Portable Oxygen Concentrator Improvements to Physical Activity, Oxygen Usage, and Quality of Life in Chronic Obstructive Pulmonary Disease Patients using Long-term Oxygen Therapy (POC-STEP)

Protocol Version: 1.0; 29 Jan2018

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Clinical Study Protocol

for

Portable Oxygen Concentrator Improvements to Physical Activity, Oxygen Usage, and Quality of Life in Chronic Obstructive Pulmonary Disease Patients using Long-term Oxygen Therapy (POC-STEP)

Study ID: MA-16-05-02

Sponsors:

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Version: 1.0; 29 Jan2018

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SYNOPSIS

Study Title	Portable Oxygen Concentrator Improvements to Physical Activity, Oxygen Usage, and Quality of Life in Chronic Obstructive Pulmonary Disease Patients using Long-term Oxygen Therapy (POC-STEP)
Study ID	MA-16-05-02
Study Devices	Two POCs will be used in this study: ResMed POC and Inogen POC. Other study devices include the ActiGraph GT9X Link activity monitor to monitor physical activity.
Control Device	Ambulatory and non-ambulatory long-term oxygen therapy, including: • Oxygen tanks • Transfill devices • Stationary oxygen concentrators
Study Purpose	To evaluate changes in activity based on the use of portable oxygen concentrators combined with standard of care (SOC) long- term oxygen therapy versus SOC long-term oxygen therapy alone at 12 weeks in patients with COPD who require continuous (24/7) long-term oxygen therapy. The study will also assess oxygen usage, quality of life, hospitalizations and death.
Study Population	Patients diagnosed with COPD who are prescribed to receive continuous (24/7) long-term oxygen therapy.
Study Design	This is a post-approval, randomized, unblinded, multicenter, parallel group design study with patients randomized to either control (SOC long-term oxygen therapy [SOC arm]) or active treatment (SOC long- term oxygen therapy plus a POC [POC arm]) in a 1:1 ratio. All patients will be provided with an activity monitor to wear continuously to monitor physical activity, and a usage diary to collect oxygen usage. Eligible patients have COPD and are prescribed to receive long-term oxygen therapy. At the enrollment/baseline visit, patients will be consented, randomized, receive their study devices with training (activity monitor, oxygen use diaries, and an assigned POC if randomized to the POC arm), and complete the Visit 1 assessments. At Weeks 1 and 6 after the enrollment/baseline visit, they will receive a phone call from the site to reinforce training on study devices, oxygen usage and study requirements, and adverse event assessment. At the12-week follow-up/final visit, they will complete an in-clinic visit to return all study devices (POC, activity monitor and oxygen use diaries); have activity monitor device data downloaded by the site; and complete the 12-week assessments. Assessments include a 6MWT, St. George's Respiratory Questionnaire and HADS. Data from the activity monitor will be used to document changes from baseline through 12-week physical activity measures for primary endpoint analysis. Patients will be assessed for adverse events at each encounter after signing the ICF. Study participation is complete when the 12-week follow-up visit is completed. Data from the ActiGraph device will be uploaded by the study sites for compliance assessment and statistical analyses.
Study Centers	Up to 20 centers in the United States will participate in this study.

Inclusion Criteria	1. Patient is 40 years or older. 2. Patient has a documented diagnosis of COPD. 3. Patient qualifies for continuous (24/7) long-term oxygen therapy. 4. Patient is prescribed oxygen at ≤ 5 L/min. 5. Patient is POC-naïve, i.e., has not used a POC prior to enrolling in this study. 6. Patient is able to tolerate pulsed oxygen therapy, i.e., oxygen delivered via a POC. 7. Patient is able to fully understand study information and provide signed informed consent and HIPAA authorization. 8. Patient agrees to comply with all study requirements including wearing study devices continuously, using oxygen as prescribed, and completing visits, phone calls and assessments.
Exclusion Criteria	1. Patient's condition is contraindicated for the use of a POC. 2. Patient has documented sleep-disordered breathing that is uncontrolled or untreated. 3. Patient is unable to perform the 6-minute walk test. 4. Patient has a diagnosis (within less than two weeks prior to study entry) of pneumonia or respiratory infection, and/or acute bronchitis requiring antibiotics, or new/increased dose of systemic corticosteroids. 5. Patient has had thoracic surgery or another procedure in the six months prior to enrollment that is likely to cause instability of pulmonary status. 6. Patient has an open skin ulcer or rash where the activity monitor will be worn on the body. 7. Patient has a life expectancy < 1 year. 8. Patient has non-COPD lung disease that may affect oxygenation or survival. 9. Patient has a planned intervention(s) requiring hospitalization within the three months of study participation. 10. Patient is pregnant or planning to become pregnant. 11. Patient is participating in a clinical study of a medical product and has not completed the required follow-up period. 12. Patient, in the opinion of the investigator, should be excluded from the study.
Study Objectives	1. To compare the effect of POC-delivered oxygen on physical activity, oxygen usage, and quality of life compared to non-POC oxygen therapy. 2. To assess the effect of POC-delivered oxygen therapy on COPD mortality and all hospitalizations.
Primary Effectiveness Endpoint	The mean change in physical activity level from baseline at the 12 week visit

Secondary Study Endpoints	1. Average oxygen usage/day 2. Quality of Life o St. George's Respiratory Questionnaire o Hospital Anxiety and Depression Scale 3. 6MWT distance 4. Frequency of COPD exacerbation 5. COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours 6. Average number of steps taken/day (non-hospital days) 7. Mortality due to COPD or other respiratory condition (primary cause of death) 8. All-cause mortality
Exploratory Study Endpoints	1. Time to hospitalization for a COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours 2. Number of days in hospital for COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours 3. All-cause unplanned hospitalizations 4. Average daily activity duration and intensity 5. Average energy expenditure/day
Study Management Center	Regulatory and Clinical Research Institute (RCRI®) 5353 Wayzata Blvd Minneapolis MN 55416 P: 952-746-8080 Email: POC-STEP@rcri-inc.com

1 Disease and Current Treatment

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow blockage and breathing-related problems. According to the CDC, COPD was the third leading cause of death in 2014 (Centers for Disease Control and Prevention, 2016). Smoking is the greatest risk factor for COPD. Other risk factors include exposure to air pollution, genetics, airway hyper-responsiveness, and poor lung growth during childhood (GOLD, 2017). COPD severity can be stratified with the use of spirometry, which is a series of tests to measure the volume of air a patient can inhale, the volume of air a patient can exhale, and how quickly a patient can exhale. COPD treatment options are relative to the severity of a patient's condition.

