Clinical Protocol

Determination of the Prevalence and Severity of Expiratory Flow Limitation in Chronic Obstructive Pulmonary Disease Patients

Protocol #: SRC-HRC-VectorEFLScreening-2018-10242

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

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Reporting of Adverse Events or Adverse Device Effects
Report the occurrence of serious adverse event(s) or serious adverse device effect(s) to Philips within 24 hours of the occurrence.

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Investigator Agreement.

As Investigator of the study entitled "**Determination of the Prevalence and Severity of Expiratory Flow Limitation in Chronic Obstructive Pulmonary Disease patients**" Protocol # SRC-HRC-VectorEFLScreening-2018-10242, 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]

Protocol Revisions

Revision Level	Changes Made to Protocol	Date	By
1.0	Original Release	09/JAN/2019	C. Cain, J. McKenzie, B. Romano, J. Jasko, M. Weiner
2.0	Updates to definitions of AEs/SAEs, collection of CT scans within the past 2 years to assess presence of emphysema/chronic bronchitis, and minor administrative changes/ clarifications	13/MAY/2019	M. Weiner
3.0	Clarification of SAE reporting language, addition of Kristi Seese as study monitor and contact for AE reporting, addition of COVID-19 risk and precautions, update to Philips name/address/logo, administrative changes	09/MAR/2021	M. Weiner, K. Seese
4.0	Clarification of EFL definition, updates to objectives and endpoints, administrative changes	12/APR/2022	M. Weiner, K. Seese

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.

AVAPS: Automatically adjusts pressure to meet a target tidal volume. Inspiratory pressure fluctuates between the minimum and maximum settings to reach the set Tidal volume

Bi-Level PAP Therapy: Two levels of pressure therapy, one during inspiration IPAP and another during expiration EPAP.

COPD: Chronic Obstructive Pulmonary Disease

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

ODI: 4% Oxygen Desaturation Index

EFL: Expiratory Flow Limitation **-** occurs when the airways become compressed which usually results when a pressure outside the airway exceeds the pressure inside the airway

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.

Final EPAP: EPAP that is determined to abolish EFL.

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}: Delta Xrs – is the difference between the mean value of X_{rs} during expiration ($\overline{X}_{exp}$) and the mean value of X_{rs} during inspiration ($\overline{X}_{insp}$).

Protocol Synopsis

Title:	Determination of the Prevalence, and Severity of Expiratory Flow Limitation in Chronic Obstructive Pulmonary Disease Patients
Study Design:	Cross-sectional, non-randomized epidemiology study designed to assess the prevalence and severity of expiratory flow limitation in a community COPD population.
Primary Objective:	To gain insight and understanding on the prevalence and severity of expiratory flow limitation and how it relates to other physiological characteristics and endpoints in patients with COPD. For purposes of this trial, overall prevalence includes indeterminate EFL and EFL.
Primary Endpoint:	Overall Prevalence of EFL, as defined as the percentage of participants exhibiting a Delta Xrs value greater than or equal to 2.8.
Other Objectives & Endpoints:	See: *II. Study Objectives and Purpose*
Study Population:	Approximately 100 patients with COPD
Study Type/Phase:	Epidemiology Study
Study Site:	University of Florida Jacksonville
Description of Study Intervention:	Expiratory Flow Limitation detection via Non-Invasive Ventilation (NIV) device

I. 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), lung volume reduction surgery 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 lacking evidence on long term outcomes of this therapy. [2] Lung volume reduction surgery and 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) also known as noninvasive ventilation (NIV) is one therapy that may prove beneficial to stable COPD patients. 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]

NIV 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 NIV it would allow the respiratory muscles to rest, resulting in muscle function recovery, increased respiratory muscle strength, reduced tendency for fatigue, and improvement in pulmonary function and gas exchange.[11]

COPD is a disease that results in varying degrees of dyspnea, or shortness of breath. Spirometry is a method of diagnosing COPD with the presence of a post bronchodilator FEV1 <70% of the predicted value in combination with an FEV1 / FVC <70%. This would confirm that there is a presence of airflow limitation that is not fully reversible.

