Pilot Study to Assess the effect of Providing Intermittent Positive Airway Pressure in COPD Patients In Order to Relieve Their Exertion Related Shortness of Breath

HRC-17007-VBIDEPILOT-PN

Confidential

PROTOCOL TITLE:	Pilot study to assess the effect of Providing Intermittent Positive Airway Pressure in COPD Patients in order to Relieve Their Exertion Related Shortness of Breath
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Study Name

Pilot Study to Assess the Effect of Providing Intermittent Positive Airway Pressure in COPD Patients in Order to Relieve Their Exertion Related Shortness of Breath

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Investigator Agreement

As Investigator of the study titled "Pilot Study Assessing the Effect of Providing Intermittent Positive Airway Pressure in COPD Patients in Order to Relieve Their Exertion Related Shortness of Breath." (the "Study"), I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the Institutional Review Board (IRB) (the "Protocol"); all applicable laws and regulations; and any IRB or FDA conditions of approval;
(ii) await IRB approval for the Protocol before obtaining informed consents;
(iii) ensure that all requirements for informed consent are met and not let any subject participate in the Study before obtaining that subject's informed consent;
(iv) not make modifications to the Protocol as supplied to me by Philips Respironics, Inc. (the "Sponsor"), without first obtaining the written approval of the Sponsor;
(v) provide the Sponsor with accurate financial information as required by FDA regulations;
(vi) supervise all testing of investigational devices that involves any Study subject;
(vii) maintain Study documentation for the period of time as required by FDA regulations; and
(viii) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

INVESTIGATOR

Signature:_____

Printed Name: _____

Date:_____

PROTOCOL REVISIONS

Rev Level	Changes Made for HRC-17007-VBIDEPILOT-PN	Date	Contributors
2.0	• Updates to make study visit language consistent • Update I/E to exclude pregnant subjects, specify short-acting • Update study procedures to indicate pregnancy screening, information collection, and randomization • Update risk section with fetus CT scan risk language • Updated formatting	10/05/2017	C. Cain, P. Nisha, K. Doty, J. Hughes
1.0	• Updated Study Procedures to obtain a CT Scan if not available in recent medical history • Update to include CT Scan risk language • Updated study monitors and investigator first name	08/01/2017	C. Cain, P.Nisha
0.0	Original Draft	03/01/2017	C. Cain, P.Nisha, J.Jasko

BACKGROUND SIGNIFICANCE

Chronic Obstructive Pulmonary Disease (COPD) is a condition associated with expiratory airflow limitation leading to dynamic hyperinflation and an increase in Functional Residual Capacity (FRC) (the amount of air left in the patients lungs at the end of a normal exhalation) as well as an increased Residual Volume (RV) (the amount of air left in the patient's lungs at the end of a forced exhalation). Such increase in functional residual capacity can in turn lead to increased work of breathing and dyspnea.

Dyspnea in COPD

Impairment of lung function (usually measured as FEV_1) is one of the common guidelines for defining the severity of COPD. Forced Expiratory Volume 1 (FEV_1) is the amount of air forcibly exhaled during the first second of a forced expiratory maneuver. It is by far the most frequently used index for assessing airway obstruction. Dyspnea symptoms (perceived shortness of breath) also contribute to the severity of the disease and are the basis of treatment. Breathlessness and exercise intolerance are the most common symptoms in chronic obstructive lung disease, and they can present in all severity stages either at rest or under conditions of exertion and exercise. These symptoms also progress as the disease advances, which leads to inactivity and muscle deconditioning. This can continue in a cycle leading to further inactivity, social isolation and fear of dyspnea. Finally, given that exercise is a recommendation in patients with COPD, dyspnea can interfere with the best treatment regimen.

In GOLD COPD, classifications are used to describe the severity of the obstruction or airflow limitation. The worse a person's airflow limitation is, the lower their FEV_1. As COPD progresses, FEV_1 tends to decline. GOLD COPD staging uses four categories of severity for COPD, based on the value of FEV_1 [30]

Stage I	Mild COPD	$FEV_1 \geq 80\%$ normal
Stage II	Moderate COPD	FEV_1 50-79% normal
Stage III	Severe COPD	FEV_1 30-49% normal
Stage IV	Very Severe COPD	$FEV_1 < 30\%$ normal, or $< 50\%$ normal with chronic respiratory failure present

Physical Exertion and Exercise in COPD

COPD is associated with a considerable burden of disease, even affecting many things that are fundamental to everyday life such as the ability to breathe, talk, walk, sleep, or work. A telephone survey of patients with COPD living in North America and in Europe documented the frequency of breathlessness with daily activities of 3,265 participants with a diagnosis of COPD. According to this questionnaire, one-fifth of the patients reported that they were breathless even when just sitting or lying still and 24% when talking. One-third said they were breathless when doing light housework or while getting washed or dressed, and nearly 70% were short of breath when walking up a flight of stairs [1, 2].

