOC titration will take place under the supervision of the study investigator, research coordinator and / or healthcare professional (Respiratory Therapist, Sleep Technician, etc.).

After successful completion of the device titration, participants will be given one-on-one operational instructions on the Vector device by clinical study staff. The Vector therapy will not be enabled. The device will be set up with the optimal pressures determined from the SOC titration. In addition to the application of the settings determined by the SOC titration, the Automated Airway Management (AAM) feature will be enabled with the minimum set EPAP to 4 cmH_2O and a maximum of 20 cmH_2O. This feature will adjust the EPAP to maintain upper airway patency.

The purpose of the 2 week NIV acclimation period is to determine if the patients that are naïve to NIV will adhere to therapy and also if they potentially have underlying OSA that require 90% EPAP pressures higher than the determined EFL titrated EPAP at the screening visit. After receiving training on the device, participants will also be given a user manual, mask, and tubing and be asked to use the device at home for 2 weeks.

Study Visit 2 (Randomization and Titration)

Upon successful completion of the screening procedures, participants in the NIV current user cohort will be asked to return to the research center within the next 7 days (+2 days). Study participants in the NIV naïve Cohort will be asked to return to the research center in 14 days (+ 2 days). Participants in the NIV naïve cohort will have the data from their device downloaded and reviewed.

Participants in the NIV naïve cohort will be excluded from continuing in the study if the average nightly device use is < 4 hours per night **OR** the average nightly 90% EPAP pressures are greater than the titrated EFL EPAP pressure determined during the screening visit. 90% EPAP values will be accessed through the CareOrchestrator patient management platform.

During study visit 2, qualified participants will be randomized to one of the two therapy orders. In addition to being randomized, participants will be set up with the activity

monitor, fill out baseline study questionnaires, receive one-on-one training and instructions on how to use the Vector device.

Randomization:

Participants will be randomly assigned to either 1) Vector NIV followed by SOC NIV or 2) SOC NIV followed by Vector NIV. Randomization will be generated via a randomization website. For the SOC NIV therapy, participants will be required to use a Vector Device in place of their current NIV device. The Vector therapy will not be enabled, and the device will be set according to their current SOC NIV prescription.

Cohort 1 (NIV Current Users): Participants in Cohort 1, regardless of randomized therapy order, will be required to undergo the Vector device titration at study visit 2. (Appendix A) For the participants randomized to SOC NIV first, the settings determined from the Vector device during the randomization visit will then be applied when they cross over to Vector NIV at visit 3.

Cohort 2 (NIV Naïve): Participants in Cohort 2, regardless of randomized therapy order, will be required to undergo the Vector device titration at study visit 2. (Appendix A) Participants in cohort 2 who were randomized to SOC NIV first will have previously been titrated to SOC NIV therapy at visit 1.

Initiation of the Vector NIV titration will take place under the supervision of the study investigator, research coordinator and / or healthcare professional (Respiratory Therapist, Sleep Technician, etc.). Appendix A outlines the protocol and device settings that will be used for the Vector device titration. For the participants in Cohort 2 that are initially randomized to SOC arm, clinical study staff will follow currently established NIV standard of care titration protocols. After successful completion of the of the Vector NIV titration, participants will be given one-on-one operational instructions on the device by clinical study staff. They will also be given a user manual, mask, and tubing and be asked to use the device at home for 4 to 6 weeks. For the participants in Cohort 2 that are randomized to SOC arm, they will continue to use the Vector device as they did during the 2-week home acclimation period with the previously determined SOC NIV settings.

Phone Follow-ups:

Participants will be sent home with the Vector device with their randomized therapy. During the initial week, the participant will be contacted daily to determine if there are any problems with the device and to encourage compliance. Participants will be asked to use the Vector device at night for the following 6 weeks. Participants will then be contacted weekly from week 2 to the last week of their take home period (maximum of 6 weeks). During the second take home period, all participants will be called daily during the first week only.

