# Protocol

# POC-LEAN

# Evaluation of a Portable Oxygen Concentrator during Ambulation for Patients Who Require Supplemental Oxygen

This protocol has been written in accordance with current applicable guidelines as well as all other relevant additional references, medical and legal. The information herein is confidential and the property of ResMed. It is to be used in confidence for the conduct of the clinical study according to written agreement.

## ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Definition |
|---|---|
| **6MWT** | Six Minute Walk Test |
| **6MWD** | Six Minute Walk Distance |
| **AE** | Adverse event |
| **AO** | Ambulatory oxygen |
| **ATS** | American Thoracic Society |
| **COPD** | Chronic obstructive pulmonary disease |
| **EC** | Ethics committee |
| **EDC** | Electronic data capture |
| **ERS** | European Respiratory Society |
| **FDA** | U.S. Food and Drug Administration |
| **FiO2** | Fraction of inspired oxygen |
| **GCP** | Good Clinical Practice |
| **GP** | General practitioner |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent ethics committee |
| **IRB** | Institutional Review Board |
| **LTOT** | Long-term oxygen therapy |
| **LO** | Liquid oxygen |
| **mBORG** | Modified BORG Scale |
| **OC** | Oxygen concentrators |
| **POC** | Portable oxygen concentrator |
| **PPG** | Photoplethysmography |
| **SAE** | Serious adverse event |
| **SpO2** | Oxygen saturation |
| **TMF** | Trial Master File |

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## 1. Summary

**Design:** Prospective randomized study with a cross-over design.

**Device:** All participants entered into the study will be randomized to complete a 6MWT with either of the following devices, in a cross-over fashion and with a one-hour wash-out period between tests:

- Control device (portable oxygen cylinder) first; or
- Study device (Mobi™, POC) first.

**Objectives:** The primary objective of this study is to compare mean oxygen saturations (SpO2) between using the Mobi ™ and an oxygen cylinder during the Six Minute Walk Tests (6MWTs).

The secondary objective of this study is to evaluate the participant experience when using Mobi™ and an oxygen cylinder whilst walking, based on levels of dyspnea and distance covered during the 6MWTs.

**Primary Endpoint:** Mean SpO2 during Six Minute Walk Tests (6MWTs) for use of Mobi™ compared use of oxygen cylinder.

**Secondary Endpoints:**

- Distance covered during the 6MWTs
- Post-6MWT SpO2
- Time spent ≥ 90% SpO2 during 6MWT
- Participant acceptance questionnaire around ease of use and other aspects specific to portable oxygen use
- Dyspnea and fatigue levels measured by Modified Borg scale (mBorg)

**Enrollment:** Up to 32 participants who meet the inclusion and exclusion criteria are anticipated to be randomized for this study

**Study Site(s)** 1 site in the United States

**Selection Criteria:**

Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent.
3. Diagnosed with COPD and currently in a stable state (at least 4 weeks since last exacerbation episode[22]).
4. Current prescription for long-term oxygen therapy.
5. Participant meets the criteria for pulse-dose portable oxygen delivery, defined as being mobile within the home and the qualifying blood gas study was performed at rest/ awake or during exercise.
6. Participant can read and comprehend English.

Exclusion Criteria

Participants who meet any of the following exclusion criteria are not to be enrolled in this study:

1. Clinically unstable, which in the investigator's opinion, may jeopardize the participant's safety or compliance with the protocol.
2. Current oxygen therapy prescription which requires >5 L/min continuous flow.
3. Known or suspected contraindication for pulse-dose (e.g. using oxygen for life-sustaining or life-supporting purpose.
4. Unable to complete 6MWTs, e.g., unstable angina and myocardial infarction during the previous month.
5. Female who is pregnant, breast-feeding, or intends to become pregnant, or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

**Duration of study:** Participation can last up to a week, which includes a 1-hour Screening Visit, an optional 7-day screening period, and a 2.5-hour Visit 1. Screening Visit and Visit 1 may take place at the same day depending on the preference of participants, however, Visit 1 must be conducted entirely within one visit.