Pathophysiological factors known to contribute to exertional dyspnea in COPD patients include increased intrinsic mechanical loading of inspiratory muscles (PEEPi), inspiratory muscle weakness, and increased ventilatory demand relative to capacity, gas exchange abnormalities, dynamic airway compression, cardiovascular factors, and any combination of the above. [3, 4] In addition to lung function, peripheral muscle force is also an important determinant of exercise capacity in COPD. By gaining muscle mass and strength through exercise training, there would be an improvement in peripheral muscle function, which could be a reasonable therapeutic target for patients with COPD.

Well-designed exercise training programs are essential for patients with COPD to achieve a physiological training effect. Substantial improvements in exercise tolerance and overall improvements in disease can be obtained as a result of properly designed exercise training programs. The improvements of exercise tolerance have been found to be linked with physiological changes, such as improved muscle function and altered breathing pattern (higher tidal volume) and lower breathing frequency that leads to a reduced dead space to tidal volume ratio and thus to a lower ventilatory requirement for exercise. [5, 6]

In order to enhance exercise training programs, patients with COPD need to feel relief from their breathlessness. Treatments to reduce airflow obstruction and/or dynamic hyperinflation include pursed lip breathing (PLB) [7, 8], anti-inflammatory drugs [9], breathing helium-oxygen mixtures [10, 11] bronchodilators, [9, 11] placement of endobronchial valves [12, 13], and lung volume reduction surgery [14, 15].

Different reports have shown that the administration of continuous positive pressure (CPAP) or pressure support ventilation (PSV) by mechanical non-invasive ventilation (NIV) devices, can improve exercise tolerance and breathlessness in stable COPD patients. It is believed that increased respiratory muscle effort, associated with high ventilatory demand relative to respiratory muscle capacity, may contribute to dyspnea in many patients with chronic respiratory disease. There have been multiple studies that have evaluated the effect of NIV on dyspnea but only a few studies have considered dyspnea as an endpoint measure.

A systematic study of COPD patients in pulmonary rehabilitation found that short-term administration of NIV during exercise training significantly improved dyspnea and exercise endurance[16]. This was also supported by a compiled review of 15 studies suggesting that NIV support during exercise may acutely reduce exertional dyspnea and improve exercise endurance in patients with COPD[18]. Another study compared two different levels of inspiratory pressure support – 5 and 10 cm H_2O, and found statistically significant and large improvements in exercise performance and dyspnea relief using pressure support of 10 cm H_2O as compared to that of 5 cm H_2O[17]. Two studies examining long-term nocturnal use of NIV in patients with severe COPD reported significant improvements in dyspnea ratings [19, 20]. It has also been studied that the use of NIV as well as CPAP during exercise decreases dyspnea and increases exercise tolerance [21, 22] which may facilitate patients' participation in pulmonary rehabilitation.

Although there has been research involving the benefit of providing NIV during exercise to increase tolerance overall, there is little research specifically looking at shortening dyspnea recovery times associated with exercise. Additionally, NIV is usually applied via a face mask and devices need to be connected to a power source thus limiting the portability of the therapy. In the comparative pressure support study referenced above[17], the application of NIV was very similar to the use case of the VitaBreath (Study device) via a mouthpiece interface, but with critical additional benefits of independent usage by patients and being portable. Open mouthpiece ventilation is also emerging as a useful technique

that may prevent further deterioration of gas exchange in COPD patients with mild to moderate acidosis, similar to traditional NIV delivered by a nasal mask[23].

We hypothesize that providing intermittent non-invasive positive pressure therapy (a form of NIV or PAP) with a handheld device to COPD patients immediately after exertion can relieve their dyspnea, and consequently allow them to be more active. This hypothesis will be tested by comparing the distance walked by COPD patients with the help of VitaBreath device versus Pursed Lip Breathing as measured by a modified 6-Minute Walk Test (6MWT).