The economic impact of COPD is evident in direct costs including hospital stays and indirect costs such as missed work due to illness. Guarascio et al. estimated the combined annual costs of COPD in the USA in 2010 to be $50 billion, with the most severe COPD cases resulting in the greatest expenditures. Twelve million Americans are known to have COPD, and expenditures related to this debilitating condition are expected to increase due to recent advances in screening initiatives (GOLD, 2017) (Guarascio, et al., 2013).

Therapy options for COPD symptoms include smoking cessation, pharmacologic therapy, coaching on inhaler technique, vaccinations against respiratory diseases, and pulmonary rehabilitation. Long-term oxygen therapy (LTOT) is defined by the British Thoracic Society as ≥15 hours of oxygen use per day and is typically prescribed only for chronically hypoxemic patients (BTS Home Oxygen Guideline Development Group, 2015). Patients with more significant COPD symptoms are expected to benefit from LTOT as it has been shown to improve survival, exercise, sleep and cognitive performance (GOLD, 2017) (Celli, et al., 2004).

Patients who are prescribed LTOT for their condition have multiple options from which to choose. Portable Oxygen Concentrators (POCs) represent a higher level of convenience as compared to other ambulatory systems (e.g. liquid oxygen) and non-ambulatory oxygen systems (e.g. stationary oxygen tanks). A recent crossover trial of COPD patients who were randomized to either 1) a combined system of a stationary continuous flow device + a portable pulsed-flow device (either a liquid oxygen system or a POC), or 2) a portable pulsed-flow device alone (POC), showed that 43% of patients preferred using the POC as a single oxygen delivery device, and 36% of patients preferred the combination of a stationary and a POC device. The remaining patients expressed no preference. The fact that all patients were using both stationary and portable oxygen at baseline points to the perceived value of POCs from the patient perspective. Furthermore, POCs offer numerous advantages over liquid oxygen, including lower cost, the convenience of not having to refill tanks, and relatively light weight of the system (Parker Hannafin Corp, 2015).

The purpose of this study is to explore an additional potential benefit of POCs. Physical activity is a component of the "COPD vicious circle" diagrammed below.

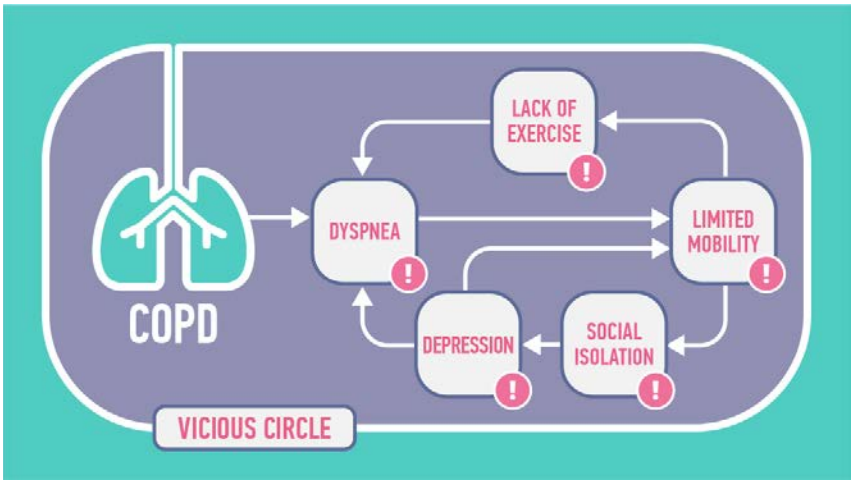

Figure 1. COPD Vicious Circle

Source: http://hitconsultant.net/2016/07/28/powering-copd-management-with-digital-health/

Expanding upon the diagram, lower levels of physical activity in daily life are related to higher risk of hospital readmission and shorter survival (Pitta, et al., 2006). It is hypothesized that the addition of a POC device may lead the patient to become more active compared to patients who use SOC long-term oxygen without a POC device therapy, and that increased activity relative to POC use may lead to better quality of life for patients with severe COPD.

2 Device Description

2.1 Study Devices: Portable Oxygen Concentrators (POCs)

Two versions of commercially available POCs, one from ResMed Corp and another from Inogen Inc., will be used in this study to provide portable oxygen to study patients using pulsed-flow technology. Pulsed-dose oxygen is provided using a pre-programmed bolus amount only as the patient inhales.

Both POCs have been cleared for market by FDA through the 510(k) process and are to be used in accordance with their respective indications for use and User Manual/Operator's Manual. A site will only have one POC device available for distribution during the study.

Both POCs consist of the following system components:

- The main POC body/housing (with battery)
- A carrying case and/or backpack for the device body
- Adjustable straps to be used with the carrying case
- DC power supply
- AC power supply

A nasal cannula must be used with POC and is provided separately. An optional additional battery and/or battery charger may also be used with the device.

The interface of both devices consists of the following features:

- A power button

- A display screen
- Plus/minus buttons to adjust oxygen flow

Additional lights, symbols, and audible signals are featured on each of the POC device types to guide correct use of the device. A battery symbol is included on the display screen of each device to inform the user of remaining battery life. User manuals are included with each device for patient reference and full reference materials are in the eTMF.

The POCs are to be used in accordance with their respective approved indications for use. The POCs are indicated for patients who require supplemental oxygen, including COPD patients. The POCs provide supplemental, high oxygen concentration to these patients. The POCs are available via prescription only and may be used in home, institution, and hospital settings, as well as travel environments.

2.2 Control Device: Standard of Care (SOC) Long-Term Oxygen Therapy

Long-term oxygen therapy (LTOT) is prescribed for patients whose COPD is considered to be severe. Oxygen is provided continuously to the patient in either a continuous-flow or pulsed delivery pattern.

Long-term oxygen therapy can be provided to patients through stationary LTOT systems including large gas cylinders, large liquid oxygen cylinders, and large oxygen concentrator systems. Some stationary oxygen systems also offer an ambulatory component; an example of this is a small liquid oxygen device which can be trans-filled from the larger container.

For the purposes of this study, patients who are randomized to the control arm may not use a POC device as an ambulatory oxygen option.

