

CLINICALTRIALS.GOV ADMINISTRATIVE COVER PAGE**STUDY PROTOCOL**

Official Title

A Phase II Randomized Crossover Pilot Study to Assess Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients With Obstructive Sleep Apnea

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SRC-301124-Trillium Pilot

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Clinical Investigation Plan

Project:

Trillium

Study Title:

A Phase II Randomized Crossover Pilot Study to Assess Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea

Study Identification Number:

SRC-301124-Trillium Pilot

Study Sponsor:

Philips RS North America LLC f/k/a Respireonics, Inc.
1010 Murry Ridge Ln
Murrysville, PA 15668 USA

Legal Representative (if applicable):

N/A

Study Funding:

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

Document Control Page

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Title: Clinical Study Manager

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Details on safety event types, reporting methods, and reporting timelines are provided in Section 15.

Investigator Agreement

As Investigator of the study entitled “A Phase II Randomized Crossover Pilot Study to Assess Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea”; Protocol ID: SRC-301124-Trillium Pilot I agree to:

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

Investigator Signature: _____ **Date:** _____

Printed Name: _____

Table of Contents

Document Control Page	3
Investigator Agreement	4
Table of Contents	5
1 Clinical Investigation Synopsis	8
2 Purpose/Introduction	12
3 Study Products	12
3.1 Investigational Device(s)	12
3.2 Comparator(s)	13
3.3 Technical & Functional Features of the Device(s)	13
3.4 Other Study Products	16
4 Objectives, Endpoints & Hypotheses	17
5 Design of the Clinical Investigation	26
5.1 General Information	26
5.2 Subjects	26
5.2.1 Vulnerable Population	26
5.2.2 Eligibility Criteria	26
5.3 Minimization of Bias	28
6 Study Procedures	28
6.1 Pre-Screening	29
6.2 Recruitment Methods	29
6.3 Visit 1 (Baseline Visit)	29
6.3.1 Informed Consent Process	29
6.3.2 Mask Fitting and Use	30
6.4 Visit 2 (First Follow-Up Visit)	30
6.4.1 Mask Survey	30
6.4.2 Review of AEs	30
6.4.3 Sleepiness and Health-Related Quality of Life	30
6.4.4 Collection of Device Data	31
6.4.5 Mask Fitting and Use	31
6.5 Visit 3 (Second Follow-Up Visit)	31
6.5.1 Mask Survey	31
6.5.2 Review of AEs	31
6.5.3 Sleepiness and Health-Related Quality of Life	31
6.5.4 Collection of Device Data	31
6.6 Unscheduled Phone Calls	31
6.7 Completion	32
6.7.1 Subject	32

6.7.2 Clinical Investigation	32
6.8 Participant Compensation.....	32
6.9 Arrangements for Subjects Following Participation	32
6.10 Suspension or Premature Termination	32
6.10.1 Subject.....	32
6.10.2 Clinical Investigation	33
7 Statistical Design & Analysis.....	33
7.1 Determination of Sample Size.....	33
7.2 General Considerations.....	33
7.3 Populations for Analysis.....	34
7.3.1 Performance Analysis Set.....	34
7.3.2 Safety Analysis Set	34
7.4 Participant Disposition	34
7.5 Statistical Analysis	34
7.5.1 Primary Outcome Analysis	34
7.5.2 Pass/Fail Criteria	34
7.5.3 Subgroup Analysis	34
7.5.4 Multiplicity Control	34
7.5.5 Level of Significance	34
7.5.6 Multicenter Investigations	35
7.5.7 Management of Bias	35
7.6 Participant Accountability and Missing Data	35
7.7 Safety Analysis.....	35
7.8 Interim Analysis.....	35
7.9 Exploratory Analysis.....	35
7.10 Deviations from Planned Analysis.....	35
8 Data Management	35
8.1 Case Report Forms	35
8.2 Documentation Collection and Maintenance	36
9 Quality Assurance/Quality Control	37
9.1 Monitoring Plan	37
9.2 Training	37
10 Benefits & Risks.....	37
10.1 Benefits	37
10.2 Risks.....	37
10.3 Benefit–Risk Ratio	38
11 CIP Modifications/Amendments & Deviations	38
11.1 Modifications/Amendments	38

11.2 Deviations	38
12 Product Accountability.....	39
13 Confidentiality.....	39
14 Statements of Compliance	40
15 Safety Monitoring	40
15.1 Definitions of Reportable Events	40
15.1.1 Definition of Adverse Event (AE).....	40
15.1.2 Definition of Serious Adverse Event (SAE)	40
15.1.3 Definition of Adverse Device Effects (ADE).....	40
15.1.4 Definition of Serious Adverse Device Effects (SADE)	40
15.1.5 Definition of Device Deficiencies (DD)	40
15.2 Foreseeable Adverse Events	40
15.3 Adverse Event Classification	41
15.3.1 Expected Side Effects	41
15.3.2 Other Adverse Events	42
15.4 Relationship of Adverse Event to the Study Product.....	42
15.5 Reporting Process	42
15.5.1 Adverse Event, Adverse Device Defect, and Device Deficiencies Reporting	42
15.5.2 Serious Adverse Event or Serious Adverse Device Effect	43
15.6 Data Safety Monitoring.....	43
16 Publication Policy	43
17 Bibliography	43
18 Choice of Evaluators.....	48
19 Appendices.....	48
20 Record Version History	49

1 Clinical Investigation Synopsis

Table 1. Protocol Synopsis

Clinical Investigation Title	A Phase II Randomized Crossover Pilot Study to Assess Clinical Safety, Performance and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea
Clinical Investigation ID	SRC-301124-Trillium Pilot
Project Name	Trillium
Sponsor Name and Address	Philips RS North America LLC f/k/a Respireonics, Inc. 1010 Murry Ridge Ln Murrysville, PA 15668 USA
Participating Location and Country	Florida Lung & Sleep Associates <u>Study Records Storage</u> 2625 Lee Blvd., Suite 100 Lehigh Acres, FL 33971 USA <u>Study Conduct</u> 14651 Palm Beach Blvd, Suite 105 Fort Myers, FL 33905
Investigational Device	Trillium Full Face Mask
Comparator	ResMed AirFit F20 Full Face Mask
Purpose/Introduction	Sleep disordered breathing (SDB) is characterized by an abnormal respiratory pattern during sleep and is highly prevalent in the general population. One example is obstructive sleep apnea (OSA), which accounts for 80–90% of SDB cases. OSA is a chronic condition characterized by repetitive and partial or complete pharyngeal collapse during sleep and is accompanied by strenuous breathing efforts leading to sleep disruption, arousals, and oxyhemoglobin desaturation. A number of significant potential consequences of untreated OSA have been described in the literature including coronary artery disease, stroke, peripheral vascular disease, heart failure, cardiac arrhythmias, and death from cardiovascular disease.¹ A broad range of therapy options exist today to treat OSA. However, positive airway pressure (PAP) therapy is the gold standard treatment for OSA, and it has been used since the early 1980s.^{2,3} PAP therapy is the recommended therapy to treat OSA symptoms and nocturnal hypoxemia.⁴ PAP therapy results in a clinically significant reduction in OSA severity and sleepiness and is associated with reduced blood pressure and motor vehicle accidents.⁵ PAP therapy is provided non-invasively using a patient interface, most typically a mask, which may be oronasal (full face), nasal, or nasal pillows. However, skin issues (i.e., localized skin irritation, breakdown, lesions, and/or peeling), mask leaks, dryness and irritation (i.e., oral, nasal, upper airway, and eye), anxiety (related to claustrophobia), and general discomfort are commonly associated with masks.^{6,7} These issues can be exaggerated by poor fit and among traditional, over-the-nose (OTN) full-face masks (FFMs) due to their large, bulky designs. Considerable evidence indicates that mask comfort and fit strongly influence therapy adherence. And, since therapy adherence is critical to achieving the clinical benefits of therapy, mask design is very important.^{3,5,7–11} As such, it is crucial that sufficient clinical evidence is obtained to support the suitability of new mask designs. The Trillium FFM is being developed to help address issues with traditional, OTN FFMs on the market today. The cushion and patented wrap back-style headgear are designed to reduce pressure points on the face and back of the neck, respectively. The dual durometer cushion uses a softer silicone for comfort and a more rigid silicone to maintain the cushion's shape and seal under higher pressures. The present clinical investigation described in this clinical investigation plan (CIP) aims to objectively evaluate clinical safety, clinical performance, and clinical benefit of the Trillium FFM. This CIP uses a randomized crossover study design to measure clinically relevant outcomes with