Study Visit 3 (Overnight Sleep Study) (within 4 to 6 weeks of visit 2)

Participants will be asked to come to the sleep lab at a scheduled date and time. The sleep testing will begin near the subject's usual bedtime and ends at approximately 6 A.M.

Prior to the sleep study with the therapy device, the trained technologists will verify mask size, fit, and adjustment. The sleep test will involve using the device the participant has been receiving therapy from in the initial 4 to 6 weeks. Details of the PSG set up can be found in the standard procedures section of the protocol.

Morning ABG, Therapy Comfort and HRQL assessments: Following the completion of the sleep study (morning after), all participants will return to the research center where their activity monitors will be downloaded, fill out study-related questionnaires as well as have their ABGs collected. Details on ABG collection and study questionnaires can be found in the standard procedure section of the protocol. Participants in Cohort 1 that were randomized to their current NIV device for the initial 6 weeks will now be asked to use the Vector device for the next 6 weeks. The Vector device will be set up with the

Device settings determined during the titration procedure at study visit 2.

Study Visit 4 (Overnight Sleep Study - within 4 to 6 weeks of visit 3)

Participants will be asked to report to the sleep lab for the second overnight sleep study at a scheduled date and time. The sleep testing will begin near the subject's usual bedtime and end at approximately 6 A.M.

Prior to the sleep study with the therapy device, the trained technologists will verify mask size, fit, and adjustment that was determined at study visit 1. Details of the PSG set up can be found in the standard procedures section of the protocol.

Morning ABG, Therapy Comfort and QOL assessments: Following the completion of the sleep study (morning after), all participants will have to return to the research center where their activity monitors will be downloaded, fill out study related questionnaires as well as have their ABGs collected. Details on ABG collection and study questionnaires can be found in the standard procedures section of the protocol.

In the event that participants are unable to come into the research clinic for visit 3 or 4, remote administration of questionnaires via telephone or direct mail may be conducted. Participants may be asked to return their device SD cards via direct mail using a provided postage-paid envelope.

Procedures	Determine eligibility	Enrollment/Baseline Visit 1 (day 0)	Visit 2 Daytime Titration	Week 1: Daily Check-in Calls	Weeks 2-6: Weekly Check-in Calls	Week 4: Diary Reminder Call 1	Visit 3 Overnight PSG study	Week 1: Daily Check-in Calls	Week 4: Diary Reminder Call 2	Visit 4 Overnight & Final Visit
Chart Review	X									
Informed consent		X								
H&P , demographics		X								
QoL Questionnaires			X				X			X
EFL assessment		X								
Morning ABG							X			X
In Lab Sleep Study (PSG)							X			X
Device titration (NIV Current)			X							
Device Titration (NIV Naïve)		X	X							
Clinical follow up (assess patients concerns/issues with device, mask, or other							X	X		X
Actigraphy set up/ data download		X					X			X
Device data download (NIV Current)							X			X
Device data download (NIV Naïve)			X							
Sleep Diary Reminder						X			X	
Side effects and AE assessment			X	X	X	X	X	X	X	X

A. Standard Procedures

Arterial Blood Gas / Room Air SpO_2 assessment

Arterial blood gases and SpO_2 should be collected with the participant breathing room air for at least 15 minutes prior. The participant should rest in the seated position for 10 minutes prior to drawing the sample.

Quality of Life Questionnaires (QOL)

Health related quality of life (QOL) measurement is an important tool for measuring health status changes in participants receiving an intervention. The COPD Assessment Test (CAT)[12], St. George Respiratory Questionnaire[13] and Modified Medical Research Council Dyspnea Questionnaire (MMRC)[14] will be used in this study. Participants will be asked to complete these questionnaires at Visits 2-4.