## 2. Introduction

The study will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practice (ICH-GCP)[1] and applicable regulatory requirements (Section 11.1.1). In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical study at a study site.

## 2.1 Background

### 2.1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow blockage and breathing-related problems. COPD was the third leading cause of death in the United States in 2014 and is projected to be the fourth leading cause of death worldwide and seventh in morbidity burden by 2030[1,3]. Smoking is by far the greatest risk factor for COPD. Other risk factors include exposure to air pollution, genetics, airway hyper-responsiveness, and poor lung growth during childhood[4]. 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 depend directly on the severity of a patient's condition. Therapy options for COPD symptoms include: smoking cessation, pharmacologic therapy, coaching on inhaler technique, vaccinations against respiratory diseases, and pulmonary rehabilitation[5].

### 2.1.2 Long-term oxygen therapy

Long-term oxygen therapy (LTOT) is prescribed for patients whose COPD is considered severe. LTOT is defined by the British Thoracic Society as ≥15 hours of oxygen use per day[6]. Oxygen is provided continuously to the patient in either a continuous-flow or pulsed delivery pattern. 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[7]. LTOT systems include oxygen concentrators (OC), liquid oxygen (LO) and portable oxygen concentrators (POCs). OCs remain the most economical way to provide oxygen at home. Many modern LTOT users are considered highly active and ambulatory when compared to their historic counterparts, who often were considered truly homebound[8, 9]. However, to comply with physician prescription to breathe oxygen for ≥ 15 hours per day, patients using many of the LTOT modalities are forced to stay at home and to limit their outdoor activities.

#### 2.1.2.1 Oxygen Cylinders – Liquid or Gas

Oxygen is delivered to the patient either via a flow meter attached to the cylinder or via an oxygen conservation device. Unlike continuous flow devices, oxygen conservation devices deliver oxygen predominantly during inspiration and therefore avoid wastage caused by oxygen flow during expiration. The most common oxygen conservation devices are 'demand flow', which deliver a pre-set volume or bolus of oxygen in early inspiration. Another type of oxygen conservation device consists of a nasal cannula set with an integrated pendant-shaped reservoir that fills with oxygen during exhalation and delivers a bolus of oxygen during subsequent inspiration.[10] A less efficient combination is the use of an OC at home and pressurized oxygen in small lightweight cylinder for ambulation. Need for frequent refilling and cumbersome logistics make this source less convenient[9], for this reason, POCs represent a higher level of convenience as compared to other ambulatory systems (e.g., LO)[8].

#### 2.1.2.2 Portable Oxygen Concentrators

Like stationary OCs, POCs separate nitrogen from ambient air and are capable of delivering 93–95% oxygen at a rate of 3–4 L/min. They are small and lightweight (maximum weight 4 kg for intermittent flow systems, or 9 kg for continuous flow systems) and can be powered by electricity, car, or rechargeable batteries[11]. Two types of POCs are available: continuous flow and pulse flow. Unlike continuous flow oxygen, pulse flow devices provide a pre-set oxygen bolus (measured in milliliters per breath) during the first 60% of inspiration thus reducing oxygen waste. The pulse flow system is capable of delivering the same volume of oxygen per breath, regardless of respiratory rate.

POCs, such as Mobi™, have been shown to help improve moderate to severe COPD patient's functional ability, quality of life, prevent emergency room encounters, and hospital admissions by increasing compliance with oxygen therapy[12]. There may be some improvements in quality of life with use of POCs compared with liquid oxygen cylinders, but study results are inconsistent[13].

### 2.2 Rationale for the Study

Mobi™ is a relatively new POC in the market and thus it is valuable to compare data from COPD patients using supplemental oxygen against data from Mobi™ use during ambulation. The purpose of the present study is to compare Mobi™ with a continuous flow oxygen cylinder, with mean SpO2 during a 6MWT as the primary endpoint.

## 3. Description of the Medical Devices

### 3.1 Portable Oxygen Concentrator (POC)

Mobi™ is indicated for patients who require supplemental oxygen, including COPD patients. It provides supplemental, high oxygen concentration to these patients. It is available via prescription only and may be used in the home, institution, and hospital settings, as well as travel environments as the Mobi™ is portable.