Table 1. Protocol Synopsis

	prespecified acceptance criteria among patients with OSA that are already established on PAP therapy.
Clinical Development Stage	Pre-Market Pilot Clinical Investigation Using Production-Equivalent Trillium FFM devices
Objectives	This clinical investigation has three objectives: • Clinical Safety—To objectively evaluate the clinical safety profile of the Trillium FFM. • Clinical Performance—To objectively and subjectively evaluate the clinical performance of the Trillium FFM. • Clinical Benefit—To objectively and subjectively evaluate the clinical benefit of the Trillium FFM.
Endpoints	This clinical investigation has following endpoints: • Clinical Safety— ○ AE Rate for Skin Effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling) ○ AE Rate for Oronasal Dryness ○ AE Rate for Eye-Related Side Effects ○ AE Rate for Anxiety ○ AE Rate for Allergic Reaction ○ AE Rate for Headache • Clinical Performance— ○ Device Detected Unintentional Leak ○ Subjective Patient-Reported Comfort of Breathing • Clinical Benefit— ○ Device Detected Apnea-Hypopnea Index (AHI) ○ Device Use (Proxy for Therapy Adherence) ○ Subjective Epworth Sleepiness Scale (ESS) Score ○ Subjective European Quality of Life-5D (EQ-5D) Score
Subject Population	Approximately 40 participants will be enrolled and randomized, with 35 subjects expected to complete all study procedures. <u>Inclusion Criteria</u> • Aged 21–85 years (inclusive) • Diagnosed with OSA • Established on PAP therapy for ≥90 days at the time of consent • Currently prescribed and using fixed pressure, Auto CPAP, or BiPAP therapy on a regular basis (average PAP usage of ≥4 hours/night, ≥4 days per week for ≥3 months) • Able to read, write, speak and understand English • Willing and able to provide informed consent • Willing and able to follow instructions and complete all activities required by the study • Able to remove a sleep apnea mask without assistance • Currently using a ResMed PAP therapy device with a connection to ResMed’s AirView system • Currently using ResMed AirFit F20 <u>Exclusion Criteria</u> • Significant risk of aspiration (i.e., active vomiting or taking a prescription drug that induces vomiting) • Known allergy to silicone, latex, polyamide (nylon), spandex, polyurethane, acetal, polycarbonate, or polypropylene • Active infection or inflammation in an area in contact with the mask • Recent head or facial surgery unless cleared by a healthcare provider to resume regular therapy • Planned head or facial surgery during the study • Any congenital or acquired craniofacial malformations or abnormalities, acute trauma, or burns that would interfere with the mask’s placement or ability to deliver therapy

Table 1. Protocol Synopsis

	- Employee or family member who works for Philips or any of its direct competitors in the sleep industry - Prescribed oxygen at night or continuously - Currently participating in another interventional research study or planned participation in another interventional clinical research study during the trial period - Prescribed an ASV (adaptive servo-ventilation) device - Prescribed mechanical ventilation - Pre-existing conditions such as bullous lung disease, pathologically low blood pressure, bypassed upper airway, pneumothorax, pneumocephalus, cerebral spinal fluid (CSF) leaks - Any unstable medical condition (e.g., uncontrolled cardiac, lung, or neurological disease) or limitation that would affect the participant's ability to complete trial activities - Experiencing any acute illness (e.g., acute sinusitis, ear or eye infections, upper respiratory infections, pharyngitis, bronchitis, pleurisy, pneumonia, or facial dermatitis) that would impact their ability to use the mask and/or PAP therapy during the trial - Pregnant (self-report) - Advised by a health care provider to avoid magnets - Patient or patient's household member, caregiver or bed partner in close vicinity that have implanted devices that may be affected by magnets, including but not limited to: - Pacemakers - Implantable cardioverter defibrillators (ICD) - Neurostimulators - Magnetic metallic implants/electrodes/valves placed in upper limbs, torso, or higher (i.e., neck and head) - Cerebral spinal fluid (CSF) shunts (e.g., ventriculo peritoneal (VP) shunt) - Aneurysm clips - Emboloc coils - Intracranial aneurysm intravascular flow disruption devices - Metallic cranial plates, screws, burr hole covers, and bone substitute devices - Metallic splinters in the eye - Ocular implants (e.g., glaucoma implants, retinal implants) - Certain contact lenses with metal - Implants to restore hearing or balance that have an implanted magnet (such as cochlear implants, implanted bone conduction hearing devices, and auditory brainstem implants) - Magnetic denture attachments - Metallic gastrointestinal clips - Metallic stents (e.g., aneurysm, coronary, tracheobronchial, biliary) - Implantable ports and pumps (e.g., insulin pumps) - Hypoglossal nerve stimulators - Implanted devices labeled as MR (magnetic resonance) unsafe - Magnetic metallic implants not labeled for MR or not evaluated for safety in a magnetic field - Paralysis of the hemi-diaphragm
Study Design	This will be a single-center, open-label randomized crossover design pilot study to evaluate the clinical safety, clinical performance, and clinical benefit of the Trillium FFM.
Duration of the Clinical Investigation	There are 3 visits planned for this clinical investigation. This study is expected to last approximately 30 days for each participant. The total time of execution (i.e., first subject enrolled to last subject completed) is expected to be approximately 45 days.
Statistical Considerations	This is the first clinical investigation of the final design of the Trillium FFM in patients with OSA. The data will be used to assess the performance and safety of the Trillium FFM, and to assess

Table 1. Protocol Synopsis

	the appropriateness of acceptance criteria. Accordingly, statistical models may be used, but all analyses will still be considered informative in nature. For continuous outcomes, liner mixed effect models will be used to estimate treatment effects. The models will account for the crossover design of the study and may adjust for covariates or other factors deemed relevant and appropriate. For categorical outcomes, results will be summarized using frequency counts and percentages.
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2 Purpose/Introduction

Sleep disordered breathing (SDB) is characterized by an abnormal respiratory pattern during sleep and is highly prevalent in the general population. One example is obstructive sleep apnea (OSA), which accounts for 80–90% of SDB cases. OSA is a chronic condition characterized by repetitive and partial or complete pharyngeal collapse during sleep and is accompanied by strenuous breathing efforts leading to sleep disruption, arousals, and oxyhemoglobin desaturation. A number of significant potential consequences of untreated OSA have been described in the literature including coronary artery disease, stroke, peripheral vascular disease, heart failure, cardiac arrhythmias, and death from cardiovascular disease.¹