3 Study Design

This is a post-approval, randomized, unblinded, multicenter, parallel group design study with patients randomized to either control (SOC long-term oxygen therapy alone [SOC arm]) or active treatment (SOC long -term oxygen therapy plus a POC [POC arm]) in a 1:1 ratio. All patients will be provided with an activity monitor to wear continuously to monitor physical activity, and an oxygen use diary to collect oxygen usage data. Eligible patients have COPD and are prescribed to receive long-term oxygen therapy. At the enrollment/baseline visit, patients will be consented, randomized, receive their study devices with training (activity monitor, oxygen use diaries, and an assigned POC if randomized to the POC arm), and complete the Visit 1 assessments. At Weeks 1 and 6 after the enrollment/baseline visit, they will receive a phone call from the site to reinforce training on study devices, oxygen usage and study requirements, and adverse event assessment. At the 12-week follow-up/final visit, they will complete an in-clinic visit to return all study devices (POC, activity monitor and oxygen use diaries); have activity monitor device data downloaded by the site; and complete the 12-week assessments. Assessments include a 6MWT, St. George's Respiratory Questionnaire and HADS. Data from the activity monitor will be used to document changes from baseline through 12-week physical activity measures for primary endpoint analysis. Patients will be assessed for adverse events at each encounter after signing the ICF. Study participation is complete when the 12-week follow-up visit is completed.

4 Study Purpose and Objectives

4.1 Study Purpose

The purpose of the study is to evaluate changes in activity based on the use of POCs combined with SOC long- term oxygen therapy versus SOC long-term oxygen therapy alone. The final assessment will be done at 12 weeks post-randomization for patients with COPD who require long-term oxygen therapy. The study will also assess oxygen usage, quality of life, hospitalizations and death.

4.2 Study Objectives

The main study objectives are to compare the effect of POC-delivered oxygen on 1) physical activity, 2) oxygen usage, and 3) quality of life compared to non-POC oxygen therapy.

Additional study objectives are to assess the effect of POC-delivered oxygen therapy on 1) COPD mortality, and 2) all hospitalizations.

5 Study Endpoints

5.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the mean change in physical activity level from baseline at the 12 week visit.

5.2 Secondary Endpoints

Secondary Endpoints include:

1. Average oxygen usage/day
2. Quality of Life
   - St. George's Respiratory Questionnaire
   - Hospital Anxiety and Depression Scale
3. 6MWT distance
4. Frequency of COPD exacerbation
5. COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours
6. Average number of steps taken/day (non-hospital days)
7. Mortality due to COPD or other respiratory condition (primary cause of death)
8. All-cause mortality

5.3 Exploratory Endpoints

Exploratory endpoints include:

1. Time from enrollment to hospitalization for a COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours
2. Number of days in hospital for COPD or other respiratory condition-related inpatient hospitalization ≥ 24 hours
3. All-cause unplanned hospitalizations
4. Average daily activity duration and intensity
5. Average energy expenditure/day

6 Investigational Study Centers

Up to 20 study sites in the United States will be approved to enroll patients in this study. Minimum criteria for study site qualification will be explored via site completion and submission of a comprehensive questionnaire. Sites which initially meet the minimum criteria may be visited by a qualified monitor to further discuss study details, requirements, and expectations, as well as to ascertain adequacy of site facilities. Qualified sites will be provided with the study documents necessary for IRB submission. The IRB approval letter and all other critical study documents will be finalized and filed electronically prior to enrollment of the first patient at each study site.

7 Study Population

The study population includes up to 190 men and women over 40 years of age who have been diagnosed with COPD and who are prescribed to receive long term oxygen therapy.

7.1 Inclusion Criteria

An enrolled patient must meet the following inclusion criteria for enrollment; all criteria must be answered "yes:"

1. Patient is 40 years or older.
2. Patient has a documented diagnosis of COPD.
3. Patient qualifies for continuous (24/7) long-term oxygen therapy.
4. Patient is prescribed oxygen at ≤ 5 L/min.
5. Patient is POC-naïve, i.e., has not used a POC prior to enrolling in this study.
6. Patient is able to tolerate pulsed oxygen therapy, i.e., oxygen delivered via a POC.
7. Patient is able to fully understand study information and provide signed informed consent and HIPAA authorization.

7.2 Exclusion Criteria

An enrolled patient cannot meet any of the following exclusion criteria; all criteria must be answered "no":

1. Patient's condition is contraindicated for the use of a POC.
2. Patient has uncontrolled or untreated sleep-disordered breathing that is uncontrolled or untreated.
3. Patient is unable to complete the 6-minute walk test.
4. Patient has a diagnosis (within less than two weeks prior to study entry) of pneumonia or respiratory infection, and/or acute bronchitis requiring antibiotics, or new/increased dose of systemic corticosteroids.
5. Patient has had thoracic surgery or another procedure in the six months prior to enrollment that is likely to cause instability of pulmonary status.
6. Patient has an open skin ulcer or rash where the activity monitor will be worn on the body.
7. Patient has a life expectancy < 1 year.
8. Patient has non-COPD lung disease that may affect oxygenation or survival.
9. Patient has a planned intervention(s) requiring hospitalization within the three months of study participation.
10. Patient is pregnant or planning to become pregnant.
11. Patient is participating in a clinical study of a medical product and has not completed the required follow-up period.
12. Patient, in the opinion of the investigator, should be excluded from the study.

8 Informed Consent

Prior to any study assessments or procedures, all potential study patients must document their consent for study participation and authorization for use and disclosure of health information by signing the study-specific IRB-approved Informed Consent Form (ICF). As part of the consent process, the patient will have the opportunity to ask questions of, and receive answers from the personnel conducting the study. Patients will be considered to be enrolled in the study once they have signed the ICF, it is confirmed that they meet all inclusion/exclusion criteria, and they are randomized to a study arm.

9 Study Assessments

9.1 6-Minute Walk Test

The 6-Minute Walk Test (6MWT) is a commonly used test in both practice and clinical research to determine exercise tolerance and to predict morbidity and mortality in COPD patients. The test measures the distance a patient can walk on a flat, hard surface in six minutes. Patients will complete this test at the baseline and 12-week visits. Potential study patients who are unable to complete the 6MWT at baseline will not be randomized (i.e., enrolled) in the study. See the 6MWT guide in the eTMF for details regarding this test.

9.2 St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a validated tool that can be used to measure health impairment in COPD patients. (Morishita-Katsu, et al., 2016). It is a two-part questionnaire; Part 1 (questions 1-8) covers the patient's recollection of their symptoms over a preceding period, and Part 2 (questions 9-16) addresses the patient's current state. In this study, patients will be asked to recall their symptoms over the preceding 3 months for Part 1. See the SGRQ manual in the eTMF for details regarding administration of the questionnaire. See the SGRQ manual for reference in the eTMF.