The presence of airflow limitation 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 airways become compressed which usually results when the pressure outside the airway exceeds the pressure inside the airway. 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**).

Early 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).

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 $\Delta\overline{X}_{rs}$.

Individuals with a ΔX_{rs} value of:

- less than 2.8 cm H_2O/l/s are not flow limited
- between 2.8 and 3.8 cm H_2O/l/s, inclusive, have indeterminate EFL. Some breaths were calculated to be flow limited.
- greater than 3.8 cm H_2O/l/s have EFL.

For purposes of this trial, participants who have indeterminate EFL or EFL (i.e., ΔX_{rs} value is greater than or equal to 2.8 cm H_2O/l/s) will continue to titration.

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 2006, Dellaca et al., suggested the forced oscillation technique may be useful in chronic obstructive pulmonary disease patients using nasal pressure support by identifying continuous positive

airway pressure levels that support breathing without increasing lung volume, which in 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 (Murrysville, PA) overall platform (K121623). The device has been designed to produce a 5 Hz sine wave with peak-to-peak amplitude of approximately 2 cmH_2O superimposed upon the pressure and flow generated by the device. The resultant feedback waveform is then filtered and analyzed to measure reactance (delta Xrs) and thus determine if EFL is present. Subsequently, the EPAP (and concurrently and proportionally the IPAP) 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.

Description of the Intervention Studied

Study Device Descriptions:

1. Vector Device

The Vector ventilator 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, institution/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.

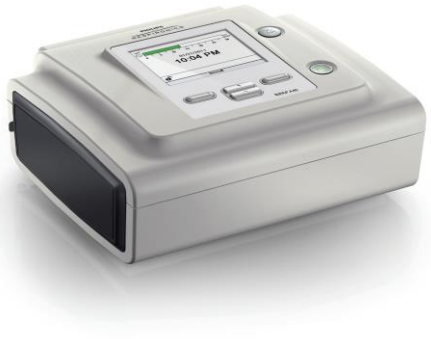
The Vector ventilation method auto-titrates PEEP or EPAP on a breath by breath basis. Vector is a new noninvasive method to continuously detect EFL during spontaneous breathing and minimizing it using EPAP.

The device has been designed to produce a 5 Hz sine wave with peak to peak amplitude of approximately 2 cmH_2O superimposed upon the pressure and flow generated by the device. The resultant feedback waveform is then filtered and analyzed to detect the change of a reactance (delta Xrs). Subsequently the EPAP (and concurrently and proportionally the IPAP) 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. Given that forced oscillation technique can be easily applied during noninvasive nasal ventilatory support, it could be used during routine noninvasive ventilation.

This Vector screening mode is an automated five-minute screening test that can be done in a clinical environment under supervision to determine if EFL is present and its level of severity.

The screening test will have built-in logic that determines the test's validity during the screening as well as the conclusion of the test. The screening test will be at a relatively fixed pressure (typically between 3-4 cmH_2O) that will remain constant throughout the session. The screening session results, which will consist of near real-time pulmonary mechanic information, will be kept on a display until the next session is enabled.

The Vector Ventilator is not currently approved by the FDA. It is considered an investigational device.



2. Resmon Pro Device

   The Resmon Pro (St. Paul, MN) also uses the forced oscillation technique (FOT) which is a noninvasive method to measure the mechanical properties of the lung and airways during tidal breathing. In addition to measuring total impedance (resistance and reactance), the Resmon Pro can measure expiratory flow limitation which is a key index of respiratory obstruction. Restech has developed patented technology to determine the breath-by-breath presence and severity of expiratory flow limitation (EFL) during quiet breathing. Using the Resmon Pro, a physician can detect the presence, severity and reversibility of EFL, and evaluate the degree of airflow obstruction and shortness-of-breath experienced by the patient.

   The Resmon PRO FULL (K152585) is intended to measure respiratory system impedance using the Forced Oscillation Technique (FOT). Is intended for use with pediatric and adult patients 4 years of age or older. The device is designed to be used by pulmonologists, general practitioners, nurses, respiratory therapists, laboratory technologists, medical researchers and similarly trained personnel in hospitals, clinics, and private physician offices.