A broad range of therapy options exist today to treat OSA. However, positive airway pressure (PAP) therapy is the gold standard treatment for OSA, and it has been used since the early 1980s.^{2,3} PAP therapy is the recommended therapy to treat OSA symptoms and nocturnal hypoxemia.⁴ PAP therapy results in a clinically significant reduction in OSA severity and sleepiness and is associated with reduced blood pressure and motor vehicle accidents.⁵

PAP therapy is provided non-invasively using a patient interface, most typically a mask, which may be oronasal (full face), nasal, or nasal pillows. However, skin issues (i.e., localized skin irritation, breakdown, lesions, and/or peeling), mask leaks, dryness and irritation (i.e., oral, nasal, upper airway, and eye), anxiety (related to claustrophobia), and general discomfort are commonly associated with masks.^{6,7} These issues can be exaggerated by poor fit and among traditional, over-the-nose (OTN) full-face masks (FFMs) due to their large, bulky designs. Considerable evidence indicates that mask comfort and fit strongly influence therapy adherence. And, since therapy adherence is critical to achieving the clinical benefits of therapy, mask design is very important.^{3,5,7–11} As such, it is crucial that sufficient clinical evidence is obtained to support the suitability of new mask designs.

The Trillium FFM is being developed to help address issues with traditional, OTN FFMs on the market today. The cushion and patented wrap back-style headgear are designed to reduce pressure points on the face and back of the neck, respectively. The dual durometer cushion uses a softer silicone for comfort and a more rigid silicone to maintain the cushion's shape and seal under higher pressures.

The present clinical investigation described in this clinical investigation plan (CIP) aims to objectively evaluate clinical safety, clinical performance, and clinical benefit of the Trillium FFM. This CIP uses a randomized crossover study design to measure clinically relevant outcomes with prespecified acceptance criteria among patients with OSA that are already established on PAP therapy.

3 Study Products

3.1 Investigational Device(s)

The Trillium Full Face Mask (FFM) (Philips Respironics, Murrysville, PA) is an over-the-nose, full-face mask with the hose connection in the front. The mask is used with a positive airway pressure (PAP) therapy device and covers both the nose and mouth, ensuring pressurized air is delivered directly into the patient's airways.

Trillium is designed for single-patient reuse in the home and institutional environments.

Trillium is intended for use in adult patients with:

- sleep disordered breathing conditions
- obstructive pulmonary diseases
- restrictive pulmonary diseases
- central respiratory diseases
- obesity hypoventilation syndrome

This study will use a production-equivalent version of the Trillium FFM.

Products will be labeled as investigational (“CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use”) and identified by a unique and sequential lot number. Devices will be tracked per quality system procedures (QSP), as applicable.

3.2 Comparator(s)

The AirFit F20 (ResMed, San Diego, California) is an externally placed vented mask covering the mouth and the nose of the patient. It provides a seal such that pressure from a positive pressure source is directed to the patient's nose and/or mouth. The mask connects via a standard conical connector to a conventional air delivery hose, which in turn connects to the positive pressure source. The mask is held in place with an adjustable headgear that straps the mask to the face. The AirFit F20 mask system comprises four subassemblies: cushion, frame, elbow and headgear. The elbow incorporates the vent array and anti-asphyxia valve safety features. The cushion and headgear are available in various sizes to fit a wide patient population. AirFit F20 is a prescription device supplied non-sterile.

The AirFit F20 is to be used by patients weighing more than 66lb (30kg) for whom positive airway pressure therapy (non-invasive CPAP or bi-level positive airway pressure (PAP) therapy) has been prescribed. It is intended for single-patient reuse in the home environment and multi-patient reuse in the hospital/institutional environment.

The AirFit F20 is an FDA-cleared medical device (K170924) currently available for sale in the United States. The product will be used in accordance with its labeling.

3.3 Technical & Functional Features of the Device(s)

Table 2. Device Description for Study Products

Device Name	Trillium	AirFit F20
Product Description	Refer to Section 3.1 for product description	Refer to Section 3.2 for product description
Device Image		
Dimensions	Mask, fully assembled with elbow assembly (no headgear): 172 mm (H) x 168 mm (W) x 146 mm (D)	Mask fully assembled with elbow assembly (no headgear): 154 mm (H) x 159 mm (W) x 147 mm (D)
Mechanical Characteristics	<u>Built-in exhalation:</u> Anti-asphyxia valves and exhalation (multi holes) are both integral to the elbow. The cushion does not contain any exhalation. <u>Dead space volume:</u> Small Cushion: 186.5 mL Medium Cushion: 213.8 mL Large Cushion: 236.7 mL Small Wide Cushion: 211.4 mL <u>Pressure drop:</u>	<u>Built-in exhalation:</u> Multi-hole vent array in elbow assembly - vent holes providing continuous air leak to flush out and minimize the amount of CO2 re-breathed by the patient; - anti-asphyxia valves to enable the patient to breathe fresh air in the event that airflow from the flow generator is impeded <u>Dead space volume:</u> ≤240 mL <u>Pressure drop:</u>

Table 2. Device Description for Study Products

Device Name	Trillium	AirFit F20
	≤ 2.9 cm H₂O @ 50 SLPM ≤ 9.5 cm H₂O @ 100 SLPM <u>Leakage:</u> < 31 SLPM @ 4 cm H₂O <55 SLPM @ 13 cm H₂O < 72 SLPM @ 22 cm H₂O < 85 SPLM @ 31 cm H₂O < 97 SLPM @ 40 cm H₂O <u>Pressure range:</u> 4 cm H₂O to 40 cm H₂O <u>Anti-asphyxia feature:</u> <10 cm H₂O Resistance @ 50 SLPM Close to Atmosphere @ <4 cm H₂O Open to Atmosphere @ ≤ 4 cm H₂O <u>Breathing Resistance (single fault) (cmH₂O):</u> <10cmH₂O inspiratory <10cmH₂O expiratory	≤ 0.2 cm H₂O @ 50 SLPM ≤ 0.6 cm H₂O @ 100 SLPM <u>Leakage:</u> 19 SLPM @ 3 cm H₂O 22 SLPM @ 4 cm H₂O 42 SLPM @ 13cm H₂O 57 SPLM @ 22 cm H₂O 70 SLPM @31 cm H₂O 82 SLPM @40cm H₂O <u>Pressure range:</u> 3 cm H₂O to 40 cm H₂O <u>Anti-asphyxia feature:</u> Close to Atmosphere @ ≤ 3 cm H₂O Open to Atmosphere @ ≤ 3 cm H₂O <u>Breathing Resistance (single fault) (cmH₂O):</u> <10cmH₂O inspiratory <10cmH₂O expiratory
Physical Properties	<u>Sizes:</u> 4 cushion sizes (small, small wide, medium, large); adjustable frame; 2 headgear sizes (small, standard) <u>Temperature:</u> Operating temperature: 5 °C to 40 °C Storage temperature: –20 °C to 60 °C <u>Patient Circuit connection:</u> 22 mm	<u>Sizes:</u> 3 cushion sizes (S, M, L); 3 frame sizes (S, M, L); 3 headgear sizes (S, Std, L) <u>Temperature:</u> Operating temperature: 5 °C to 40 °C Storage temperature: –20 °C to 60 °C <u>Patient Circuit connection:</u> 22 mm
Chemical Properties	<u>Materials and biocompatibility:</u> The following materials are used in the Trillium FFM: • Silicone • Polycarbonate • Thermoplastic Copolyester Elastomer • Polybutylene terephthalate • Nickel coated magnet • Nylon • Spandex • Polyurethane foam (headgear only) • Polypropylene	<u>Materials and biocompatibility:</u> Polymeric materials are used for the construction of the pneumatic and structural components. A silicone elastomer cushion to achieve air seal at the patient's mouth and nose. Foam padded fabric materials are used for the construction of the head strap.
Software (if applicable)	N/A – no associated software	N/A – no associated software
Incorporated Medicinal Substances	N/A – no incorporated medicinal substances	N/A – no incorporated medicinal substances
Sterile/Non-Sterile	Non-sterile	Non-sterile
Disposable/Reusable	Reusable	Reusable
Cleaning and Maintenance	<u>Cleaning:</u> Daily: Hand wash the elbow, mask frame, and cushion Weekly: Hand wash the headgear 1. Disassemble your mask.	<u>Cleaning:</u> Handwash your mask and headgear by gently rubbing in warm (approximately 30°C) water using mild liquid detergent. Rinse all components well under running water and allow to air dry out of direct sunlight. <u>Maintenance:</u>