9.3 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a commonly used, validated questionnaire that measures anxiety and depression (Stern, 2014). The questionnaire consists of a total of 14 questions, seven which pertain to anxiety and seven of which pertain to depression.

Patients will complete the HADS questionnaire in a similar manner to the SGRQ at the baseline and 12-week visits. See the HADS guide in the eTMF for details regarding administration of the questionnaire.

9.4 ActiGraph

For this study, activity will be measured using the ActiGraph GT9X Link. It combines validated accelerometry measurement technology with a wear sensor, which can provide information on whether or not the device was being worn by a patient at a given time. ActiGraph has been used to collect activity data in numerous research studies and is the most frequently used brand of accelerometers in the research field (Migueles, et al., 2017). For this study, the ActiGraph device will be worn on the patient's non-dominant wrist virtually all the time to utilize the wear detection feature and to minimize extraneous accelerometry measurements that may occur if it is worn on the dominant wrist. Specific ActiGraph parameters that will be used in this study include physical activity level (PAL), steps per day, and activity intensity level. See the eTMF for ActiGraph user guides.

9.4.1 Physical Activity Level (PAL)

As it relates to the primary study endpoint, PAL will be calculated using the following ratio:

$$\frac{\text{Total Energy Expenditure (TEE) (kcal)}}{\text{Sleep Energy Expenditure (SEE) (kcal)}}$$

The TEE measurement is reported directly by ActiGraph. The baseline calculation will use the average wear-filtered TEE reported within the first week of study participation. The 12-week calculation will use the average wear-filtered TEE reported within the twelfth week of study participation.

The baseline SEE measurement will be derived from average TEE values reported only during the patient's sleep time within the first week of study participation. The 12-week SEE measurement will be

derived from average TEE values reported only during the patient's sleep time within the twelfth week of study participation.

Note: The TEE measurement will also be reported as a stand-alone measurement as a representation of average energy expenditure per day (see section 9.4.4 below).

9.4.2 Steps per Day

Wear-filtered steps per day will be reported by ActiGraph in daily summary reports. The baseline steps per day value will be calculated from the average wear-filtered steps per day reported within the first week of study participation. The 12-week steps per day value will be calculated from the average wear-filtered steps per day reported within the twelfth week of study participation.

9.4.3 Activity Intensity Level

Wear-filtered, waking physical activity level will be reported by ActiGraph and will be categorized per minute in the following three categories:

1. (SVLPA) Sedentary to Very Low: VMU (sum of all three axis counts) < 3000
2. (LMPA) Low to Moderate: VMU ≥ 3000 AND vertical axis count < 1952
3. (MVPA) Moderate to Vigorous: vertical axis count ≥ 1952

The baseline durations per day will be calculated from the average waking wear-filtered duration per day reported within the first week of study participation. The 12-week durations per day will be calculated from the average waking wear-filtered durations per day within the twelfth week of study participation.

9.4.4 Average Energy Expenditure per Day

Wear-filtered energy expenditure will be reported in kilocalories (kcal or calories) by ActiGraph in daily summary reports. The baseline estimated calories used per day will be calculated from the average wear-filtered calories per day reported within the first week of study participation. The 12-week estimated calories used per day will be calculated from the average wear-filtered calories per day reported within the twelfth week of study participation.

9.5 Oxygen Use - Diaries

Patient diaries will be used to collect oxygen usage during the study. All study patients will receive a diary to record their daily use of oxygen therapy. Patients will record their usage of the SOC oxygen and patients assigned to the POC arm will also record use of POC oxygen.