PSG's

During all lab nights, participants will be set-up with a standard PSG montage that will include the following sensors:

- Two RIP 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
- Lead II ECG electrode derivation
- EEG electrodes attached to the scalp and face to measure sleep stages (including at least C4, C3, A1, A2, O1, O2, GND EEG, Left Outer Canthus (LOC) and Right Outer Canthus (ROC) EOG and submental EMG)
- A flexible finger sensor placed on the finger to measure oxygen saturation (average signaling time of 3 seconds)
- A microphone attached to the skin at the base of the neck to measure snoring sounds
- Surface electrodes attached to the skin bilaterally over the anterior tibialis muscle, to measure leg movements
- Transcutaneous CO_2 monitoring

Scoring

All sleep studies will be scored by the qualified site personnel. All sleep variables will be classified and scored using the 2007 AASM criteria[15] additionally, all sleep variables will be scored using a modified Hypopnea rule as defined below.

- 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 with a nadir below 90%.

For hypopneas yielding desaturations with a nadir of 90% or greater, a modified rule VIII.4.A will be used that requires an arousal (rule V.1.A) to accompany the event for scoring as a hypopnea.

NOTE: If the participant slept less than 3 hours on any lab night, they, may be asked to repeat the overnight sleep test. If the patient is unwilling to repeat the sleep test, furthermore, a replacement participant will then be enrolled.

Actigraphy Measurements & Sleep Diary

Actigraphy is a method of measuring activity and sleep which is achieved by wearing a small watch-like device for an extended period of time. Most units contain an accelerometer and continually record the movement it undergoes. These data are later read to a computer for analysis. These data will provide an objective record of physical activity and sleep / wake patterns throughout the 6 weeks of home use.

The wrist-worn actigraph device will provide a continuous measure of both how much the participant has slept during the night and how active they are during the day. There is an event button that the participant will be asked to press when the participant is in bed, near asleep and also upon awaking.

Participants may be asked to keep a sleep diary during the last two weeks of each arm of the study in order to supplement the actiwatch data. The study team will call the participant to remind them to start using the diary.

VI. Selection and Withdrawal of Subjects:

Inclusion Criteria

1. Age ≥ 40 years of age; ≤ 80 years of age
2. Ability to provide consent
3. COPD patients with hypercapnia (as defined as ≥ 52mmHg) who are either current NIV users or naïve to NIV
4. On average, use NIV more than 4 hours per night (Current NIV users).
5. Must present with EFL via screening of the Vector device at 3 cmH_2O
6. Have an EPAP to abolish EFL greater or equal to 6cmH_2O

Exclusion Criteria:

1. Any major non-COPD uncontrolled disease or condition, such as congestive heart failure, malignancy, liver or renal insufficiency (that requires current evaluation for liver or renal transplantation or dialysis), amyotrophic lateral sclerosis, or severe stroke, or other condition as deemed appropriate by investigator as determined by review of medical history and / or participant reported medical history
2. Suffering from a COPD exacerbation (Defined as hospital admission, ER/urgent care visit, MD visit with medication change or other intervention deemed to be

clinically significant by the investigator at the time of data collection or in the 14 days prior to data collection
3. Self-reported Pregnancy or positive pregnancy test for women of childbearing potential.
4. Employee or family member that is affiliated with Philips
5. Currently employed by a manufacturer of respiratory products or family member employed by a manufacturer of respiratory products
6. Any history of giant bulla (size >1/3 hemi-thorax)
7. History of pneumothorax ≤ 6 months
8. Participants currently using a PAP or NIV device at home with a documented EPAP setting on their current device that is greater than the calculated EPAP determined during the therapy session of the screening visit (Current NIV Users).
9. Life expectancy ≤12 months as determined by clinical investigator
10. Low BP: Systolic <90
11. Recent cranial surgery (i.e, less than 1 year)
12. Impaired swallowing as reported by participant or diagnostic exam
13. Recent upper airway or GI surgery within the past 6 months
14. Unable to be fitted with mask
15. Excessive secretions as reported by clinical investigator/physician assessment, inability to maintain a patent airway or adequately clear secretions, or at risk for aspiration of gastric contents
16. Diagnosed with acute sinusitis or otitis media
17. Epistaxis, causing pulmonary aspiration of blood
18. Existing respiratory failure
19. Participants who are naïve to NIV (Cohort 2) that use the device fewer than 3 out of 7 nights during the second week of the 2-week acclimation period
20. Participants who are naïve to NIV (Cohort 2) that average less than 4 hours of device use during the second week of the 2-week acclimation period
21. Participants who are naïve to NIV (Cohort 2) with an average nightly 90% EPAP pressure during the second week of the 2-week acclimation period that is higher than the titrated EFL EPAP pressure determined at the screening visit.