Table 2. Device Description for Study Products

Device Name	Trillium	AirFit F20
	- Mix 1 teaspoon (5 ml) of mild liquid detergent per 1 gallon (3.8 liters) of warm potable water (80-90°F/27-32°C). - Fully submerge the mask parts in the warm water/detergent mixture and agitate for at least one minute. For the elbow, a soft-bristled brush may be used to remove adhering substances. Note: Make sure there are no air bubbles inside the mask parts while they are submerged. - Remove the mask parts from the water/detergent mixture. Rinse parts thoroughly by submerging in 1 gallon (3.8 liters) of warm water for a least 1 minute. - Lay the headgear flat or line dry. Air dry mask parts out of direct sunlight. Make sure the entire mask is dry before use. <u>Maintenance:</u> N/A – this is a non-serviceable part	N/A – this is a non-serviceable part
Principles of Operation	Trillium is operated by the user by placing the headgear over the head and the cushion over the nose and mouth, adjusting the fit if necessary. Trillium acts by non-invasively directing positive airway pressure therapy into the airways.	The AirFit F20 provides a seal such that pressure from a positive pressure source is directed to the patient's nose and/or mouth. The mask connects via a standard conical connector to a conventional air delivery hose, which in turn connects to the positive pressure source. The mask is held in place with an adjustable headgear that straps the mask to the face.
Key Performance Parameters, Modes, and Features	There are no key modes or features associated with this product. Refer to Section 4 for key performance parameters.	There are no key modes or features associated with this product. Refer to Section 4 for key performance parameters.
Method of Application	The mask is a full face mask (oral nasal) positioned around the mouth and nose. The frame contacts the cheek and the headgear wraps around the head.	The AirFit F20 is an externally placed vented mask covering the mouth and the nose of the patient. It provides a seal such that pressure from a positive pressure source is directed to the patient's nose and/or mouth. The mask is held in place with an adjustable headgear that straps the mask to the face.
Invasive/Noninvasive, Implantable	Non-Invasive, non-implantable The Trillium mask is a non-implantable device intended for non-invasive delivery of positive airway pressure.	Non-Invasive, non-implantable The AirFit F20 mask is a non-implantable device intended for non-invasive delivery of positive airway pressure.
Maximum Number of Repeat Applications	Mask is to be replaced no later than 12 months after the date of first use.	The service life of the AirFit F20 mask system is dependent on the intensity of usage, maintenance, and environmental conditions to which the mask is used or stored. As this mask system and its components are modular in nature, it is recommended that the user maintain and inspect it on a regular basis and replace the mask system or any components if deemed necessary or according to the 'visual criteria for product inspection' in the 'Cleaning your mask at home' section of the IFU.

3.4 Other Study Products

No other study products will be used.

4 Objectives, Endpoints & Hypotheses

Objectives, outcomes, acceptance criteria, high-level analyses, and supporting information are provided in **Table 3**.

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
<i>Clinical Safety Objective: To objectively evaluate the clinical safety profile of the Trillium FFM.</i>			
Skin Effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling)	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): Red marks that go away quickly without any treatment. Any AE rate (0–100%) is acceptable. • Minor (S1): Red marks that remain but no intervention required. Mild peeling. An AE rate of <20% for PAP therapy or <30% for NIV therapy is acceptable. • Moderate/Major (S2): Red marks, peeling, or breakdown that require professional medical intervention. An AE rate of 0% for PAP therapy or <10% for NIV therapy is acceptable. • Critical/Serious (S3): Serious breakdown or pressure necrosis that may cause scarring. An AE rate of 0% is acceptable.	Number and percent of participants with at least one event will be reported by treatment. Severity levels across treatments will be compared using shift tables.	Skin irritation and lesions (i.e., erythema, infection, pimples, ulcers) on the nose and face at the sites of mask contact comprise a large proportion of PAP/NIV therapy mask complaints/complications yet generally benefit-risk assessment still favors benefit. Mild or moderate skin issues are very common with both PAP and NIV therapy, especially at higher pressures, especially over longer durations, and especially with full-face (oronasal) masks like Trillium; benefit-risk assessment still strongly favors benefit of therapy. <u>Relevant Considerations for Interpretation of Results:</u> • Pre-Existing Skin Issues: Pre-existing skin conditions (e.g., rosacea) or propensity to skin presentations of atopy (e.g., contact dermatitis; see Allergic Reaction below) may indicate device-unrelated or device-exacerbated, rather than device-caused skin AEs. • Device Use: If device use results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for skin issues. • Quality of Life (QOL): If QOL results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for skin issues. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Carron et al. 2013¹³; Esquinas et al. 2017⁷; Lemyze et al. 2023¹⁴; Logger et al. 2020¹⁵; Ma et al. 2018¹⁶; Parthasarathy 2008¹⁷; Ryan et al. 2011¹⁸; Singh & Pitoyo et al. 2014⁶; Ulander et al. 2014¹⁹; Van Ryswyk et al. 2019²⁰; Yasuda et al. 2021²¹; Zhu et al. 2024²²
Oronasal Dryness	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): Temporary discomfort that resolves when the device is removed. Any AE rate (0–100%) is acceptable. • Minor (S1): Dryness persists but treated by the patient (e.g., saline spray). May complain of minor cough or sore throat. An AE rate of <50% for PAP therapy or	Number and percent of participants with at least one event will be reported by treatment. Severity levels across treatments will be compared using shift tables.	Nasal and/or oral dryness affects 10–20% of NIV patients and congestion 20–50% of NIV patients. Over time, the nasal and oral mucosa lose the ability to apply heat and humidity to inspired air, causing dryness, irritation, and inflammation. Secretions may also become dry, causing mucous plugging and atelectasis. Mild or moderate oral, nasal, and/or upper airway (UA) irritation and/or dryness are very common with both PAP and NIV therapy, especially at higher pressures, lower temperatures, and lower humidity, and over longer durations. <u>Relevant Considerations for Interpretation of Results:</u>