#### 3.1.1 Reprocessing the device

When the device is used for multiple patients, the device should be cleaned between each participant per the Mobi™ Provider Guide[15]. The nasal cannula and inlet air filter should be disposed of and replaced between patients.

### 3.2 Portable Oxygen Cylinder

Participant will use a portable, continuous flow E oxygen cylinder provided by the study site as a comparison.

### 3.3 Other Medical Devices

#### 3.3.1 $SpO_2$ Monitoring

Pulse oximeter oxygen saturation ($SpO_2$) and pulse rate are monitored continuously with approved devices.

##### 3.3.1.1 Oximeter

The PalmSat 2500 oximeter (Nonin Medical, Inc) will be used in this study. Trained study staff will place the oximeter on the patient's non-dominant forefinger just before beginning each 6MWT. This study staff representative will hold the oximeter device during the 6MWT, so they can continuously monitor the SpO2 levels of the patient during this assessment.

# 4. Objectives and endpoints

### 4.1 Objectives

#### 4.1.1 Primary objective

To compare mean oxygen saturations (SpO2) between using the Mobi TM and an oxygen cylinder during the Six Minute Walk Tests (6MWTs).

### 4.1.2 Secondary objective

To evaluate participant experience when using Mobi™ and an oxygen cylinder whilst walking, levels of dyspnea and distance covered during the 6MWTs.

## 4.2 Endpoint

### 4.2.1 Primary endpoint

Mean SpO2 during Six Minute Walk Tests (6MWTs) for use of Mobi™ compared use of oxygen cylinder.

### 4.2.2 Secondary endpoints

- Distance covered during the 6MWTs.
- Post-6MWT SpO2
- Time spent ≥ 90% SpO2 during 6MWT
- Participant acceptance questionnaire around ease of use and other aspects specific to portable oxygen use
- Dyspnea and fatigue levels measured by Modified Borg scale (mBorg)

# 5. Study Design

## 5.1 Study Design

This is a prospective, randomized, cross-over study design with participants serving as their own controls. Eligible participants will complete two 6MWTs: one while using portable oxygen cylinder and one while using Mobi™. All participants entered into the study will be randomized to complete a 6MWT with either of the following devices in a cross-over fashion, with a one-hour wash-out period between tests:

- Control device (portable oxygen cylinder) first; or
- Study device (Mobi™, POC) first.

## 5.2 Study Site(s)

One (1) site in the United States will be approved to enroll participants in this study. Minimum criteria for study site qualification will be documented in the site qualification questionnaire, and filed in the Trial Master Files. Sites that 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 site will be provided with the study documents necessary for IRB submission. Site readiness will be determined prior to enrollment of the first participant at the study site, and is contingent upon the electronic filing of final IRB approval letter and all other critical study documents.

## 5.3 Participant recruitment

The participants will be recruited by qualified study staff at the study site via flyer and/or telephone contact. Participants who may be interested in taking part will be told about the study details, and qualified study staff will go through the Informed Consent Form process with them. Participants are encouraged to ask questions and/or consult with family members with any questions on the study. Participant's that sign the Informed Consent Form may enroll into this study.

## 6. Study Population

Eligible COPD participants using home oxygen will be included in this study and the dropout rate is anticipated to be 5%.

### 6.1 Number of Study Participants

Number of participants planned to be screened: up to 100
Number of participants planned to be randomized: 32

### 6.2 Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Participant has given informed consent before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Participant is male or female, age ≥ 18 years, at the time of signing informed consent.
3. Participant has been diagnosed with COPD and is currently in a stable state (at least 4 weeks since the last exacerbation episode).
4. Participant is currently prescribed long-term oxygen therapy.
5. Participant meets the criteria for pulse-dose portable oxygen delivery. Criteria is defined as being mobile within the home and has undergone a qualifying blood gas study at rest (awake) or during exercise.
6. Participant can read and comprehend English.