The modified 6MWT will be a variation of the standard 6MWT[32,29] where the participant will be stopped at the 3 minute mark to use the study device as intervention or controlled conditions for 30 seconds. Following this 30 seconds pause, the participant will continue with the remaining 3 minutes of the 6MWT. The distance walked by the participant for the entire 6 minutes will be recorded along with independent distances walked during the first and second 3 minute halves.

Although this product may have some anticipated benefit in the Pulmonary Rehab (PR) setting, this study is not intending to be directly associated with a PR program. Use of a similar environment may be coincidental and only to facilitate operational execution in a safe and monitored environment for the study.

STUDY INTERVENTIONS

VitaBreath (Investigational)

The Philips Respironics investigational device VitaBreath is a handheld, battery powered, intermittent positive airway pressure device that is non-invasive, and provides positive airway pressure (PAP) of 18 cm H_2O during inspiration and 8 cm H_2O on expiration, thus creating 10 cm H_2O of pressure support. Pressure support is defined as the difference between inhalation pressure and exhalation pressure. **The study device is intended as an adjunct therapy to relieve shortness of breath in COPD patients who experience exertion-related dyspnea to allow them to be more active**. The air is delivered to the patient via a mouthpiece on the device.

The VitaBreath is not intended to replace participant's bronchodilators, anti-inflammatory medicines, and/or supplemental oxygen. It is not intended to replace pulmonary rehabilitation as well.

The VitaBreath device is designed for non-continuous use only and typical device use is expected to be for 2-3 minutes. The device should only be operated for less than 10 minutes at a time**.** After such time, the device should be turned off for at least 30 minutes.

Participants will be instructed that the device is intended to provide effective relief of dyspnea. It will be further communicated to them that the device may or may not help them recover from shortness of breath.

The VitaBreath device is intended to relieve exertion-related shortness of breath in COPD patients. For the majority of patients, this would occur as a result of activities of daily living, such as retrieving the

mail or climbing stairs. Although patients may use the device when participating in an exercise program that is not the primary intended use of the device.

Pursed Lip Breathing (Control condition)

Pursed lip breathing (PLB) is the standard of care and will be used as the control condition comparator.

STUDY DESIGN

This will be laboratory-based study with a 2-arm, randomized, controlled, crossover design where the participants will be tested with the investigational device VitaBreath and control condition (PLB) in a random order.

STUDY AIM

The aim of this study is to evaluate that intermittent positive airway pressure therapy given to COPD patients with the VitaBreath device will relieve their exertional dyspnea allowing them to walk further in a modified 6MWT.

STUDY OBJECTIVES

The primary objective will be to compare the distance walked in 6 minutes by COPD participants using Pursed Lip Breathing (PLB) versus an intermittent positive airway pressure handheld device, VitaBreath.

Primary Efficacy Endpoint: Distance walked as measured by modified 6MWT evaluated during the Study Intervention Visit

Primary Hypothesis

Participants will walk further during the modified 6-Minute Walk Test when using VitaBreath compared to pursed-lip breathing at the Study Intervention Visit.

SUBJECT SELECTION / ENROLLMENT

Participants will be identified by investigators at each site. Following IRB approval and after obtaining written informed consent, participants found to possibly meet criteria for participation will be screened to determine their eligibility. The inclusion and exclusion criteria of this study are listed below.

Participants with a diagnosis of COPD who experience shortness of breath may be eligible for participation in this study

Sample Size

This will be a 20 patient pilot study to provide a power analysis for the Pivotal IDE protocol. The previous engineering clinical study included three treatment conditions, whereas the planned pivotal design will only have two conditions, VitaBreath and pursed-lip breathing. This pilot study will test this new trial design.