Withdrawal:

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.
- Further admission with AECOPD as the primary diagnosis

The study team 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.

For the naïve NIV patient cohort, participants will be allowed to keep the device until a marketed device can be provided to them through normal commercial distribution pathways.

The study goal is to have 30 participants successfully complete the study. It is estimated that 50 patients may need to be enrolled in order to complete 30

VII. Treatment of Subjects:

A. Intended Use

The BiPAP A40 EFL Ventilator (Vector ventilator) is intended to provide non-invasive ventilatory support to treat patients weighing over 10Kg (22lbs.) with Obstructive Sleep Apnea (OSA) or Respiratory Insufficiency. It is intended to be used within the home, institutional/hospital, and diagnostic laboratory environments. This device is not intended for life support. The BiPAP A40 EFL screening and therapy is intended for patients weighing over 30Kg (66lbs.) with obstructive sleep apnea (OSA) or Respiratory Insufficiency with primary cause being chronic obstructive pulmonary disease (COPD) to screen for the presence, and abolishment of Expiratory Flow Limitation

B. Contraindications:

- Inability to maintain a patent airway or adequately clear secretions
- At risk for aspiration of gastric contents
- Diagnosed with acute sinusitis or otitis media
- Epistaxis, causing pulmonary aspiration of blood
- Hypotension, defined as systolic BP < 90
- Existing respiratory failure

There will be no restrictions on concomitant medications during the course of the study. If medications change during the study, participants will be asked to let their pulmonologist know.

C. Monitoring:

This clinical study will be monitored by Philips (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, reliability and accuracy of study data and to resolve any issues that arise during the conduction of the study. The Sponsor will conduct monitoring visits periodically as specified by the monitoring plan. Monitoring will be conduct by trained clinical research professionals.

It has been determined that this study does not require a Data Safety Monitoring Board (DSMB).

D. Unscheduled Visits

Unscheduled calls and or visits will be documented in the participant study file upon occurrence. Participants may be asked to receive additional phone calls and or visits in order to evaluate any device issues should they occur.

VIII. Assessment of Performance

Device performance will be based on the following patient physiological and device recorded parameters:

- Daytime $PaCO_2$ levels after 30-day period, method (Visits 3 and 4)
- Nocturnal TCO_2 levels during sleep study (Visits 3 and 4)
- Nocturnal SpO_2 levels during sleep study (Visits 3 and 4)
- Ventilator collected parameters over the 30-day use period (RR, MV, usage hours) (Visits 3 and 4)

IX. Assessment of Safety

Serious adverse events, occurring during the course of the study will be collected, fully documented, and reported to the Western Institutional Review Board, according to their guidelines, by the Principal Investigator, Dr. Gerald Criner, MD or sponsor staff. Serious adverse events will be reviewed by the Sponsor within 24 hours of the study team being aware of the event.

Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

Serious Adverse Events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unanticipated Serious Adverse Device Effect

A USADE is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Severity of Event

The following guidelines will be used to describe AE severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgement. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable

possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Adverse Event Assessment and Follow-Up

Adverse events will be collected on an ongoing basis following signing of informed consent. Detailed information regarding the event will be recorded on the appropriate form in the electronic case report form (eCRF), where the Investigator will determine the severity of the event, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. Follow-up data to ascertain the existence of residual effects from the event will be obtained. Serious adverse events must be reported to the sponsor within 24 hours of discovering the occurrence of the SAE. The research staff is required to complete and submit the sponsor's standard SAE form detailing the event.

Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

The study investigator will complete an SAE/Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to local regulatory authorities and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect to local regulatory authorities.

Device Deficiencies

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. Unanticipated device deficiencies that lead to SAE's will be reviewed with the principal investigator (PI) and reported to the IRB as required.

All unexpected adverse events will be collected and reviewed. As any events will be reported electronically or directly from a person the study team will collect the onset, duration, intensity and treatment required, outcome and action taken. In addition to

adverse event reporting, the study staff will report a summary of the protocol findings, participant recruitment, drop-outs, and events to the IRB annually.

All Adverse Events will be followed for 30 days or until resolution, whichever comes first.

X. Device Deficiencies

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. Unanticipated device deficiencies that lead to SAE's will be reviewed with the PI and reported to the IRB as required.

XI. Statistical Methods

Determination of Sample Size

No power analysis was performed to determine the sample size for this pilot study. The results of this study may be used to power a larger pivotal trial.

General Considerations

The primary analysis will be performed including all consented participants. Descriptive data tables will be provided for all variables of interest. Continuous data will be presented by mean, standard deviation, median, minimum, and maximum observation. Data will be presented in the untransformed and transformed format (if applicable) for each continuous variable. Categorical data will be presented as frequencies and percentages. All formal statistical analyses will be performed using either SAS® or SPSS® software. Significance tests will be conducted at a two-sided significance level of $p < 0.05$.

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

Participant Disposition

Participant disposition, including the total number of participants enrolled, completed, early terminations and withdrawals, will be presented. A listing will be provided with the reasons for discontinuation.

Demographics and Baseline Characteristics

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

Primary Analysis

Since this was a crossover study, the endpoints were compared between the two therapies as paired samples. For each continuous endpoint, the paired differences will be examined for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests, and if the distribution does not deviate significantly from normality, the treatment effect will be examined using a paired t-test; otherwise, the endpoint was examined using the non-parametric Wilcoxon Signed-Ranks test. Categorical data will be evaluated using the McNemar Test.

Safety Analysis

Safety evaluations will be performed by recording clinical adverse events at the time originally reported, and they will be followed at regular intervals until resolution. Adverse events will be provided in data listings.

Missing Data

It is not anticipated that imputation methods will be necessary in this study.

Interim Analysis

Since this is a pilot study, descriptive statistics may be reviewed as the study is ongoing, but formal statistical comparisons will be performed after the study is completed.

XII. Direct Access to Source Data / Documents

Only site clinical study staff and approved Philips staff working with the research will know the identity of the participants. All information recorded by the study team and provided for analysis will be given a study ID number. A unique source record will be available for each study participant and will include informed consent review process, HIPAA completion (as applicable), medical history, and concomitant medications.

Privacy rules and requirements according to federal and state 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. 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 to Philips participants will be assigned a unique code number.

Results of the study related data, medical history, and information obtained from the questionnaire and device data will be reported and received by Philips. Philips will use participant study data for research purposes to support engineering objectives described in this protocol.

In addition, participant records may be reviewed in order to meet federal and state regulations. Reviewers may include representatives from the FDA or similar government authorities in other countries where the device is being used, and Philips for the purposes of the following side effects, and to gather additional information related to the study, and the Institutional Review Board (IRB). Participant permission for review of confidential information is granted by signing the associated informed consent. Philips will ensure that it follows all applicable state and federal data protection regulations.

A. Provisions to Protect the Privacy Interests of Participants:

Participants will only interact with approved members of the research staff and will have the option to decline to provide any information that they are uncomfortable revealing. All research staff (site and sponsor) will receive training regarding the protection of human subject data. Participant's medical records will only be accessed after obtaining written consent from the participant and will only be reviewed by members of the research staff for whom review of this information is necessary for continued participation in the study (e.g. Philips research staff and study investigator reviewing the medical records). Participant identifiers, other than study ID number must be redacted in date before sending to sponsor.