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
	<60% for NIV therapy is acceptable. • Moderate/Major (S2): Chronic nose bleeds or cough. Requires professional medical intervention. An AE rate of 0% for PAP therapy or <10% for NIV therapy is acceptable. • Critical/Serious (S3): N/A – This severity rating does not apply to this AE.		• Pre-Existing UA Issues: Pre-existing UA conditions or propensity to UA discomfort may indicate device-unrelated or device-exacerbated, rather than device-caused oronasal irritation/dryness AEs. • Device Use: If device use results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for oronasal irritation/dryness. • QOL: If QOL results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for oronasal irritation/dryness. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Carron et al. 2013¹³; Ma et al. 2018¹⁶; Deng et al. 2023²³; Rotty et al. 2021¹¹; Ryan et al. 2011¹⁸; Ulander et al. 2014¹⁹; Van Ryswyk et al. 2019²⁰; Zhu et al. 2024²²
Eye-Related Side Effects	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): Dryness resolves when the device is removed. Any AE rate (0–100%) is acceptable. • Minor (S1): Eye redness/dryness. Eye drops may be used by the patient to treat. An AE rate of <5% for PAP therapy or <10% for NIV therapy is acceptable. • Moderate/Major (S2): Redness/dryness/irritation persists and requires professional medical treatment. An AE rate of 0% for PAP therapy or <5% for NIV therapy is acceptable. • Critical/Serious (S3): N/A – This severity rating does not apply to this AE.	Number and percent of participants with at least one event will be reported by treatment. Severity levels across treatments will be compared using shift tables.	Lack of humidity can also cause eye irritation in the case of considerable leak. Mild or moderate eye irritation or dryness or excessive tear production are very common with both PAP and NIV therapy, especially at higher leak and lower humidity, and over longer durations. <u>Relevant Considerations for Interpretation of Results:</u> • Pre-Existing Eye Issues: Pre-existing eye conditions or propensity to eye discomfort may indicate device-unrelated or device-exacerbated, rather than device-caused eye irritation/dryness or excessive tear production AEs. • Device Use: If device use results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for eye irritation/dryness or excessive tear production. • QOL: If QOL results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for eye irritation/dryness or excessive tear production. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Carron et al. 2013¹³; Conde et al. 2022²⁴; Deng et al. 2023²³; Ma et al. 2018¹⁶; Rotty et al. 2021¹¹; Ryan et al. 2011¹⁸; Ulander et al. 2014¹⁹; Van Ryswyk et al. 2019²⁰; Yasuda et al. 2021²¹; Zhu et al. 2024²²
Anxiety	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): Temporary, able to continue therapy, doesn't impact	Number and percent of participants with at least one event will be reported by treatment.	Claustrophobia can have a broad range of presentations, from minor discomfort to a feeling of suffocation or choking, that negatively impacts both NIV initiation and continuation. Discomfort is thought to be responsible for 12–33% of NIV failure. Thoughtful selection of a properly sized and fitted interface (helmets or nasal masks

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
	sleep. Any AE rate (0–100%) is acceptable. • Minor (S1): Persists throughout the night, impact to sleep or therapy. An AE rate of <5% for PAP therapy or <10% for NIV therapy is acceptable. • Moderate/Major (S2): Professional medical intervention needed to continue therapy. An AE rate of 0% for PAP therapy or <5% for NIV therapy is acceptable. • Critical/Serious (S3): N/A – This severity rating does not apply to this AE.	Severity levels across treatments will be compared using shift tables.	may be better than full face masks in some patients) and use of lower pressures may reduce risks of these complications. Noise, influenced by both interface and ventilator selection, can contribute to claustrophobia and general discomfort and additionally to sleep disruption and hearing loss. Mild or moderate anxiety (having a broad range of presentations including minor discomfort, claustrophobia, feeling of suffocation/ choking, failure to initiate or continue therapy) is common with both PAP and NIV therapy, especially with bulky full-face (oronasal) masks like Trillium, narrow tubing, louder therapy devices, higher pressures, or greater leak. <u>Relevant Considerations for Interpretation of Results:</u> • Pre-Existing Anxiety Issues: Pre-existing anxiety conditions or propensity to claustrophobia may indicate device-unrelated or device-exacerbated, rather than device-caused anxiety AEs. • Device Use: If device use results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for anxiety. • QOL: If QOL results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for anxiety. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Carron et al. 2013¹³; Deng et al. 2023²³; Esquinas et al. 2017⁷; Ma et al. 2018¹⁶; Parthasarathy 2008¹⁷; Ryan et al. 2011¹⁸; Ulander et al. 2014¹⁹; Van Ryswyk et al. 2019²⁰
Allergic Reaction	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): N/A – This severity rating does not apply to this AE. • Minor (S1): Minor symptoms that resolve without treatment or with self-treatment. An AE rate of <5% is acceptable. • Moderate/Major (S2): Requires professional medical intervention. An AE rate of <5% is acceptable. • Critical/Serious (S3): Anaphylaxis. An AE rate of 0% is acceptable.	Number and percent of participants with at least one event will be reported by treatment. Severity levels across treatments will be compared using shift tables.	Allergic reactions to mask materials (e.g., silicone cushions, fabric headgear) are exceedingly rare, and largely only documented in the clinical literature in the form of isolated case reports. There is some evidence to indicate that the few documented cases may actually be attributable to lack of cleaning or chemicals used in cleaning. <u>Relevant Considerations for Interpretation of Results:</u> Determination of allergic reaction requires clinical diagnosis, and as such PRO for allergic reaction is not appropriate. Additionally, it should be noted that allergic reaction may be interpreted as Localized Skin Irritation, Breakdown, Lesions, and/or Peeling (outcome above) or conversely Localized Skin Irritation, Breakdown, Lesions, and/or Peeling (outcome above) may be interpreted as allergic reaction <u>Relevant Sources:</u> Felmingham et al. 2019²⁵; Ma et al. 2018¹⁶; Parthasarathy 2008¹⁷; Prasad & Reeder 2021²⁶; Rath & Kaplish 2022²⁷; Scalf & Fowler 1999²⁸

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
Headache	<u>Objective Adverse Events (AEs):</u> • Negligible/No Harm (S0): Resolves after mask is removed. Any AE rate (0–100%) is acceptable. • Minor (S1): Resolves with self-treatment. An AE rate of <5% for PAP therapy or <10% for NIV therapy is acceptable. • Moderate/Major (S2): Chronic or severe enough that professional medical intervention(s) is required. An AE rate of 0% is acceptable. • Critical/Serious (S3): N/A – This severity rating does not apply to this AE.	Number and percent of participants with at least one event will be reported by treatment. Severity levels across treatments will be compared using shift tables.	Headache in the morning is a well-known symptom of SDB, specifically OSA. It is also known to be an expected adverse effect of therapy mask use both in SDB and respiratory insufficiency and failure. Headache can be especially common in conditions of mask headgear being too tight, and is more common with full-face (oronasal) masks like Trillium <u>Relevant Considerations for Interpretation of Results:</u> • Pre-Existing Headache Issues: Pre-existing headache conditions or propensity for headaches may indicate device-unrelated or device-exacerbated, rather than device-caused anxiety AEs. • Device Use: If device use results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for headaches. • QOL: If QOL results meet acceptability criteria despite high AE rates or PRO ratings, then this may suggest perceived benefit overrides concern for headaches. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Bettega et al. 2022²⁹; Chang et al. 2022³⁰; Deng et al. 2023²³; Ma et al. 2018¹⁶; Massongo et al. 2022³¹; Reddy et al. 2022³²; Ryan et al. 2011¹⁸
Clinical Performance Objective: To objectively and subjectively evaluate the clinical performance of the Trillium FFM.			
Unintentional Leak	<u>Objective Leak via Device Leak Data:</u> • Device Detected Unintentional Leak: <24 LPM (based on upper bound of the 95% confidence interval)	Mixed model analyses will be used to estimate the mean leak per treatment, and the treatment difference.	Unintentional leak can be common with both PAP and NIV therapy, especially at higher pressures, especially over longer durations, and especially with full-face (oronasal) masks like Trillium. Higher levels of leak and full-face (oronasal) masks like Trillium are associated with higher residual AHI. Leak is one of the most frequent complaints among long-term PAP therapy patients and these patient-reported leaks are not predicted by PAP device data on leaks. Patient perception of leak is a complex issue involving not only strength of leak flow but also how that leak flow feels on the skin or eyes and how bothersome the noise is to the patient and the patient's bed partner. Automatic titration PAP (auto-PAP or APAP) algorithms detect respiratory events and adjust delivered pressures throughout the night. Expiratory pressure relief is another feature that has been developed in order to provide lower pressures, specifically during exhalation. NIV effectiveness can be reduced by inadvertent leak due to poor mask fit. Leak and discomfort can moreover negatively impact sleep quality, patient-ventilatory synchrony, and therapy delivery to the patient, and therefore, therapy effectiveness.