   Resmon PRO FULL consists of a main unit which has been designed to be used stand-alone, without the need of any personal computer, and an adjustable holder with a clamp to fix such unit to a table/desk and to regulate its height and orientation to the patient during an FOT test.

II. Study Objectives and Purpose

Primary Objective

To gain insight and understanding on the prevalence and severity of expiratory flow limitation and how it relates to other physiological characteristics and endpoints in patients with COPD. For purposes of this trial, overall prevalence includes indeterminate EFL and EFL.

Secondary Objectives: To understand the correlation of the final EPAP with FEV1, final EPAP with screening delta Xrs value and the percent of participants with EFL per the Resmon Pro that have their EFL abolished during the Vector screening.

Primary Endpoint:

- Overall Prevalence of EFL, as defined as the percentage of participants exhibiting a Delta Xrs value greater than or equal to 2.8

Secondary Endpoint:

- Correlation of titrated Final EPAP to participants' FEV1
- Correlation of titrated Final EPAP to participants' screening Delta Xrs value
- Percent of participants with EFL per the Resmon Pro that have their EFL abolished during the Vector screening

Exploratory Endpoints: – Correlation and relationship of participant's therapy settings to the following:

- Classification of COPD (Chronic Bronchitis or Emphysema)
- Airflow limitation severity in COPD via Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [12]
- Presence of indeterminate EFL and EFL in a seated position
- Presence of indeterminate EFL and EFL in a supine position
- Quality of Life via COPD Assessment Test (CAT)[13] score
- Exacerbation History
- Healthcare Utilization
- Smoking History
- Oxygen therapy usage
- Documented $PaCO_2$
- Presence of Sleep Disordered Breathing and risk of obstructive sleep apnea (OSA) via STOP-BANG Questionnaire[14]
- Therapy Comfort assessment via Questionnaires

Device Related Exploratory Endpoints:

- Vector Device collected parameters: Delta Xrs value, % flow limited breaths, Total System Resistance mask leak values
- Comparison of Delta Rx calculation of the Resmon Pro at 5 Hz vs. Vector study ventilator
- Correlation between screening Delta Xrs (measurement in liters per second) at final EPAP in cmH_2O in supine position and any other variables from the analysis
- Therapy Comfort assessment via Questionnaires

Observational Endpoints/Learnings:

- Clinicians will be able to know when EFL is present or not present through the screening feature of the Vector device
- Understanding of how patients who present with varying degrees of EFL severity are being medically managed differently or similarly
- Percentage of patients that were successfully screened as not having EFL by the Vector device but determined to have flow limitation measured by Resmon Pro

III. Study Design:

This will be a cross-sectional, non-randomized epidemiology study designed to assess the prevalence and severity of expiratory flow limitation in a community COPD population. In the study we will also investigate how the presence of EFL may correlate to other physiological biomarker endpoints in the COPD patient.

Site COVID-19 safety procedures and documentation will be followed. Study devices and materials will either be single use or will be cleaned and disinfected per the Instructions for Use.

Schedule of Events:

Study Visit

- Once the participant arrives, 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: gender, date of birth, ethnicity, race, level of education will be collected.
- Current Medications: all current medications will be collected.

- Medical History Assessment: information will be collected regarding historical spirometry data, COPD history and other relevant medical history including the diagnosis of Sleep disordered breathing and Oxygen therapy usage. Chest computerized tomography (CT) scans will be collected if they have been done within the past two years. A new CT scan will not be required.
- Physical examination with anthropometric data (weight, height, temperature) collected and vital signs to include heart rate (HR), blood pressure (BP), respiratory rate (RR), and oxygen saturation (SPO_2) maintained at least 88% on room air, and chest auscultation.
- Review of inclusion/exclusion to ensure participant is eligible to continue
- Administration of Study Questionnaires
- Mask Fitting: Participants will have up to two mask fittings in order to determine the best possible masks while using the Vector NIV device during the EFL screening and titration
- Spirometry testing will be performed for participants who have not had a test in the previous 6 months

Resmon Pro EFL Measurement

- Participants may be required to wear nose clips during the measurement
- Participants will also be required to hold their cheeks during the measurement to prevent any air leaks around their mouth.
- While seated, participants will be instructed to breathe normally into the device for at least 30 seconds or until at least 10 breaths were successfully accepted by the device
- Participants will be asked to repeat test while in the supine or semi-recumbent position.