B. Case Report Forms

Study related case report forms (CRF's) and source documentation will be collected and maintained by the sponsor, will be kept confidential, and stored in a secure location if on paper or on a secure server or protected device. Only staff delegated by the PI will have the ability to enter in, or make changes to, the CRF's and source documents.

XIII. Quality Control and Quality Assurance

The PI and study personnel will be trained to the study protocol, study product, TMF documents, monitoring plan, CRFs and/or eCRFs, direct data reporting, and all Sponsor expectations, as applicable. Once complete, training and delegations will be documented for PI and study personnel.

Data queries will be addressed by delegated study personnel and CRF/ eCRFs will be reviewed and signed off by PI prior to study closure. Monitoring will be completed in accordance with US CFR, ICH-E6 GCP Section 6, and ISO 14155:2011 as applicable.

XIV. Ethics

This study will be submitted and reviewed by the Western Institutional Review Board. All participants will be consented prior to completing the trial. The Primary Investigator will review all adverse events as it relates to the study device.

All data will be kept confidential and in a secure location if on paper or on a secure server or device. Only approved study personnel will have access to study related documents. All electronic data shall be stored in a coded data set. All paper documents shall be kept in a secure area. Study data and source will be made available for study related monitoring or audits by the IRB/IEC, sponsor, or regulatory inspection(s). Results of the study related data, and information obtained from the engineering study, will be collected, received and reported by Philips. Philips will use participant study data for research purposes to support scientific and marketing objectives described in this protocol.

XV. Data Handling and Recordkeeping

Hard copies of the study will be kept on site for at least 2 years after study completion. The sponsor will maintain study records indefinitely. Records will be stored at Iron Mountain, a secure information management services company.

XVI. Financing and Insurance

If the participant is injured during the course of the trial and as a direct result of this trial, they should contact the Principal Investigator, Gerald Criner, MD. The participant will be directed to seek clinically appropriate medical care for that injury. However, we cannot guarantee that the medical care and treatment will be provided without charge or that it will be paid for by the participant's insurance company, and the costs incurred may ultimately be the participant's responsibility.

XVII. Registration on ClinicalTrials.gov or other applicable registry

This trial will be registered on Clinical Trials.gov. It is the intent that these data may be used for to support regulatory clearance and/or consideration for a submission to peer review publication.

XVIII. Risk and Benefit Analysis

A. Potential Risks and Discomforts

Adverse effects of 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.

The risks of using the Vector NIV Device are minimal. Use with the NPPV devices may cause a decrease in the inability to adequately clear secretions, an increased risk for aspiration of gastric contents**,** increase in symptoms of sinusitis or otitis media, and decrease in blood pressure. These are minimal risks of using the device and should they occur during the course of the study, they be recorded. 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. Significant adverse events will be reported to the Institutional Review Board. Patients currently on NIV may find Vector to be less comfortable than their previous NIV, but this is not a real medical risk.

Arterial blood gas determinations are part and parcel of routine pulmonary function testing and are performed by trained respiratory therapists on a daily basis. The blood gas draws as part of this study is consistent with usual care in initiating NIV. The research technician will employ the usual precautions while performing such a procedure by employing adequate aseptic technique. The arterial blood gas sampling test can cause pain, tenderness or swelling at the puncture site and possibly bleeding, local infection, lightheadedness or fainting.

Standard PSG (sleep study) risks might include: complaints of skin irritation from the adhesives or tapes used to secure the electrodes and any necessary skin preparation.

Participants may also find some of the chemical adhesive smells offensive. The participant may sleep poorly.

The patient may sleep poorly during the nocturnal sleep study and thus may be sleepy the next day. If the patient is too sleepy to drive home, other forms of transportation will be utilized.

COVID-19 is a risk with any in-person activity, but proper mitigation strategies, including COVID-19 screening, disinfection, and other site safety procedures, will be implemented to minimize patient risk.

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

B. 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 device design and function

C. Compensation for Research-Related Activities

Participants will only be compensated for the activities that they complete. Participants' payment will be in the form of a Gift card/Clinicard according to the following schedule.