### 6.3 Exclusion Criteria

Participants who meet any of the following exclusion criteria are not to be enrolled in this study:

1. In the investigator's opinion, participant is clinically unstable and their participation may jeopardize the participant's safety or compliance with the protocol.
2. Participant is currently prescribed long-term oxygen therapy of >5 L/min continuous flow.
3. Participant has a known or suspected contraindication for pulse-dose oxygen (e.g. using the device for life-sustaining or life-supporting purposes).
4. Participant is unavailable to complete 6MWTs (e.g., unstable angina and myocardial infarction during the previous month[16]).
5. Participant is a female who is pregnant, breast-feeding, or intends to become pregnant, or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measure as required by local regulation or practice).

## 7. Study Procedures

Participation includes a 1-hour Screening Visit, up to 7-days screening period (optional), and a 2.5-hours Visit 1. Screening Visit and Visit 1 may be combined depending on the preference of participants. Each participant is to attend both visits at the site. The Investigators must document any deviation from study procedures and notify ResMed.

### 7.1 Screening Visit

7.1.1 Participants will be screened to determine eligibility for participation in the study. Before any study-related activity, the Investigator or designee must provide the subject with the Informed Consent Form, explaining the trial and the procedures involved. Each potential

participant must sign and date the Informed Consent Form before any study-related activities are performed. Once a person agrees to participate in this trial, by signing and dating the Informed Consent Form, the following will be performed and documented at screening:

### 7.1.2 **Demography**

Demography will be recorded in the eCRF at screening and consists of:

- Date of birth
- Sex
- Ethnicity
- Race

### 7.1.3 **Body weight and height**

Body weight (with an empty bladder, without shoes and only wearing light clothing) must be measured and recorded in the eCRF in kilogram or pound (kg or lb), to one decimal place. The body weight should be assessed on the same scale throughout the study, if possible.

Height (without shoes) is measured in centimeters or inches (cm or in), and recorded in the eCRF to the nearest ½ cm or ¼ inch.

### 7.1.4 **COPD history and comorbidities**

- Date of diagnosis of COPD
- Stage of COPD, if known
- Comorbidities
- History of Pulmonary Rehabilitation: last date of Pulmonary Rehabilitation

### 7.1.5 **Medical history**

Medical history is a medical event that the participant has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

The information collected for medical history includes diagnosis, date of onset and date of resolution or continuation, as applicable.

### 7.1.6 **Concomitant medication**

In this study, only medications related to respiratory disease will be collected, as well as if a participant is using an antianginal medication. All relevant medications in use at time of screening through completion of the study will be recorded.

Details of any concomitant medication must be recorded at the screening visit. Changes in concomitant medication must also be recorded (for example, if participant completes Visit 1 on a different date than Screening visit).

### 7.1.7 **Oxygen prescription** [24]

- Long-term oxygen therapy history
- POC use history
- Normal practice with oxygen use during ambulation/exertion

Participants meeting all of the inclusion criteria and none of the exclusion criteria are qualified to enroll in this study. A qualified participant can continue to Visit 1 immediately, or return to the investigational site within 7 days.

## 7.2 **Visit 1**

Eligible participants will be randomized into one of two study groups, which will define the order in which they use the control device or Mobi™ device during the 6MWT. The overall Visit 1 procedure is presented graphically in Figure 7-1:

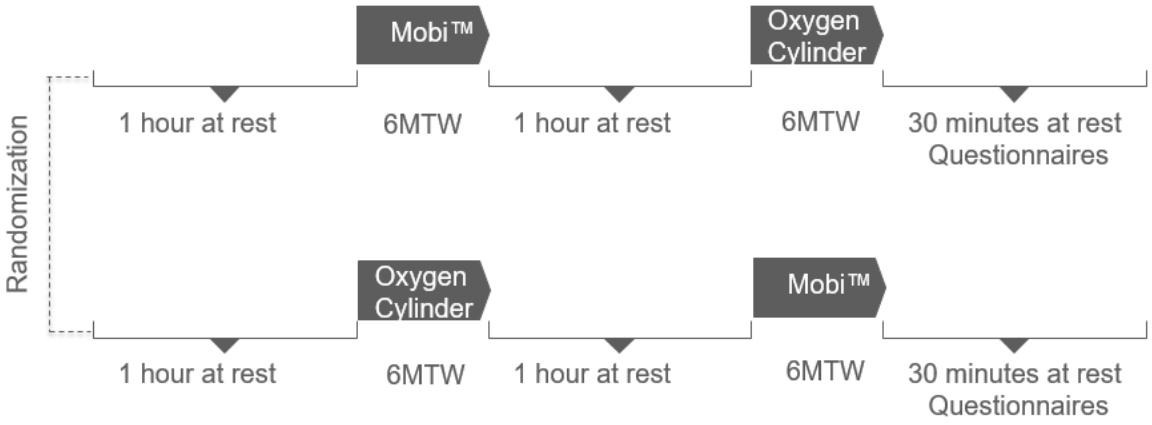


Figure 7-1

The order of 6MWTs will be randomized within the EDC, and in each of the two 6MWTs the participants will use either:

- Mobi™; or
- A portable oxygen cylinder.

Site staff will pull the oxygen cylinder via a trolley or carry the Mobi™ device via its carrying bag. This will ensure consistency across tests. 6MWTs will be conducted according to current ERS/ATS field test guidelines[16,17].

### 7.2.1 **Prior to 6MWT**

Prior to 6MWT, the following will be performed and documented:

#### 7.2.1.1 **Oxygen titration**

Each participant will undergo titration using Mobi™ to reach SpO2 of ≥90%. After the Mobi™ titration, each participant will rest for at least 1 hour while breathing their supplemental oxygen device to obtain resting SpO2 levels. Participants shall have a resting SpO2 of ≥90% prior to starting each 6MWT.

During use of the oxygen cylinder 6MWT, the settings will be based on the patient's original prescription.

During the use of the Mobi™ device 6MWT, the patient will use Mobi™ based on the titrated Mobi™ setting.

After starting therapy, the site staff should also wait for approximately 5 minutes to make sure no alarms turn on. Both of these oxygen system settings will be recorded.

#### 7.2.1.2 **Vital signs**

- Respiratory rate
- Systolic and diastolic blood pressure should be measured in a sitting position after the participant has been resting and by using the standard clinical practice at the site.
- Pulse (beats per minute) must be recorded after the participant has been resting for 5 minutes in a sitting position.

#### 7.2.1.3 **Modified Borg scale**

Each participant will rate their baseline dyspnea and fatigue levels using the modified Borg scale (see Appendix 4) and move to the starting point

### 7.2.2 **During 6MWT**

During each 6MWT, the following will be measured[25]:

- $SpO_2$
- Time to participant's first rest, if applicable
- Distance at point of participant's first rest, if applicable
- Number of rest times, if applicable
- 6MWD

If the participant uses walking aids (cane, walker, etc.), these aids should be used during each 6MWT.
Trained study staff will walk alongside the participant for each 6MWT. This study representative will carry the SpO2 monitor, and monitor the participant during the walk, assessing for any variables that may require the participant to rest or terminate the test (eg: study representative may terminate the 6MWT if the participant's SpO2 is below 80%).

### 7.2.3 **Post 6MWT**

Post each 6MWT, participants will record

- Respiratory rate
- Pulse (beats per minute)
- Post-walk dyspnea and fatigue levels measured by the Modified Borg scale

Before the next 6MWT, participants will rest for at least 1 hour breathing their supplemental oxygen device prior to switching to the alternate device for the second test.

After each of the two 6MWTs, participants will complete a participant acceptance questionnaire involving questions about ease of use and other aspects specific to portable oxygen use.

## 7.3 **End of Study**

End of study is considered to be the completion of Visit 1. There is no follow up period.

# 8. Adverse Events

## 8.1 Definitions

### 8.1.1 Adverse Event

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in participants, whether or not related to the investigational medical device.

An AE includes:

- A clinically significant worsening of a pre-existing condition.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening or other study procedures performed before exposure to study product (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first study related activity after the participant has signed the informed consent.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** - no or transient symptoms, no interference with the participant's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the participant's daily activities.
  - **Severe** - considerable interference with the participant's daily activities; unacceptable.
- **Causality**
  Relationship between an AE and device(s):
  - **Unrelated:** The event is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.
  - **Unlikely 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
- **Final outcome**
  - **Recovered/resolved** - The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study -related activity after the participant signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the participant is expected to recover from the event. This term is only applicable if the participant has completed the study or has died from another AE.