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
			<u>Relevant Considerations for Interpretation of Results:</u> • Device Use: If device use results meet acceptability criteria despite high leak level or poor PRO ratings, then this may suggest perceived benefit overrides concern for leak. • AHI: If AHI results meet acceptability criteria despite high leak level or poor PRO ratings, then this may suggest actual benefit overrides leak or concern for leak. • QOL: If QOL results meet acceptability criteria despite high leak level or poor PRO ratings, then this may suggest perceived benefit overrides concern for leak. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Carron et al. 2013¹³; Chihara et al. 2013³³; Deng et al. 2023²³; Donovan et al. 2015³⁴; Esquinas et al. 2017⁷; Kang et al. 2022³⁵; Lebrete et al. 2017³⁶; Ma et al. 2018¹⁶; Preutthipan 2015³⁷; Rossetto et al. 2023³⁸; Rotty et al. 2021¹¹; Ryan et al. 2011¹⁸; Shrivastava 2013³⁹; Ulander et al. 2014¹⁹; Van Ryswyk et al. 2019²⁰; Zhu et al. 2024²²
Comfort of Breathing	<u>Subjective Patient-Reported Outcomes (PRO):</u> • Comfort of Breathing: Average satisfaction rating ≥ 7.5 on a 0–10 scale (0 indicating extremely dissatisfied, 5 neutral, 10 extremely satisfied) based on lower bound of the 95% confidence interval.	Mixed model analyses will be used to estimate the mean score per treatment, and the treatment difference.	Bi-level PAP therapy was the first solution developed to lower the pressure level delivered to the patient and improve therapy comfort. Instead of applying a fixed pressure, BiPAP applies a lower expiratory positive airway pressure (EPAP) during exhalation and a higher inspiratory positive airway pressure (IPAP) during inhalation. This therapy seems to be useful in patients who complain of pressure intolerance and can be an alternative option in patients with hypoventilation syndrome. Facial masks are the “gold standard” choice for the NIV interface because they address the tendency of NIV patients, who generally receive relatively higher pressures (compared to CPAP), to “mouth breathe.” The nasal airway, which is considered the recommended/preferred delivery route for PAP therapy, generally accounts for 50% of total upper airway resistance. Yet, the frequency and severity of nasal airway resistance (due to cross-sectional area of the nasal passages, nasal cavity volume, peak inspiratory flow, etc.) and/or frequency and severity of nasal symptoms (e.g., nasal congestion, clear/purulent nasal discharge, nasal dryness, rhinocnesmus, rhinorrhagia, sneezing, dysosmia, headache) are variable between individuals and within individuals over time. Different masks are thought to alter patient perception of congestion and congestion is known to be an independent predictor of PAP non-compliance. <u>Relevant Considerations for Interpretation of Results:</u>

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
			• Device Use: If device use results meet acceptability criteria despite poor PRO ratings, then this may suggest perceived benefit overrides concern for comfort of breathing. • AHI: If AHI results meet acceptability criteria despite poor PRO ratings, then this may suggest actual benefit overrides concern for comfort of breathing. • QOL: If QOL results meet acceptability criteria despite poor PRO ratings, then this may suggest perceived benefit overrides concern for comfort of breathing. <u>Relevant Sources:</u> Atwood et al. 2013⁴⁰; Carron et al. 2013¹³; Donovan et al. 2015³⁴; Deng et al. 2023²³; Esquinas et al. 2017⁷; Lebret et al. 2021⁴¹; Ma et al. 2018¹⁶; Marini, 2013⁴²; Parthasarathy 2008¹⁷; Ryan et al. 2011¹⁸; Ulander et al. 2014¹⁹; Wu et al. 2022⁴³
Clinical Benefit Objective: To objectively and subjectively evaluate the clinical benefit of the Trillium FFM.			
Apnea-Hypopnea Index (AHI)	Objective AHI via Device AHI Data: • Established Patients: No clinically meaningful increase in AHI in patients already established on therapy (non-inferiority margin <5 events/h)	Mixed model analyses will be used to estimate the mean AHI per treatment, and the treatment difference. Severity levels across treatments will be compared using shift tables.	First-line treatment for SDB is PAP therapy and the gold standard measure for effectiveness of PAP therapy is apnea-hypopnea index (AHI). AHI quantifies the number of apneas (complete pauses in breathing) and hypopneas (partial reductions in breathing) per hour of sleep. AHI value ranges are standardly used to categorize severity of disease among adult patients as follows: • Mild: AHI = ≥5 to <15 events/hr • Moderate: AHI = ≥15 to <30 events/hr • Severe: AHI = ≥30 events/hr There are many confounding factors related to SDB treatment. Thus, an acceptable AHI range may be different for different patient populations. High variability in AHI data is expected due to differences in treatment groups, measurement equipment, and criteria for defining apneas and hypopneas. This limits confidence with which acceptability criteria can be determined. Additionally, higher levels of leak and full-face (oronasal) masks like Trillium are associated with higher residual AHI. <u>Relevant Considerations for Interpretation of Results:</u> • Device Use: If AHI results do not meet acceptability criteria despite good device use (adherence) results, then this may suggest significant leak or other issues are affecting AHI. If AHI results do not meet acceptability criteria and device use (adherence) results do not meet acceptability criteria, then this may suggest lack of therapy use is leading to poor AHI results.