Inclusion / Exclusion Criteria:

Inclusion Criteria	Exclusion Criteria
All participants: • Age ≥ 40 • Ability to provide consent • COPD diagnosis • FEV_1 <55 and ≥ 25 percent of predicted value • Perceived Shortness of Breath via the Modified Medical Research Counsel Dyspnea questionnaire (rating of 2 or greater) (Appendix B) • Able to follow directions • Able to tolerate mild physical activity • Pursed Lip Breathing as standard of care • No evidence of bullous lung disease (with any bullae greater than 3cm in diameter) as confirmed by a CT scan within the past one year.	All participants: • Subjects who are acutely ill, medically complicated or who are medically unstable as determined by the investigator. • Suffering from COPD exacerbation at time of enrollment or 60 days prior • Subjects who are not currently prescribed oxygen and manifest oxygen desaturation below 88% on the screening 6MWT • Subjects with heart disease or neuromuscular disease. • Subjects who are not prescribed short-acting bronchodilator medication • Patients who have experienced recent barotrauma or pneumothorax • Unstable angina or Myocardial Infarction during past month • Uncontrolled Hypertension (systolic blood pressure of >180mmHg and a diastolic >100mmHg) • Heart Rate >120 at rest • Subjects who have trouble coordinating their breathing with the device during the device training, or cannot tolerate the device mouthpiece resulting in leaks from the nasal cavity • Women of child-bearing potential (WOCP) who are pregnant, breast-feeding, or planning pregnancy during the course of the study. *(WOCP must have a negative pregnancy test at every visit)*

Pregnancy Screening

All women of childbearing potential, (defined as any woman, unless surgically sterile or postmenopausal for at least 1 year) must be instructed to contact the Investigator immediately if they suspect they might be pregnant while participating in this study. If a participant becomes pregnant, she will be discontinued from the study. Pregnancy urine tests of WOCP will be completed at each visit prior to CT scan or usage of the VitaBreath study device.

STUDY PROCEDURES

The study will be explained to the potential participant and sufficient time provided to the subject to ask questions regarding the study. Study related procedures will commence only after the informed consent is signed by the subject. This is a multi (2 or 3) visit study as part of which, participants will be asked to complete in-lab six minute walk tests.

Screening Visit/s 1 and 2 - Screening and Randomization

Recruited participants will be asked to report to the clinical site where consenting and screening related procedures will take place. After consenting, subject eligibility will be evaluated and the following will be collected, demographics, anthropometric measurements, concomitant medications, vital signs and medical history review at Screening Visit 1. WOCP will complete a pregnancy urine test at Screening Visit 1 prior to any CT scan.

The rest of the screening procedures may commence if a recent CT scan (in the past year) of the participant is available and confirms eligibility. If the study participant has not had a CT scan within the past year, they will be scheduled for one by study staff. The participants will be asked to return for Screening Visit 2 once the CT scan review confirms their eligibility.

If a Screening Visit 2 is required, WOCP will complete a pregnancy urine test prior to any usage of the VitaBreath study device at Screening Visit 2.

Upon confirmation of their CT scan review at either Screening Visit 1 or if needed, Screening Visit 2, participants will undergo the remaining screening procedures to assess study eligibility: spirometry, 6 minute walk test (Standard 6MWT)[29, 32] , device training/acclimation, and a dyspnea rating assessment (Modified Medical Research Counsel - Appendix B)[34].

Participants will be asked to take their short-acting bronchodilator medication 15 minutes prior to start of the 6MWT.

The participant's medical history will include an assessment of their medication use, smoking history, and how often they rely on their rescue medication (at rest and with exertion). Any participation in a Rehabilitation Program will be captured as well.

Participants will be allowed to begin exercise assessments 15 minutes after their bronchodilator administration. Concomitant medication and any adverse events will be recorded. The Participants oxygen level will be monitored during the standard 6MWT by continuous finger pulse oximetry. If the participant is not currently prescribed and using supplemental oxygen and their oxygen level is

consistently ≤ 88% during the test, the test will be stopped and the participant will be excluded. If the participant is currently prescribed and using supplemental oxygen during the test and their oxygen level consistently falls ≤ 88%, supplemental oxygen will be titrated during the test by trained study staff until their oxygen level persistently is at 90% or higher during the test. Oxygen equipment will be available at the sites.

We will follow the American Thoracic Society Statement Guidelines for the Six-Minute Walk Test which include the following criteria for immediately stopping a 6MWT: Intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

Device Training

Participants will be asked to train on the VitaBreath device to practice breathing with it. The purpose of this training period is to get the participant acclimated to the device prior to using it during the modified 6MWTs at the Study Intervention Visit. If the participants have trouble coordinating with the device or cannot tolerate the mouthpiece resulting in leaks from the nasal cavity, they will be excluded from the study.

All participants will also be asked to practice pursed lip breathing with proper instruction and training by site staff.