10 Study Procedures

10.1 Flow Diagram and Procedures Table

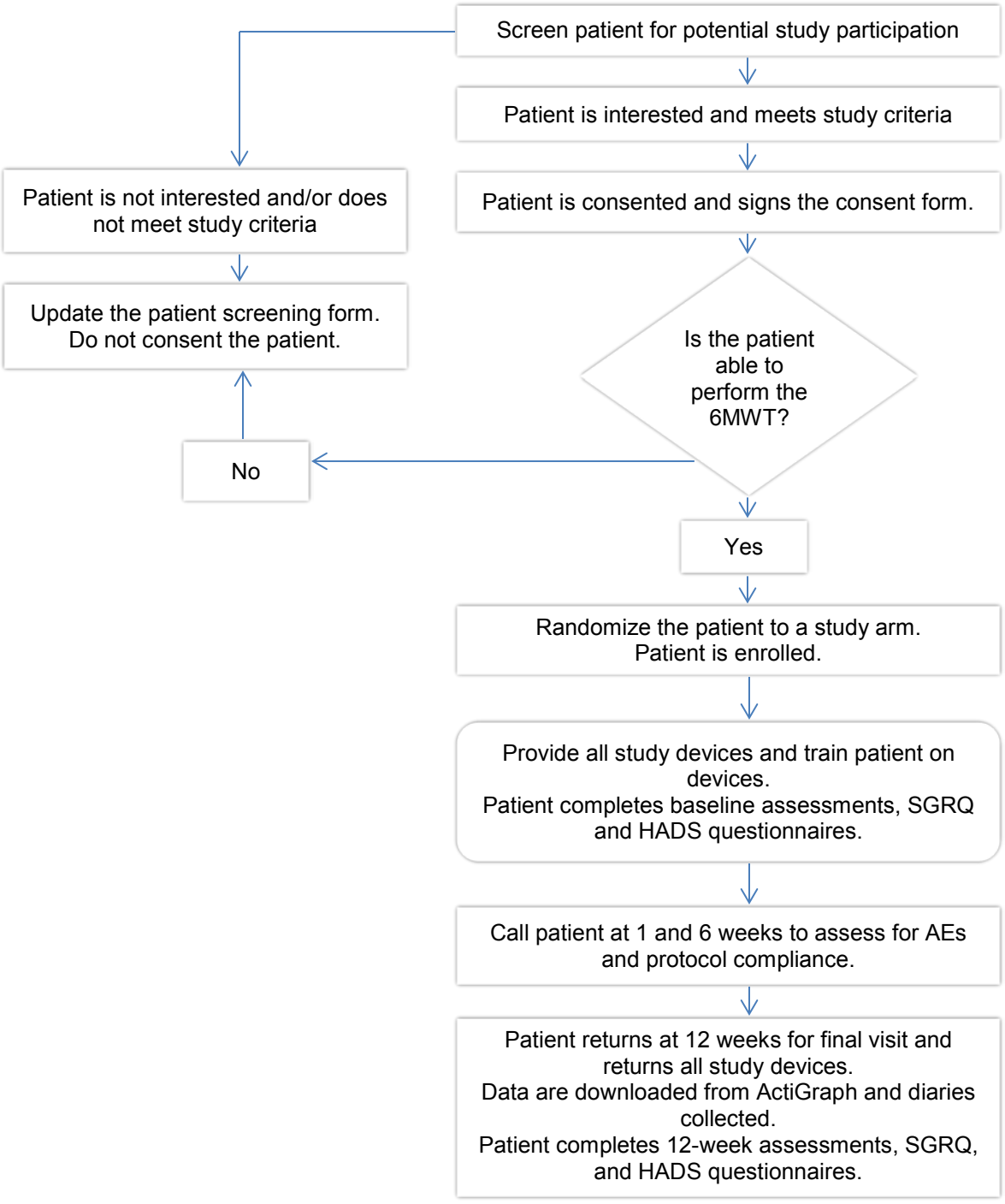

Figure 2. Study Flow Chart

Table 1. Schedule of Study Procedures

Activity	Visit 1 Enrollment/Baseline/ Randomization	Phone Calls Week 1 and Week 6 ± 3 days*	Visit 2 Week 12 ± 7 days Follow-up*
Informed Consent	X		
Demographics and medical history	X		
Modified physical exam	X		
Vital signs	X		X
Inclusion/exclusion criteria	X		
PaO_2 at rest	X		X
Randomization	X		
ActiGraph and oxygen usage diary distribution	X		
POC distribution^	X		
Device training	X	X	
ActiGraph set-up and initialization	X		
ActiGraph data download			X
Usage diary collected			X
St. George's Respiratory Questionnaire	X		X
HADS	X		X
6MWT	X		X
Concomitant meds†	X	X	X
Adverse events	X	X	X
Return all study devices**			X

*After Visit #1
^ for patients assigned to the POC arm
† Respiratory condition-related medications only
** Patients will have the option to purchase their POC device used in the study

10.2 Screening

Trained site study personnel will screen patients for study participation by two methods:

1) review COPD patient medical records for existing LTOT users who appear to meet study criteria to approach them about their interest in study participation;
2) Ask COPD patients who are prescribed LTOT for the first time during the study enrollment phase and who appear to meet study criteria about their interest in study participation.

10.3 Visit 1: Randomization and Baseline Visit

After a potential study patient has 1) completed the initial informed consent process and signed the study-specific informed consent form, 2) successfully completed the baseline 6MWT, and 3) been determined to meet all inclusion criteria and none of the exclusion criteria, the patient will be randomized in a 1:1 ratio to either SOC long-term oxygen therapy only (control arm) or SOC long- term oxygen therapy plus a POC (treatment arm). Randomization will be stratified by site and will be implemented via small permuted blocks. Randomization assignments will be assigned through the electronic study database and will be obtained by trained site personnel. A patient is considered enrolled at the time of randomization. Patients will be given all study devices relevant to their study arm assignment and will receive training on all devices at the baseline visit. Patients will be instructed to contact their site study staff with any questions pertaining to the study.

10.3.1 Baseline Data Collection

The following information will be collected at baseline:

- Inclusion and exclusion criteria confirmation
- Demographics
- Medical history
- Modified physical exam
- Vital signs (temperature, pulse, respiratory rate, and blood pressure)
- PaO_2 at rest
- SGRQ questionnaire
- HADS questionnaire
- 6MWT results
- Concomitant medications*
- Adverse events
- Protocol deviations

*Respiratory condition-related medications only

10.3.2 Distribution of Study Devices

During the baseline visit, all patients will receive the following devices:

- ActiGraph activity monitor

In addition to the above devices, treatment arm patients will also receive one POC device.

Patients will be trained on the use of all study-related devices during the baseline visit and will be provided with the associated device instructions/guides for reference. All patients will be instructed to complete oxygen use diaries each day.

10.3.3 Initializing the ActiGraph GT9X Device

The following components of the ActiGraph GT9X device will be used for this study. Items in **bold** will be distributed and explained to the patient by a trained research team member.

- **ActiGraph Link**
- **Link Wrist Band**
- **Single Dock**
- **CentrePoint (CP) Data Hub**
- USB Cables
- AC Wall Plug

A trained member of the study team will install the ActiSync software on a designated computer in advance of enrolling the first study patient. Study personnel will be emailed invitations to the CentrePoint platform. The battery for each patient's ActiGraph device will be fully charged (for approximately three hours) in anticipation of enrollment. The ActiGraph device will be programmed using applicable instructions found in the ActiGraph GT9X Link + CentrePoint Quick Start Guide and/or the ActiGraph Site User Guide (in the eTMF) during the baseline visit. Additional ActiGraph GT9X device programming and use instructions will be provided during the Site Initiation Visit.

10.4 Study Phone Calls

A trained member of the site research team will call patients at 1 week (±3 days) and 6 weeks (±3 days) after study enrollment. The purposes of the phone calls are to:

- Assess for previously unreported adverse events
- Obtain updates on any ongoing adverse events
- Obtain any updates on respiratory condition-related concomitant medications
- Assess patient protocol compliance, i.e., use of ActiGraph devices, oxygen usage diaries, POC usage (if randomized to the treatment arm)
- Answer any study-related questions the patient may have
- Address any study-related concerns the patient may have
- Provide additional study device training and support as needed

Phone calls will be documented on a standardized study worksheet for source documentation.

10.5 Visit 2: 12-Weeks Post Randomization

Patients will return all study devices at the 12-week visit and will continue with their prescribed COPD care plan, including LTOT. Patients will have the option to purchase their POC device used in the study.

10.5.1 Visit 2 Data Collection

The following information will be collected 12 weeks ±7 days post-randomization:

- Vital signs
- PaO_2 at rest
- SGRQ questionnaire
- HADS questionnaire
- 6MWT results
- Oxygen usage diary
- Concomitant medications
- Adverse events
- Protocol deviations

10.5.2 Data Management for the ActiGraph GT9X Device

A trained member of the study team will plug the device into the designated computer at the 12-week visit by following the instructions in the ActiGraph GT9X Link + CentrePoint Quick Start Guide and/or the ActiGraph Site User Guide (in the eTMF). The data will be automatically uploaded to the CentrePoint platform.