Vector EFL Screening/Determination and EPAP Titration

- EFL Determination: The participant will be asked to breathe quietly into the Vector device using the selected mask for 5 minutes in the seated position, and then an additional 5 minutes while in the supine or semi-recumbent position. This device has the capability of detecting EFL. If it is determined that the participant does not have EFL or indeterminate EFL by the device screening indicator, the participant will not continue with the EPAP titration.
- EPAP Titration: if it is determined by the Vector NIV device that the participant has indeterminate EFL or EFL (ΔXrs value is greater than or equal to 2.8 cm H_2O/l/s)

the Vector NIV device will be changed from screening mode to therapy mode to delivery BiPAP therapy with the following settings.

Vector Device Settings:

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

- The participants will then breathe on the Vector NIV device in the supine position (preferred) or semi-recumbent if needed for approximately an additional 20 minutes. 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 (or falls below the predetermined EFL threshold).
- While the automatic EPAP Titration is being performed, all participants' SpO_2 will be monitored via finger pulse oximetry.
- Patient must stay awake during the EPAP Titration. If the patient falls asleep, they will be woken by study staff.
- The Final EPAP that is determined to abolish the participants' EFL will be recorded. This value may be assessed by a Philips staff member using a software program designed to determine this value.
- Participants will complete an EFL Vector device post questionnaire

Unscheduled Visits:

This is a single visit study. There are no anticipated unscheduled visits.

IV. Selection and Withdrawal of Subjects:

A. Inclusion Criteria

1. Age ≥ 40 years of age; ≤ 80 years of age
2. Ability to provide consent
3. Diagnosis of COPD

B. 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 at the time of data collection or in the 30 days prior to data collection
3. Self-reported Pregnancy
4. Employee or family member that is affiliated with Philips Respironics
5. History of bullous emphysema
6. History of pneumothorax
7. Evidence of acute sinusitis or otitis media
8. Hypotension
9. Participants at risk for aspiration of gastric contents
10. Epistaxis
11. Participants in respiratory failure
12. Inability to maintain a patent airway or adequately clear secretions

C. ***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.

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.

The study goal is to have 100 participants successfully complete the study.

V. Treatment of Subjects:

A. ***Intended Use***

Vector Device Intended Use

The Vector ventilator is intended to provide non-invasive ventilatory support to treat adult patients with Obstructive Sleep Apnea (OSA), or Respiratory Insufficiency with primary cause being Chronic Obstructive Pulmonary Disease (COPD). This device is not intended for life support. It may be used to screen for the presence, and abolishment of Expiratory Flow Limitation. It is intended to be used within the home, institution/hospital, and diagnostic laboratory environments.

Contraindications:

- Existing respiratory failure
- Acute sinusitis, otitis media
- Hypotension
- At risk for aspiration of gastric contents
- Epistaxis, causing pulmonary aspiration of blood
- Inability to maintain a patent airway or adequately clear secretions

Resmon Pro Intended Use

The Resmon PRO FULL is intended for the measurement and collection of lung function parameters in humans. The system performs cooperation-independent measurements of respiratory system impedance using the Forced Oscillation Technique (FOT). The device is useful in the field of early diagnosis, in every-day-routine testing, for clinical trend observations as well as for epidemiologic studies. FOT is suitable for adult, geriatric and pediatric studies. The device is designed to be used by pulmonologists, general practitioners, nurses, respiratory therapists, laboratory technologists, medical researchers and similarly trained personnel in hospitals, clinics and private physician offices

B. 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).

VI. Assessment of Performance

Device performance will be based on the following recorded Ventilator parameters:

- Ventilator collected parameters during the EFL screening and titration; delta Xrs value, % flow limited breaths, EPAP values and mask leak values.