- **Recovered/resolved with sequelae** - The participant has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved** - The condition of the participant has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal** - This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
- **Unknown**

### 8.1.2 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 participant that:
  - results in a life-threatening illness or injury,
  - results in permanent impairment of a body structure or body function,
  - requires inpatient hospitalization or prolongation of existing hospitalization,
  - results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

### 8.1.3 Anticipated Adverse Events

Warnings, contraindications, and hazards are outlined in the User Manual for Mobi™ and should be reviewed with participants when they receive their study devices. All study devices are to be used in accordance with their respective approved, current instructions found in the manual[14]. Anticipated adverse events include events that are reasonably expected to occur as a result of the participant's disease state or treatment.

#### 8.1.3.1 COPD-related Anticipated Adverse Events:

- COPD exacerbation and related symptoms anticipated during this study include:
  - Cough
  - Dyspnea (shortness of breath)
  - Excessive mucus production
  - Wheezing
  - Chest tightness
  - Cyanosis
- Lack of energy (fatigue)

#### 8.1.3.2 LTOT-related Anticipated Events[18]:

Adverse events associated with LTOT during this study include, but are not limited to, the following:

- Nosebleed
- Dry mouth
- Dry throat
- Headache

- Tripping/falling over equipment
- Noise irritation

## 8.2 Adverse Event Assessment and Reporting

### 8.2.1 Adverse Event Assessment

Adverse event information will be collected on all participants. At every participant encounter throughout the study, the investigator will inquire about adverse events since the last encounter.

### 8.2.2 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; if requested, these documents are to be de-identified, labeled with the participant number, and an email will be promptly provided or uploaded to the electronic study database. Adverse events will be evaluated by the investigator and classified for seriousness (as defined in Section 8.1.2), relatedness, and severity.

### 8.2.3 For US only: 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 death 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.

### 8.2.4 Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error or inadequate labelling.

The investigator shall record every Device Deficiencies with assessment on the study Case Report Forms (CRF) (paper or electronic).

All Device Deficiencies assessed by the investigator that may have led to (had the potential to lead to) an SAE, if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate are treated as the same reporting category as SAEs and must be reported accordingly to the SAE process

# 9. Risk and Benefits

## 9.1 Potential Risks

Refer to Section 8.1.3 for a list of potential risks.

### 9.1.1 Minimization of Risks

This study involves the use of a FDA-cleared, Class II medical device and CE marked devices that deliver oxygen therapy with no greater than minimal risk to participants. All study devices will be used in accordance with their respective approved indications and instructions.

As per FDA good practice guidelines (21 CFR 10.115), this study protocol as well as the Mobi™ device was assessed for risk to participants. As this study does not meet the definition of significant risk as defined by 21 CFR 812.3(m), the investigative team has determined that this protocol and the Mobi device is non-significant risk. All participants will maintain all other therapy regimens per standard clinical care; this protocol does not dictate any other adjustments to the participants' care regimen and there are no protocol-required assessments or procedures that pose significant risk to the participants. As required by the FDA, the IRB will review this study protocol and make the final determination of NSR designation.

Participants should be encouraged to discuss any issues they are having with therapy during the study. The investigator should assess for changes in the health or well-being of the participant in response to general, non-directed questioning (e.g., "How are you feeling while using the therapy?"). Side effects should be documented on the site's source documents. Furthermore, if during the evaluation the participant cannot complete an assessment, the participant may sit down until they feel stable to continue. Potential expected adverse events are believed to be mild and similar to other commercially available POC systems.

The attending study staff have experience setting up the eligible patient population in this study. All participants return to their current oxygen therapy after completing the study visits.
The following will be performed to minimize risks:

#### 9.1.1.1 **Safety assessments**

During this study, participants SpO2 and heart rate will be monitored before, during and immediately following the walk to ensure devices connectivity and to ensure participant safety[19].

#### 9.1.1.2 **Site staff training and experience**

A delegated site staff will be present during each session with participants. A delegated site staff should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician) are also desirable.