Additional data download instructions may be provided during study initiation and/or throughout the study as necessary. After data have been uploaded from the ActiGraph device, a trained study team member who uploaded the data should submit the data for data management and analysis as instructed in study training materials.

11 Concomitant Medications

11.1 Medications

Only respiratory condition-related concomitant medications taken at baseline and during the study, including changes, will be recorded on the Concomitant Medication eCRF. There are no prohibited medications for this study.

12 Patient Completion and Withdrawal

12.1 Patient Completion

A patient's participation in this study is considered complete after the 12-week follow-up visit is completed.

12.2 Patient Withdrawal

A patient may withdraw (or be withdrawn) from the study prematurely for the following reasons:

- Withdrawal of consent by patient
- Withdrawal of patient by investigator
- Lost to follow-up
- Termination of study by the sponsor
- Death
- Other (to be specified).

The reason for termination will be recorded on the appropriate eCRF. In the event that a patient withdraws from the study, a final study visit should be conducted in person. At a minimum, the patient will return all study-related devices and accessories during the final study visit. If the patient wishes to purchase their study POC, they may do so upon study withdrawal. Other final study-related activities (e.g. questionnaire completion) may be conducted at the investigator's discretion and with the patient's agreement.

12.3 Screen Failures

Screen failures are those patients who have signed the informed consent but are then determined to be ineligible for randomization to a study arm. A log of all study screen failures will be maintained by each investigational site. The reason(s) for screening failure will be recorded on the log.

13 Adverse Events

13.1 Definitions

13.1.1 Adverse Event

For the purposes of this study, an adverse event (AE) is defined as any undesirable/unusual medical experience that occurs to a patient during the study, whether or not it is considered to be device related, including (but not limited to) those events that result from the use as stipulated in the protocol. If an investigator is unsure about whether to report a finding as an adverse event, s/he should report the event on the AE eCRF.

13.1.2 Serious Adverse Event

A serious adverse event is an adverse event that:

- Leads to death, or
- Leads to serious deterioration in the health of a patient that:
    - results in a life-threatening illness or injury,
    - results in permanent impairment of a body structure or body function,
    - requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization,

- results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.

13.1.3 Anticipated Adverse Events

Warnings, contraindications, and hazards are outlined in the User/Operator Manual for the POCs and should be reviewed with patients when they receive their study device(s). All study devices are to be used in accordance with their respective approved, current instructions found in the manual. Anticipated adverse events include events that are reasonably expected to occur as a result of the patient's disease state or treatment.

COPD-related Anticipated Adverse Events:

- COPD exacerbation and related symptoms including:
  - Cough
  - Dyspnea (shortness of breath)
  - Excessive mucus production
  - Wheezing
  - Chest tightness
  - Cyanosis
  - Respiratory infections
  - Headache
  - Fever
  - Confusion
  - Chest pain
- Lack of energy (fatigue)
- Unintended weight loss
- Swelling in ankles, feet, or legs
- Death

LTOT-related Anticipated Events:
Anticipated adverse events associated with LTOT include, but are not limited to, the following:

- Fires
- Burns
- Nosebleed
- Dry mouth
- Dry throat
- Headache
- Tripping/falling over equipment
- Electrical shock and damage
- Noise irritation
- Low oxygen level due to improper equipment use, improper accessory use, or device malfunction

13.2 Adverse Event Assessment and Reporting

13.2.1 Adverse Event Assessment

Adverse event information will be collected on all patients. At every patient encounter throughout the study, the investigator will inquire about adverse events since the last encounter. Patient medical records

will be reviewed throughout the study and at study completion to specifically look for AEs and AE updates. Study staff will ask specific questions during the 1- and 6-week phone calls to assess for AEs.

13.2.2 Adverse Event Reporting

Adverse events (AEs) are to be reported in the electronic study database on an AE eCRF as soon as possible after discovery by the site and are to be updated with new information and upon final resolution of the event. Supporting source documents for SAEs may be requested by RCRI; if requested, these documents are to be de-identified, labeled with the patient's study ID number, and promptly provided via email to RCRI or uploaded to the electronic study database. Adverse events will be evaluated by the investigator and classified for seriousness (as defined in Section 13.1.2), relatedness, and severity:

Relatedness
Adverse events will be judged by the Investigator as to their relatedness to the study device or procedure using the following classifications:

- Unrelated: The event is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.
- Probably Not Related: The event had no significant temporal relationship to the study-specific devices or procedures and/or a more likely alternative etiology exists.
- Possibly Related: The event had a strong temporal relationship to the study-specific devices or procedures and alternative etiology is equally or less likely compared to the potential relationship to the study-specific devices or procedures.
- Probably Related: The event had a strong temporal relationship to the study-specific devices or procedures and another etiology is unlikely.
- Unknown: Relationship of the event to the study-specific devices or procedures and alternative etiology is unknown.

Severity
Adverse events will be categorized by the Investigator as mild, moderate, or severe, depending on the event's impact on the subject's daily activity level:

- Mild: Usually transient, requiring no special treatment; does not interfere with the subject's daily activities.
- Moderate: Low-level inconvenience or concern to the subject; may interfere with daily activities, usually resolved by simple therapeutic non-interventional methods.
- Severe: Interruption in subject's daily activity requiring systemic drug therapy or other treatment.

13.2.1 Mandatory Medical Device Reporting

Manufacturers are required to report to the FDA via an electronic equivalent of Form 3500A when they learn that any of their devices may have caused or contributed to a death or serious injury or has malfunctioned and the malfunction would be likely to cause or contribute to a dearth or serious injury if it were to recur (key terms are defined in 21 CFR 803.3.). Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Should such an event occur during this study, the appropriate device manufacturer will file Form 3500A with FDA's Center for Devices and Radiological Health as required by law.

14 Statistical Analysis Considerations

Following is a summary of the Statistical Analysis Plan for this study. Please refer to the separate SAP for detailed information.

14.1 Analysis of Primary Effectiveness Endpoint

The primary endpoint is the mean change in PAL from baseline at the 12 week visit. The PAL is calculated as the ratio of total daily energy expenditure to sleep energy expenditure, as described in Section 9.4.1. The study will be considered successful if the mean change in PAL is assessed for both study arms. In addition, in the event of a successful study, the following hypothesis test will also performed.