Randomization

If the participant qualifies for the study, their device usage order (VitaBreath or control condition/ pursed lip breathing) will be randomized using a permuted-block randomization sequence at the study intervention visit. Each participant will complete two modified 6MWTs during the Study Intervention Visit, one with each therapy in a randomized order. The randomization will be stratified within each site.

Sites will use a randomization schedule in order to randomize the patients.

The Study Intervention Visit will be scheduled within 5±2 business day period of Screening Visit/s.

Study Intervention Visit – Modified 6MWT

During the study intervention visit, the participants will first complete the Chronic Respiratory Questionnaire (CRQ)[33]- initial (CRQ) (Appendix C). This survey will be completed by participants before they use the device during the modified 6MWT. The response to this questionnaire will serve as a baseline measurement.

At the Study Intervention Visit, WOCP will complete a pregnancy urine test prior to any usage of the VitaBreath study device.

Participants will be asked to practice breathing again with the VitaBreath device to get acclimated prior to using it during the modified 6MWTs at the Study Intervention Visit. Such use will be for a maximum time of 5 – 10 minutes. The coordinator will also remind the participant to practice Pursed Lip Breathing.

The participants will be asked to wait 30 minutes after using the device to wash-out any effects of training with the device before starting the 6MWT.

The coordinator will assess AEs or medication changes since the last visit. Resting Heart Rate and Blood pressure will be checked before the 6MWTs.

Participants will be asked to take their short acting bronchodilator medication after the device training, but only before the first walk test. Participants will be allowed to begin assessments 15 minutes after their bronchodilator administration. Concomitant medication and any adverse events will be assessed. If additional uses of the bronchodilator are required by participants during the in lab study, that use will be recorded / documented. Participant's blood oximetry levels will be monitored via pulse oximeter at all times.

A medically trained clinician will be present during the test in case of adverse events.

Participants will be asked to perform two 6MWT assessments on the Study Intervention Visit. Borg assessments will be made prior to the start of each test.

For one of the tests, participants will be given the VitaBreath device and the other test will be with control condition, where the patients will be instructed to use pursed lip breathing. The order of these two tests will be randomized.

Test Procedure

In order to standardize the participant use of the devices, at the 3 minute mark the test will be stopped for 30 seconds. During this 30 second pause, study participants will be instructed to use the study device in order to help them recover from being short of breath. For the test where participants are randomized to not use a device, they will be instructed to use the pursed lip breathing technique to help them recover during the 30 second duration. After the 30 second pause, the participants BORG assessment will be made and then they will be instructed to complete the remaining 3 minutes of the walk test. At the end of the test, participants will be asked to sit down and their Borg assessment will be made every 30 seconds until they reach their baseline Borg.

Participants will be required to rest at least 30 minutes between tests.

Statistical and Analytical Plan

Descriptive Data

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.

Analysis Populations

The endpoint will only be analyzed among completed cases in this pilot study.

Primary Effectiveness Analysis

The data from this trial will be evaluated to determine whether they meet the assumptions of parametric methods. The distance walked during the modified 6MWT will be compared between VitaBreath and pursed-lip breathing, using either a paired t-test or the nonparametric Wilcoxon Signed Ranks test, depending on the distribution of the data. The significance level will be a two-sided alpha of 0.05.

Safety Analysis

The incidence of adverse events will be tabulated in the descriptive statistics and compared between the treatment conditions.

Subject Accountability and Missing Data

It is expected that the number of subjects who will withdraw early from this pilot study will be small. The number and proportion of subjects eligible for and compliant with the final examination will be presented. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. The endpoint will only be analyzed among completed cases in this pilot study, and therefore data will not be imputed for missing values.

Interim Analysis

There is no interim analysis planned for this study.

Statistical Software

The statistical analyses will be done using SAS, SPSS, StatXact, or Systat. Each of these software packages provides special features that will be exploited to provide a comprehensive analysis with excellent graphics support.

RISK AND DISCOMFORTS

The FDA has determined that this study is significant risk due to the target patient population. VitaBreath is intended to be an adjunct therapy for COPD participants to utilize for relief of their dyspnea after exertion that can consequently allow them to be more active. VitaBreath delivers intermittent non-invasive positive pressure (PAP) therapy that provides positive airway pressure of 18 cm H2O during inspiration (IPAP) and 8 cm H2O on expiration (EPAP), with a handheld device to COPD participants.