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
			• Leak: If AHI results do not meet acceptability criteria and leak is high (i.e., unintentional leak >24 lpm), then this may suggest patients are not getting effective therapy even though they are wearing the mask. • Device Deficiency or Use Error: If AHI results do not meet acceptability criteria and leak meets acceptability criteria, then this may suggest a potential device deficiency or use error. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Barnes et al 2017⁴⁴; Bartolucci et al. 2023⁴⁵; Benoist et al. 2017⁴⁶; Certal et al, 2015⁴⁷; Chen et al. 2019⁴⁸; Cowie et al. 2015⁴⁹; Cowie et al. 2017⁵⁰; Deng et al. 2023²³; Fu S et al. 2023⁵¹; Gao et al. 2019⁵²; Hernandez et al. 2020⁵³; Hsu et al. 2020⁵⁴; Iftikhar et al. 2023⁵⁵; Kim et al. 2017⁵⁶; Lee et al. 2023⁵⁷; Li Y, Du J et al. 2023⁵⁸; Liu Z et al. 2023⁵⁹; Ma et al. 2018¹⁶; Meghpara et al. 2022⁶⁰; Neruntarat et al. 2021⁶¹; Patil et al. 2019⁵; Randerath et al. 2021⁶²; Reddy et al. 2022³²; Rossetto et al. 2023³⁸; Rueda et al. 2020⁶³; Ryan et al. 2011¹⁸; Sawunyavisuth et al. 2023⁶⁴; Silva de Sousa et al. 2023⁶⁵; Srijithesh et al. 2019⁶⁶; Strollo et al. 2014⁶⁷; Trindade et al. 2023⁶⁸; Trzepizur et al. 2021⁶⁹; Van Ryswyk et al. 2019²⁰; Wang Y et al. 2023⁷⁰; Woo et al 2020⁷¹; Xu J et al. 2022⁷²; Zhang F et al. 2022⁷³; Zonato et al. 2021⁷⁴; Zonato et al. 2022⁷⁵
Adherence	<u>Objective Adherence via Device Use Data:</u> • Established Patients: No clinically meaningful decrease in usage in patients already established on therapy (non-inferiority margin ≥ 0.5 hours device use per night)	For continuous adherence parameters, mixed model analyses will be used to estimate the mean response per treatment, and the treatment difference. Categorical parameters will be summarized descriptively using frequency counts and percentages. Response across treatments will be compared using shift tables.	Adherence is crucial for PAP and NIV therapy to be effective and for patients to receive the clinical benefits of this therapy. There are an enormous number of ways therapy adherence can be measured. For example, PAP therapy adherence is measured by: • proportion of patients with good compliance (use ≥ 4 hours/night), % • proportion of days with good compliance (use ≥ 4 hours/night), % • device use, hours/night • daily use (all days), hours/night Unfortunately, therapy adherence is very commonly sub-optimal for a broad range of reasons. Patients requiring PAP/NIV therapy frequently have multiple comorbid conditions that affect adherence and clinical benefit derived from adherence. For example, PAP therapy patients may have coexisting insomnia or other sleep disorders, anxiety, gastroesophageal reflux disease (GERD), allergic rhinitis, migraine headache, or other conditions, all of which can negatively influence therapy adherence.

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
			In addition to these intrinsic factors, external issues such as choice of mask type, fit of the mask, comfort of breathing using the mask, leaks around the edges of the mask, and mask-related side effects also significantly influence adherence and therefore, achievement of clinical benefits. For example, adherence is commonly worse among users of full-face (oronasal) masks, like Trillium, compared to users of other mask types. <u>Relevant Considerations for Interpretation of Results:</u> • PRO: If PRO ratings meet acceptability criteria despite poor adherence, then this may suggest factors outside of the mask are influencing adherence. • AHI: If AHI results meet acceptability criteria despite poor adherence, then this may suggest the decreased usage does not have a significant impact on treatment effect. • QOL: If QOL results meet acceptability criteria despite poor adherence, then this may suggest the decreased usage does not have a significant impact on treatment effect. <u>Relevant Sources:</u> BaHammam et al. 2017¹²; Chen et al. 2022⁸; Deng et al. 2023²³; Engleman et al. 2003⁷⁶; Lajoie et al 2023⁷⁷; Lebret et al. 2021⁴¹; Ma et al. 2018¹⁶; Patil et al. 2019⁵; Rotty et al. 2021¹¹; Ryan et al. 2011¹⁸; Sawunyavisuth et al. 2023⁶⁴; Van Ryswyk et al. 2019²⁰; Wu et al. 2022⁴³; Yi et al. 2022⁷⁸; Zhu et al. 2024²²
Sleepiness	<u>Subjective Sleepiness Outcomes:</u> • Epworth Sleepiness Scale (ESS): Clinical significance threshold/non-inferiority margin = 2 points	Mixed model analyses will be used to estimate the mean ESS response per treatment, and the treatment difference.	Excessive daytime sleepiness is a frequently self-reported symptom of SDB conditions and is typically assessed using the Epworth Sleepiness Scale (ESS), to evaluate the effectiveness of therapy. Adherence is commonly suboptimal with both PAP and NIV therapy, especially among users of full-face (oronasal) masks like Trillium. Adherence to therapy is known to influence sleepiness. Additionally, comfort of breathing, leak, and mask-related side effects also significantly influence adherence and sleepiness. <u>Relevant Considerations for Interpretation of Results:</u> • Device Use: If sleepiness results do not meet acceptability criteria despite good device use (adherence) results, then this may suggest significant leak or other issues are affecting sleepiness. If sleepiness results do not meet acceptability criteria and device use (adherence) results do not meet acceptability criteria, then this may suggest lack of therapy use is leading to poor sleepiness results. • Leak: If sleepiness results do not meet acceptability criteria and leak is high (i.e., >24 lpm), then this may suggest patients are not getting effective therapy even though they are wearing the mask.

Table 3. Objectives, Outcomes, Acceptance Criteria, High-Level Analyses, and Supporting Information

Outcomes	Acceptance Criteria	High-Level Analyses*	Supporting Information
			<u>Relevant Sources:</u> Afshar et al. 2020⁷⁹; Gao et al. 2019⁵²; Kryger & Malholtra 2019⁸⁰; Lajoie et al. 2023⁷⁷; Li et al. 2022⁸¹; Mangione et al. 2022⁸²; Patil et al. 2019⁵; Rotty et al. 2021¹¹; Ryan et al. 2011¹⁸; Stajic et al 2022⁸³; Trzepizur et al. 2021⁶⁹; Weaver et al. 2023⁸⁴
Quality of Life	<u>Subjective QOL Instruments:</u> • European Quality of Life-5D (EQ-5D): Non-inferiority margin <0.08 points for the index score • Established Patients: No significant change in QOL score in patients already established on therapy	Each EQ-5D item will be summarized descriptively using frequency counts and percentages. Response across treatments will be compared using shift tables. For the continuous parameters (EQ VAS and Index Score), mixed model analyses will be used to estimate the mean response per treatment, and the treatment difference.	The high prevalence of SDB and its impact on patient quality of life makes it critical for healthcare providers to offer effective and acceptable treatment options. Indirect clinical benefits of SDB treatments include improvements in health-related QOL. By maintaining airway patency, improving gas exchange, and reducing WOB, the management of respiratory insufficiency and failure (RI/F) also indirectly results in improved health-related QOL. However, because patients with RI/F may have RI/F due to a wide array of etiologies (e.g., chronic obstructive airway disease, neuromuscular disease, spinal injury), they also may have a broad range of comorbidities that may also independently influence patients' perceptions of QOL. <u>Relevant Considerations for Interpretation of Results:</u> • Device Use: If QOL results do not meet acceptability criteria despite good device use (adherence) results, then this may suggest leak or poor user experience that is not significant enough to cause the patient to reduce or stop using their device. However, it may also suggest disease progression or increasing disease severity or other issues are affecting QOL. If QOL results do not meet acceptability criteria and device use (adherence) results do not meet acceptability criteria, then this may suggest lack of therapy use is leading to poor QOL results. <u>Relevant Sources:</u> Afshar et al. 2020⁷⁹; Albalawi et al. 2022⁸⁵; Breen et al. 2023⁸⁶; Chen et al. 2019⁴⁸; Diaz de Teran et al. 2019⁸⁷; Hannan et al. 2014⁸⁸; Hull et al. 2014⁸⁹; Kryger & Malhotra 2018⁸⁰; Patil et al. 2019⁵; Rochwerg et al. 2017⁹⁰; Ryan et al. 2011¹⁸; Simonds et al. 2016⁹¹; Shaughnessy et al. 2019⁹²; Trzepizur et al. 2021⁶⁹; Weaver et al. 2021⁸⁴; Windisch et al. 2018⁹³; Zhang et al. 2020⁹⁴; Zhu et al. 2024²²

5 Design of the Clinical Investigation

5.1 General Information

This will be a single-center, open-label randomized crossover design pilot study to evaluate the clinical safety, clinical performance, and clinical benefit of the Trillium FFM.