For taking part in this research, participants may be paid up to a total of $750.00 or $800.00 as per the schedule below:

Visit Number	Amount
Visit 1	$50.00 ($100 for Naïve only)
Visit 2	$100.00
Visit 3	$300.00
Visit 4	$300.00
TOTAL	$750.00 ($800 for Naïve only)

D. Publication

It is the intent that these data will be used/considered for a submission to peer review publication, white paper or scientific abstract

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Appendices

Appendix A

VECTOR TITRATION PROTOCOL

Device titration will take approximately 3 hours. There will be 2 separate Titration periods. The Vector Auto EPAP will be titrated in both fixed pressure and using AVAPS that will auto titrate Pressure Support based up on a set tidal volume. Each titration session will last approximately 1.5 hours. Prior to the initiation of the device titration, a baseline TCO2, SPO2, Respiratory Rate will be recorded. If existing NIV user, the device titration initial pressure setting will start at their current device pressure settings.

Immediately prior to conducting the Vector Titration, a resting awake tidal volume determination will be conducted. The participant will be asked to sit in a chair for 30 minutes with the mask, awake, and quietly breathing. Participants will breathe on the device that is manually pressure titrated to the starting tidal volume calculation using 8 ml/kg of ideal body weight (Table 1). After 5 minutes of breathing on the device with the stable target tidal volume, a Borg Scale will be used to assess the patient's level of breathing comfort. This evaluation will continue until the participant's pressure support is manually titrated to the stable target tidal volume that is equivalent to 9 ml/kg and 10 ml/kg of the participant's ideal body weight. The setting that provided the most optimal Borg Scale rating will be the setting used for the study. If optimal tidal volume cannot be achieved after 10 minutes at 10ml/kg of ideal body weight, the participant will be then transitioned to the AVAPS titration protocol.

Vector Device Settings Fixed Pressure Titration:

Vector Device Setting – AVAPS

Once the auto EPAP has settled (approximately 20 minutes), if SpO_2 remains low, tidal volume adjustments can be made (up to 10ml/kg IBW) based on the physician's discretion.

Table 1. AVAPS Tidal Volume Setting * Based on 8ml/kg

Height	Male	Female
5'0"	400	360
5'1"	420	380
5'2"	440	400
5'3"	460	420
5'4"	470	440
5'5"	490	460
5'6"	510	470
5'7"	530	490
5'8"	550	510
5'9"	570	530
5'10"	580	550
5'11"	600	570
6'0"	620	580
6'1"	640	600
6'2"	660	620
6'3"	680	640
6'4"	690	660
6'5"	710	680
6'6"	730	700

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Appendix B

BiPAP/CPAP/Mask fitting Protocol

POLICY

Temple hospital sleep therapy to follow the BiPAP/CPAP/Mask fitting protocol, shall determine BiPAP/CPAP settings based upon each patient's diagnosis and immediate clinical demand.

PURPOSE

The objective is to facilitate the emergent application, management, and timely discontinuation of BiPAP/CPAP therapies via facemask.

SCOPE

The following guidelines transcend the solely physician driven approach to BiBAP/CPAP therapies for acute hypercapnic respiratory failure, thereby allowing the SCP to make timely, necessary adjustments to manage the patient's immediate clinical demand as his/her condition changes.

SETTINGS

When treating acute hypercapnic respiratory failure, the distance between the IPAP and EPAP pressures is of primary importance. Ventilatory assistance increases as the distance between these two settings widens. For example, an IPAP/EPAP of 16/6 provides greater ventilatory assistance than does 12/6, whereas both settings provide the same degree of oxygenation augmentation, because both 16/6 and 12/6 have EPAP settings of 6 cm H_2O.

All settings are considered dynamic, in that they may need adjustment to meet patient demand as his/her condition changes. The following guidelines provide a standardized basis from which to initiate settings and make said changes.

<u>BiPAP settings for Acute Hypercapnia</u>

1. [redacted]

2. [redacted].

3. [redacted].