We believe that although there may be discomforts associated with the use of this device, all of the study devices have been tested to help ensure safety. Should the equipment not perform as designed, ventilation could increase or decrease more than desired. This effect could be uncomfortable. The participant can easily remove the device should it become uncomfortable or make breathing difficult. Other potential side effects may include ear discomfort, and gastric distension (aerophagia), all of which are quite uncommon, but generally cited side effects of PAP therapy.

The EPAP and IPAP pressures delivered by VitaBreath may predispose COPD participants with recent barotrauma, pneumothorax or a history of bullous lung disease (large bullae greater than 3cm in diameter) to greater risk. Therefore, these participants will be excluded from the study; per the inclusion criteria, patients must have no evidence of bullous lung disease (with any bullae greater than 3cm in diameter) as confirmed by a CT scan within the past one year. Additionally, severe COPD participants with <25% predicted FEV1 will also be excluded from the study.

Computed Tomography (CT) imaging uses ionizing radiation to generate images of the body but is conducted in the COPD population to provide detailed information regarding advancement and severity of the disease state. A CT scan has risks associated with ionizing radiation exposure that could include potential damage to DNA and a small increase in the possibility that a person will develop cancer later in life.[35] CT associated risks are increased for a fetus that is exposed to CT scans. Therefore pregnant women will be excluded from participating in the study. If a CT scan detects an incidental finding, the investigator may direct the participant to seek further health assessments through standard of care pathways.

Although the occurrence rates for barotrauma and pneumothorax are not well defined, should they occur at a rate greater than two occurrences, we will suspend the study for evaluation. If any other SAE occurs, we will critically evaluate it and decide continuance of the study accordingly. Death possibly related to the use of this product is unexpected, but we will stop the study if one Severe Unanticipated Device Related Adverse Event occurs.

The clinical study design involve exercise testing. Exercise testing can have moderate and severe risks. Moderate risks can include falling, muscle soreness or joint injury, low oxygen levels and low blood pressure. In other comorbidities common with the COPD population, risks associated with exercise may include dizziness, arrhythmias, chest pain, heart attack, syncope and possibly death. All exercise testing will be done in a controlled lab environment with at least two medically trained professionals available. Participants are required to use their bronchodilators before exercise testings. Participants' oxygen levels will be checked and monitored before, during, and after the exercise testing. American Thoracic Society Statement Guidelines for the Six-Minute Walk Test include the following criteria for immediately stopping a 6MWT: Intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

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.

MONITORING AND QUALITY ASSURANCE

This clinical study will be monitored by Philips Respironics Inc. (Sponsor) in compliance with the Code of Federal Regulations (CFR) for clinical research; namely, 21 CFR Parts 50, 54, 56 and 812 and others as applicable. The purpose of such monitoring is to assure that the study remains in compliance with the approved protocol, investigator agreement and regulatory requirements, and to resolve any issues that arise during the conduct of the study. The monitoring process includes initial site qualification, periodic visits to the site, and a final visit to the site once the study is complete. Monitoring visits are scheduled periodically throughout the conduct of the study to assure compliance with the investigational plan, and to verify the completeness and accuracy of study data. Monitoring also aids in identifying any research-related problems for the sponsor and/or investigator to correct. The Sponsor will conduct monitoring visits with appropriately trained clinical research professionals.

Monitoring will be conducted by the sponsor to assure adherence to the protocol, Institutional Review Board requirements, and reporting and investigation of serious adverse events. The site investigator will evaluate and classify events. An adverse event (AE) is a situation in which the participant experiences illness or injury not addressed in the device labeling, research protocol, or research consent form. All AEs will be recorded on the AE log provided in the site binder.

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.

Participants will report any AEs or SAEs to the research staff (i.e., investigators and study coordinators) in the course of scheduled and non-scheduled participant contacts (i.e., clinic visits, phone calls, and emails). All events will be reported to the sponsor by the research staff; however, all SAEs 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.

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Appendix A

MODIFIED BORG SCALE

Please grade your level of *Shortness of Breath* using this scale

0	*Nothing at all*
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal
10	Maximal

Appendix B

Modified MRC Dyspnea Scale	
0	Breathless only with strenuous exercise
1	Short of breath when hurrying on the level or walking up a slight hill
2	Slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	Stop for breath after walking about 100 meters or after a few minutes at my own pace on the level
4	Too breathless to leave the house or I am breathless when dressing

APPENDIX G

Chronic Respiratory Questionnaire - Initial

CRQ-SR initial.pdf