VII. Assessment of Safety

All serious adverse events occurring during the course of the study and up to 72 hours post study visit will be collected, fully documented, and reported to Western Institutional

Review Board by the Principal Investigator, Dr. Mariam Louis, MD or sponsor staff per IRB guidelines. Serious adverse events will be reviewed by the Sponsor within 24 hours of the study team being aware of the event.

A serious adverse event (SAE) is an adverse event:

- Resulting in death, or
- Resulting in a serious deterioration in the health of the subject that:
  - Results in a life-threatening illness or injury,
  - Results in a permanent impairment of a body structure or body function,
  - Requires inpatient hospitalization or prolongation of existing hospitalization, or
  - Results in medical or surgical intervention to prevent permanent impairment of a body structure or body function.

All unexpected adverse events during the course of the study and up to 72 hours post study visit 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.

VIII. 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.

IX. Statistical Methods

Determination of Sample Size

Approximately 100 participants will be enrolled. No power analysis was performed.

General Considerations

Descriptive statistics will be presented for all variables of interest. Continuous data will be summarized by mean, standard deviation, median, minimum, and maximum values. Categorical data will be presented as frequencies and percentages. Any formal significance testing will be performed at $p < 0.05$.

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

Primary Analysis
The primary analysis will calculate the prevalence of EFL, including the 95% Binomial confidence interval (CI).

Secondary Analysis
Correlations between device parameters and efficacy outcomes will be performed using Pearson and Spearman correlation. Percentage of participants exhibiting EFL abolishment with Vector therapy will be presented, including the 95% Binomial confidence interval (CI).

Exploratory Analysis
Various exploratory analyses may be performed to help evaluate participant's therapy settings with other baseline data or outcomes, but these analyses are not required for the final 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.

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 or study completion, whichever comes first. Adverse events will be provided in data listings.

Interim Analysis
An interim analysis may be performed after approximately 50% of the planned study population has completed the study.

X. Direct Access to Source Data / Documents

Only site clinical study staff 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.

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 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).

B. Case Report Forms

The site study team will capture information on source documents. Data from source documents will be entered into an electronic data capture system (EDC) and will be monitored according to monitoring plan by the study sponsor. Copies of the source will remain with the site. Only staff delegated by the PI will have the ability to enter in, or make changes to, the source documents. All data 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.

XI. 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.

XII. 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 Principal 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.

XIII. 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.

XIV. 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, Mariam Louis, 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 participants insurance company, and the costs incurred may ultimately be the participant's responsibility.

XV. 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.

XVI. Risk and Benefit Analysis

A. Potential Risks and Discomforts

This is a minimal risk study. Potential risks are detailed below and will be listed in the ICF and discussed during the consenting process.

We believe that the risks of providing noninvasive ventilation with the Vector NIV device are no greater than the risks encountered with other assisted positive airway pressure (PAP) devices. We believe that no significant risks will be posed to the participants participating in this protocol, as the study is noninvasive and will be conducted in a clinical

supervised setting by trained clinical staff. The equipment has been tested to ensure safety. Should the equipment not perform as designed, therapy could increase and / or decrease more than desired. This affect could be uncomfortable.

A trained study staff member will be present monitoring the participant while the device is in use at the clinic. The study staff member will intervene should any problems be identified. One possible intervention could be for the staff to stop the study in the event that participant's oxygen saturation (SpO_2) falls below 88%. The participant can also easily remove their interface device should it become uncomfortable or make breathing difficult. Other potential side effects of PAP therapy may include: ear discomfort, conjunctivitis, skin abrasions due to non-invasive interfaces and gastric distension (aerophagia), all of which are quite uncommon. Thus, we believe that the risks and discomfort are minimal.

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.

We believe that the risks and discomforts associated with this study are minimal.

B. Potential Benefits

Although participation in this trial will not result in any direct benefit to the subjects, they will be contributing to generalizable data that will help provide the sponsor and investigator more insight into the prevalence of expiratory flow limitation in the COPD patient population.

C. Compensation for Research-Related Activities

Participants will only be compensated $75 for participation in the study. Payment for participation will be handled through the University of Florida's Human Subject Payment (HSP) Program.

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