14.1.1 Hypotheses

The hypotheses associated with the primary endpoint are defined as follows:

H_0: $\mu_t - \mu_c = 0$
H_1: $\mu_t - \mu_c \neq 0$

where μ_t is the mean change in PAL for the test patients (patients assigned to the POC arm) and μ_c is the mean change in PAL for control patients. If the null hypothesis is rejected, i.e., the conclusion of inequality is achieved, and the observed difference between the mean sample changes in PAL, $\bar{x}_t - \bar{x}_c$, is greater than 0, then higher physical activity level by the test group, as compared to the control group, will be considered demonstrated. For accuracy, non-wear time data will be excluded from analysis.

14.2 Sample Size

The following assumptions were used to determine the sample size for the primary endpoint of mean change in PAL from baseline at 12 weeks:

- Patients will be assigned to either the test or control treatment group
- The primary analysis is an inequality comparison of the test treatment to the control treatment
- The standard deviation for both test and control treatments is 0.22.
- A difference between treatment groups of ≥ 0.1 is considered clinically significant (i.e., the minimal desired detectable difference between treatment groups)
- The difference between the treatment groups is expected to be 0
- Greater than 80% power is considered sufficient
- Statistical test will be performed with a two-sided 5% significance level

To maintain at least 80% power to detect a difference between treatment groups of 0.1 with a common standard deviation of 0.22, 77 patients per treatment group would be required for a total of 154 patients. Adjusting for potential 20% attrition, 93 patients per treatment group will be required for a total of 186 patients. An additional four patients will be enrolled in order to provide more data for the success calculation, thereby bringing the total sample size to 190.

14.3 Analysis of Secondary and Exploratory Endpoints

The full list of all secondary and exploratory endpoints can be found in Section 5.3. The mean changes from baseline in continuous secondary and other endpoints will be compared between treatment groups via independent samples t-tests, or a non-parametric equivalent as appropriate. General Linear Modeling will be used to assess the impact of potentially influential covariates.

For comparisons of categorical variables, a chi-square test (if appropriate) or Fisher's exact test will be used. Standard logistic regression will also be fit to these endpoints to include center effects and relevant covariates.

For certain variables associated with only one treatment arm, such as POC usage, summaries and estimation, including 95% confidence intervals, may be provided, with no formal hypothesis test performed.

The frequencies of each individual type of adverse event will be summarized along with a 95% exact binomial upper confidence bound. Adverse events, including UADEs, will also be summarized based upon seriousness, severity and relation to the procedure and the device. Individual adverse events will be listed for both groups, including time to event and resolution.

14.4 Other Statistical Considerations

Analysis Data Sets
At a minimum, two distinct analysis sets will be used for the evaluation of primary and secondary effectiveness endpoints. The *intent-to-treat analysis set* will include all randomized patients enrolled in the study. The *per protocol analysis set* will only include patients with complete primary effectiveness endpoint data and no major protocol violations. The safety evaluation will be based on the intent-to-treat analysis set only.

Justification of Pooling Data across Centers
A formal analysis will be conducted to determine the appropriateness of pooling data across the study centers. This will include constructing a linear regression model for the primary effectiveness endpoint with three factors: center, treatment and center by treatment interaction. Furthermore, “super-centers” may be constructed from centers with small numbers of enrolled patients to be entered into models as fixed effects.

Verification of Randomization Procedure
In order to verify the success of the randomization procedure, the distribution of each baseline and demographic variable of interest will be summarized by treatment group. Continuous variables will be summarized via mean, median, standard deviation, and range. Categorical variables will be summarized via counts and frequency distributions.

Missing Data
A sensitivity analysis will be performed for each endpoint to assess the potential impact of missing data on the results. A detailed description of all planned sensitivity analyses can be found in in the Statistical Analysis Plan together with the analysis of the relevant endpoints. Missing values will be ignored for the summaries of baseline characteristics, other summaries and safety endpoints.

Standard Statistical Methods
Unless otherwise stated, all *P*-values will be considered significant at a two-sided significance level of 0.05. Summary statistics will be generated for all relevant variables. In the comparison of continuous variables, distributions will be tested for the normality assumption. If standard parametric techniques are found to be inadequate, an appropriate non-parametric technique or a Box-Cox transformation will be used. No corrections will be made for multiple testing procedures. All analyses will be conducted using SAS® version 9.1 or higher.
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15 Risk Analysis

15.1 Potential Risks

Refer to Section 14.1.3 for a list of potential risks.

15.2 Minimization of Risks

This study involves the use of FDA-cleared, Class II medical devices that deliver oxygen therapy with no greater than minimal risk to study patients. All study devices will be used in accordance with their respective approved indications and instructions. The selection of qualified investigators and the provision of study training to site personnel prior to each site's study initiation constitute additional efforts to minimize risk.

In this study, patients will be contacted at 1-week and 6-weeks and will return for a final study visit at 12-weeks post-randomization, allowing for the assessment of adverse events.

15.3 Potential Benefits

Patients may be inclined to increase their physical activity level by participating in this study; however, it is possible that patients will not experience any benefits from study participation. The results of this study may guide the future treatment of patients with COPD.

15.4 Conclusion

The study sponsors firmly believe that the value of the knowledge to be gained by conducting this clinical study to demonstrate the potential of POC devices to positively influence physical activity level in COPD patients outweighs any potential risks posed to participating patients.

16 Study Devices

16.1 Packaging and Labeling

Labeling describing relevant contraindications, hazards, adverse effects, interfering substances or device, warnings, and precautions are provided in the ActiGraph GT9X Link + ActiLife Quick Start Guide, ResMed POC User Manual, and the Inogen POC User Manual. Study devices (POC, ActiGraphs) will be sent to the sites from Sherpa Clinical Packaging. See the eTMF for logistical information on device shipment/returns and Sherpa Clinical Packaging contact information.

16.2 Handling and Storage

The investigator must ensure that all study devices are stored in a secure location until issued to a study patient. All supplies are to be used only for this study and not for any other purpose. The investigator must return all devices to the sponsor(s) at the conclusion of the study.

16.3 Device Accountability

The investigator is responsible for study device accountability, reconciliation and record maintenance. The investigator must maintain study device accountability records throughout the course of the study.

16.4 Device Distribution to/from Patients

Upon being randomized to a study arm, all patients will receive an activity monitor and a diary to record oxygen usage. Patients who are randomized to the treatment arm will also receive the POC device assigned for distribution by his/her specific study site. At the time of device distribution, patients will be informed that they must return all study devices at the end of study participation. Patients are required to return all study devices (POC [if applicable], ActiGraph) to the site at the 12-week visit (or at study termination, if earlier). Sites will return the study devices to Sherpa Clinical Packaging in a bulk shipment at the end of the study. Patients will have the option to purchase their POC device used in the study.