#### 9.1.1.3 **6MWT guidelines compliance**

6MWTs will be conducted according to the guidelines (ERS/ ATS) and participants will be followed by a delegated site staff. Safety check points for immediately stopping a 6MWT in ERS/ ATS guideline will be undertaken to minimize risk associated with this test. A delegated site staff must recognize these problems and the appropriate responses. If in their clinical judgment there are signs of participant distress, the test session will be stopped and participants will be returned to their current oxygen device.

### 9.2 **Potential benefits**

There may be no benefits to participants from taking part in the study. Benefits during the study may include:

- Symptomatic relief from dyspnea.
- Maintenance of SpO2 during 6MWTs.

However, it is not expected that these benefits will last longer than the duration of the study.

## 10. Statistical Considerations

### 10.1 Primary Objective and Endpoint

The primary endpoint is mean $SpO_2$ measured during a 6 Minute Walk Test (6MWT). The primary aim of this protocol is to show non-inferiority between the Mobi oxygen device and the control device with respect to mean $SpO_2$ during the 6MWT.

The null and alternative hypothesis is based on a one-sided non-inferiority test using a non-inferiority margin (NIM) of 2%.

$H_0$: $\mu_A - \mu_B \leq$ -NIM (Mobi is inferior)

$H_1$: $\mu_A - \mu_B >$ -NIM (Mobi is non-inferior)

where $\mu_A$ and $\mu_B$ are the mean $SpO_2$ after using the Mobi device (A) and the Control device (B), respectively, and NIM equals the non-inferiority margin. A significant level of 0.025 will be used.

### 10.2 Analysis Populations

The populations are defined as follows.

- The Intent-To-Treat (ITT) is defined as all patients who meet the inclusion/exclusion criteria and begin the first 6MWT.
- The Completed Cases (CC) population is defined as all patients in the ITT population who complete both the first and second 6MWTs.

The primary endpoint analysis will be based on the CC participant population. A participant may rest during the 6MWT and still complete the test, however if the participant stops completely then the 6MWT will be considered incomplete. A sensitivity analysis of the primary endpoint will be generated for the ITT population. The ITT population may contain some participants who complete the first study 6MWT but not the second study 6MWT. This will require the use of imputation methods for missing values which are documented in Section 10.9.

All safety analyses will be generated for participants in the ITT population. All secondary endpoints will be generated using the CC population.

### 10.3 Statistical Analysis of the Primary Endpoint

The primary hypothesis will be tested using a cross-over Analysis of Variance test (ANOVA). Specifically, a repeated-measures ANOVA with fixed treatment and period effect and random participant effects will be fit to the data. The mean difference between treatment effects will compared to a non-inferiority margin of -2%, using a Wald test. Additionally, the 97.5% lower one-sided confidence bound for the mean paired difference in mean $SpO_2$ between the Mobi device and the Control device will be calculated.

### 10.4 Justification of Sample Size

Based on a study by Khor et al.[26], evaluating the clinical effectiveness of the Inogen One G2 device compared to Continuous Oxygen Cylinder, the observed mean (standard deviation) in mean $SpO_2$ during the 6MWT was 82.3% (3.5) for Inogen and 80.3% (2.2) for continuous oxygen. For estimating the SD of the difference, we assume that the SD for the Mobi device will be similar to the Inogen One G2 results. The within patient correlation is assumed to be small, r=0.2. The standard deviation of the difference is 3.74, estimated using the following formula: sqrt($SD1^2$ +

$SD2^2 – (2*r*SD1*SD2))$, where SD1 and SD2 are the standard deviations for each study treatment and r is the correlation between the repeated measures (within a participant).

Assuming a standard deviation of the difference is 3.74, a true mean difference between treatments of 0, and one-sided significance level of 0.025, a sample size of 30 provides 80% power to detect non-inferiority when the non-inferiority margin is -2.0. This sample size was generated using the Non-Inferiority Tests for the Difference Between Two Means in a 2x2 Cross-over Design procedure, PASS Version 2019 software[27]. Since both treatments will be completed during the same visit, a small drop-out rate is assumed at 5%. Thus, a total of 32 (30/0.95) participants will be enrolled in the study, each participant randomized with respect to the order of treatment.

## 10.5 General Statistical Analysis Guidelines

Descriptive statistics will be used to summarize both continuous and categorical endpoints. The number of observations, mean, median, standard deviation, standard error, minimum and maximum will be calculated for continuous variables, unless otherwise stated. The number of significant digits reported will be as follows: minimum and maximum will have the same number of significant digits as the raw data; the mean, median, standard deviation, and standard error will be reported with one more significant digit than the raw data. Frequencies and percentages will be calculated for categorical data using one significant digit for percentages.

## 10.6 Baseline Characteristics and Medical History

Demographic, baseline characteristics (age, sex, ethnicity, race, BMI), medical history and concomitant medications collected during the screening visit will be summarized descriptively for the ITT population. For continuous variables, the mean, standard deviation (SD), number evaluated, median, minimum and maximum will be provided. For categorical variables, the number with the characteristic, the number evaluated, and the percentage will be presented

## 10.7 Statistical Analysis of Secondary Endpoints

Secondary endpoints include post-6MWT oxygen saturation (SpO2), distance walked during the 6MWT (6MWD), time spent ≥90% SpO2 during 6MWT, pre and post-6MWT modified Borg Dyspnea Scale, and acceptance questionnaires comparing patient experience and comfort between Mobi and Control treatments. Descriptive statistics will be presented for each secondary endpoint by treatment group, including mean, standard deviation, median, median, inter-quartiles, minimum and maximum values. A cross-over ANOVA with fixed treatment and period effects and random subject effects will be used to summarize the difference in means between treatment groups and the associated 95% confidence intervals for each secondary endpoint.

## 10.8 Safety Analyses

A listing of all adverse events occurring during the study period will be generated including all participants in the ITT population. The listing will include the event description, time of occurrence, severity, outcome and action taken.

## 10.9 Handling of Missing Values

The primary endpoint analysis will be based on the CC population. A sensitivity analysis will be done using the ITT population and a mixed-effects cross-over analysis. The mixed-effects analysis uses maximum likelihood to estimate parameters when there are missing values and is appropriate when data is missing at random (MAR).

# 11. Responsibility

## 11.1 Investigator Responsibilities

### 11.1.1 Statement of Compliance

This study shall be conducted:

- In accordance with the ethical principles that have their origin in the Declaration of Helsinki[20];
- FDA good practice guidelines (21 CFR 10.115)
- In compliance with ISO14455:2011: the National Statement on Ethical Conduct in Human Research[21];
- Under ethics approval;
- Under regulatory approval; and
- With appropriate insurance.

### 11.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Ethics Committee (EC) Review and Approval

The Investigator (or sponsor, as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC/EC. The Investigator will not begin any study participant activities until approval from the IRB/IEC/EC has been documented and provided as a letter to the Investigator. Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC/EC of any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC/EC approval, with the exception of those necessary to reduce immediate risk to study participants.

### 11.1.3 Informed Consent Process

Written informed consent shall be obtained for all study participants. Informed consent involves the process through which potential participants learn about the study, and make the informed decision on whether they wish to take part. This includes the participant being able to ask any questions they may have, and have ample time to consider the study. The participant is encouraged to consult with their GP and/or family members before making the decision to participate in the study.

All participation is voluntary and participants have the right to withdraw at any time for any reason.

Informed consent shall be gained through the researcher explaining the study to the participant, allowing them to read the participant information statement and informed consent form, and ask any questions they may have. If they are happy to continue they should sign and date the consent form. The investigator will then also sign and date the form. A second copy will be signed for the participant's records.

### 11.1.4 Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only partial date of birth (as applicable in certain countries), another unique identifier (as allowed by local law), and an identification code will be recorded to the Sponsor or IRB/IEC/EC.

NOTE: The investigator must keep a screening log showing codes, names, and addresses for all participants screened and for all participants enrolled in the study. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from ResMed, including but not limited to this protocol, eCRFs, the device, and any other study information, remain the sole and exclusive property of ResMed during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from ResMed. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

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