16.5 Device Troubleshooting/Help Desk

Study patients will be provided with contact information for trouble-shooting all study devices (POCs, ActiGraph).

17 Study Administration

17.1 Institutional Review Board (IRB) Approval

The study must be reviewed and approved by the site's IRB before patient enrollment begins at the site. A signed copy of the IRB approval letter and IRB-approved ICF/HIPAA form must be submitted to RCRI. Investigators are responsible for submitting and obtaining initial approval and continuing approval from the IRB and forwarding copies of the approval letters and ICF/HIPAA forms to RCRI. The investigator will notify RCRI within five (5) working days in the event of withdrawal of IRB approval.

17.2 Clinical Trial Agreement and Financial Disclosure

The investigator agrees to be responsible for conducting this study in accordance with the signed clinical trial agreement and this protocol, including study team oversight/management, reporting and record-keeping requirements and controlling the study devices. In addition, the investigator is responsible for ensuring that proper informed consent is obtained from each patient prior to participating in the study as well as protecting the rights, safety and welfare of participating patients.

All investigators will be required to sign a financial disclosure form, which certifies the investigator's and his/her immediate family's financial interest in the study sponsors and study outcomes. Investigators must inform RCRI of any changes related to financial disclosure throughout the course of the study and for a period of two years after the study is terminated.

17.3 Patient Confidentiality

All information and data sent to RCRI, the study sponsors and/or their designees concerning patients and their participation in this study are considered confidential by RCRI, the study sponsors and their designees (subcontractors or contract research organization). Only authorized RCRI and sponsor personnel or approved contracted agents will have access to some portions of these confidential files and will act in accordance with applicable regulations as required by HIPAA. The IRBs also have the right to inspect and copy all records pertinent to this study.

17.4 Patient Compensation

Patients will receive compensation from the sponsors for their participation in the study upon completion of the 12-week visit. Compensation is also contingent upon the return of all study devices and will be provided to the patient by the investigational site. The compensation amount will be specified in the Informed Consent Form and the Clinical Trial Agreement.

17.5 Investigational Site Qualification

Investigational site qualification visits or phone calls will be conducted by RCRI prior to acceptance of a site into this study. As part of the study site selection criteria, investigators will be familiar with the use of POC devices and LTOT. The site qualification visit/call will be scheduled to include time with the investigator, co-investigators, study coordinator and other study personnel. Topics of discussion will include a review of personnel qualifications, investigator qualifications, adequacy of potential patient pool, clinical study experience, study-specific requirements for procedures and equipment, and a review of staffing and equipment availability and appropriateness. A written report of the qualification visit/call will be drafted by RCRI. Resolution of any concerns and/or completion of any necessary activities identified during the visit/call will be documented and submitted to the investigator.

17.6 Site Training

Study-specific training of study personnel is the responsibility of RCRI and the investigator. Study training will occur before first enrollment. To ensure protocol compliance as well as accurate data collection, site training will include a detailed review of the protocol, eCRF completion, study-specific procedures, study devices, and monitoring logistics. Product-specific training will be provided for the POC device to be distributed by the site, the activity monitor (and associated software) and the oxygen diaries during the site initiation visit.

17.7 Data Management

Study-specific eCRFs will be used to enter study data into the EDC system. The PI or designated study personnel at each site is responsible for entering data into the CRFs. Queries/corrections will be managed within the EDC system via electronic queries. Prior to final database lock, the investigator will electronically sign each eCRF; this responsibility cannot be delegated to another person.

Data and eCRFs will be reviewed by study monitors at regular intervals throughout the study as outlined in the study monitoring plan. Data clarification requests (DCFs or queries) may be generated by a monitor during a monitoring visit and/or during remote data review. Data management, including DCFs, will be conducted in accordance with the study's Data Management Plan.

17.8 Investigator Responsibilities

The investigator is responsible for ensuring that the study is conducted according to the Clinical Trial Agreement, the protocol, IRB requirements and HIPAA. Specific responsibilities are listed in the Clinical Trial Agreement and this protocol.

Records and reports must remain on file at the investigational site for a minimum of two years after the completion/termination of this study. They may be discarded only upon written approval from ResMed and Inogen. The investigator must contact ResMed and Inogen before destroying any records and reports pertaining to the study to ensure that they no longer need to be retained. In addition, RCRI must be contacted if the investigator plans to leave the site to ensure that arrangements for a new investigator or records transfer are made prior to investigator departure.

17.8.1 Investigator Records

Records to be maintained by the investigator include:

- Protocol and all amendments
- Signed Clinical Trial Agreement
- Signed Financial Disclosure Forms
- IRB approval letter including consent and HIPAA authorization form(s)
- IRB Membership list or Letter of Assurance
- All correspondence relating to the study between the site and study sponsors and/or RCRI
- CVs and professional licenses for all investigators
- Site personnel signature and responsibility list
- Clinical monitor sign-in log
- Patient screening log
- The following records will be maintained for each patient enrolled in the study:
    - Patient-signed ICFs and HIPAA forms
    - Compete, accurate and current source documentation for CRFs
    - Adverse event reports and any supporting documentation
    - Protocol deviations
    - Complete medical records relative to the study

- Records pertaining to patient death during the study (including death records, death certificate, and autopsy report if performed).

The study sponsors reserve the right to secure data clarification and additional medical documentation on patients enrolled in this study at any time.

17.8.2 Investigator Reports

Investigators are required to prepare and submit reports to their respective IRB in accordance with the IRB's requirements.

17.8.3 Investigational Site Termination

The sponsors reserve the right to terminate an investigational site for any of the following reasons:

- Failure to secure patient informed consent or HIPAA authorization prior to enrollment
- Failure to properly report adverse events
- Repeated protocol violations
- Repeated failure to appropriately complete eCRFs
- Failure to enroll an adequate number of patients
- Loss of or unaccounted for study product inventory
- Administrative decision by the company

17.9 Protocol Amendments

Investigators may not modify this protocol without obtaining written concurrence of RCRI, the sponsors, and the IRB

17.10 Protocol Deviations

Any deviations from this protocol undertaken to protect the life or physical well-being of a patient in an emergency situation must be reported to RCRI within five working days of occurrence, and the respective IRB as soon as possible but in no event later than five working days after the emergency occurs. All protocol deviations must be reported on Protocol Deviation eCRF.

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