Subjects meeting all eligibility criteria will be enrolled and will be randomized. Based on their randomization, subjects will be asked to use either a new AirFit F20 mask or the Trillium investigational mask for approximately 15 consecutive days (± 3 days) of use. They will return for a follow-up visit to complete surveys about their experience during the first treatment period. Subjects will then be crossed over to the other mask (i.e., AirFit F20 or Trillium) per the randomization assignment. Following a second 15-day period of home use, subjects will return for a final visit to complete surveys about their experience in the second treatment period and conclude participation in the investigation.

The 15-day follow-up period is sufficient for subjects to assess the mask and provide feedback on their experience without significant confounder interference (i.e., adjustment to a new mask, poor data collection by device, etc.). This study is expected to last approximately 30 days for each participant. The total time of clinical investigation execution (i.e., first subject enrolled to last subject completed) is expected to be approximately 45 days.

No patients were involved in the development of this clinical investigation plan. The investigational site was selected based on its status as a well-established provider of quality care to patients with OSA and other sleep and respiratory conditions as well as its experience conducting clinical investigations such as this one.

5.2 Subjects

This study will enroll adult OSA patients who have been established on PAP therapy for at least 3 months and are currently using an AirFit F20 full face mask. The population selected for this trial is sufficiently representative of the product's intended OSA users. Use of patients who are naïve to therapy or those established on therapy but using a different style of FFM (e.g., AmaraView) would introduce confounders (i.e., adjustment to therapy, unfamiliar mask style), making interpretation of results difficult.

Approximately 40 subjects will be enrolled and randomized, with approximately 35 subjects expected to complete all study procedures.

5.2.1 Vulnerable Population

This study will not include vulnerable populations.

5.2.2 Eligibility Criteria

Inclusion Criteria

- Aged 21–85 years (inclusive)
- Diagnosed with OSA
- Established on PAP therapy for ≥ 90 days at the time of consent
- Currently prescribed and using fixed pressure, Auto CPAP, or BiPAP therapy on a regular basis (average PAP usage of ≥ 4 hours/night, ≥ 4 days per week for ≥ 3 months)
- Able to read, write, speak and understand English
- Willing and able to provide informed consent
- Willing and able to follow instructions and complete all activities required by the study
- Able to remove a sleep apnea mask without assistance
- Currently using a ResMed PAP therapy device with a connection to ResMed's AirView system

- Currently using ResMed AirFit F20

Exclusion Criteria

- Significant risk of aspiration (i.e., active vomiting or taking a prescription drug that induces vomiting)
- Known allergy to silicone, latex, polyamide (nylon), spandex, polyurethane, acetal, polycarbonate, or polypropylene
- Active infection or inflammation in an area in contact with the mask
- Recent head or facial surgery unless cleared by a healthcare provider to resume regular therapy
- Planned head or facial surgery during the study
- Any congenital or acquired craniofacial malformations or abnormalities, acute trauma, or burns that would interfere with the mask's placement or ability to deliver therapy
- Employee or family member who works for Philips or any of its direct competitors in the sleep industry
- Prescribed oxygen at night or continuously
- Currently participating in another interventional research study or planned participation in another interventional clinical research study during the trial period
- Prescribed an ASV (adaptive servo-ventilation) device
- Prescribed mechanical ventilation
- Pre-existing conditions such as bullous lung disease, pathologically low blood pressure, bypassed upper airway, pneumothorax, pneumocephalus, cerebral spinal fluid (CSF) leaks
- Any unstable medical condition (e.g., uncontrolled cardiac, lung, or neurological disease) or limitation that would affect the participant's ability to complete trial activities
- Experiencing any acute illness (e.g., acute sinusitis, ear or eye infections, upper respiratory infections, pharyngitis, bronchitis, pleurisy, pneumonia, or facial dermatitis) that would impact their ability to use the mask and/or PAP therapy during the trial
- Pregnant (self-report)
- Advised by a health care provider to avoid magnets
- Patient or patient's household member, caregiver or bed partner in close vicinity that have implanted devices that may be affected by magnets, including but not limited to:
 - Pacemakers
 - Implantable cardioverter defibrillators (ICD)
 - Neurostimulators
 - Magnetic metallic implants/electrodes/valves placed in upper limbs, torso, or higher (i.e., neck and head)
 - Cerebral spinal fluid (CSF) shunts (e.g., ventriculo peritoneal (VP) shunt)
 - Aneurysm clips
 - Embolic coils
 - Intracranial aneurysm intravascular flow disruption devices
 - Metallic cranial plates, screws, burr hole covers, and bone substitute devices
 - Metallic splinters in the eye
 - Ocular implants (e.g., glaucoma implants, retinal implants)
 - Certain contact lenses with metal

- Implants to restore hearing or balance that have an implanted magnet (such as cochlear implants, implanted bone conduction hearing devices, and auditory brainstem implants)
 - Magnetic denture attachments
 - Metallic gastrointestinal clips
 - Metallic stents (e.g., aneurysm, coronary, tracheobronchial, biliary)
 - Implantable ports and pumps (e.g., insulin pumps)
 - Hypoglossal nerve stimulators
 - Implanted devices labeled as MR (magnetic resonance) unsafe
 - Magnetic metallic implants not labeled for MR or not evaluated for safety in a magnetic field
- Paralysis of the hemi-diaphragm

5.3 Minimization of Bias

To ensure the integrity and validity of the study results, randomization and a crossover design will be used to minimize bias. The randomization schedule will be generated by the Medidata EDC system. Participants will be randomly assigned in a 1:1 manner to one of two treatment sequences:

- Sequence 1: Trillium mask followed by AirFit F20 mask
- Sequence 2: AirFit F20 mask followed by Trillium mask

By randomizing the order in which participants use the two masks (Airfit F20 vs. Trillium), the potential for carryover effect is mitigated. That is, any effect due to the order of treatment usage should be counterbalanced due to the randomized treatment sequence.

Participants will use both masks for an equal duration, ensuring that both are evaluated under similar conditions.

The crossover design typically reduces variability and increases the statistical power of the study. By comparing the outcomes within the same participant, the influence of confounding factors (i.e., individual preferences, differences in sleep patterns/adherence) is minimized.

This is an open-label study. Due to the different designs of masks used, the study cannot be blinded.

6 Study Procedures

The study procedures are detailed in the sections below. A summary of the schedule of events is outlined in **Table 4**.

Table 4. Summary of the schedule of events

Procedure	Performed/ Supervised by	Pre-Screen	Visit 1 Day 1	Visit 2 Day 15 ±3 days	Visit 3 Day 30 ±3 days
Preliminary eligibility assessment	Investigator/Designee	X			
Consent	Investigator/Designee		X		
Eligibility questionnaire	Study Coordinator		X		
Demographic questionnaire	Study Coordinator		X		
Mask Information Survey	Clinician		X		
Dispense Study Mask	Clinician/Study Coordinator		X	X	
Mask Survey	Clinician/Study Coordinator			X	X
Epworth Sleepiness Scale	Clinician/Study Coordinator			X	X
EQ-5D-3L	Clinician/Study Coordinator			X	X
Device Data Report	Study Coordinator			X	X
Review of potential AEs	PI/Designee Study Coordinator			X	X
Inventory check to ensure product return	Clinician/Study Coordinator			X	X
Compensation	Study Coordinator		X	X	X

6.1 Pre-Screening

Pre-screening procedures will occur at the site. To identify participants who may be eligible for the study, specifically OSA patients using a ResMed therapy device and AirFit F20 mask, the site will utilize their electronic health record to search for potential participants based on available information. Patients will be contacted based on their potential eligibility. No additional prescreening procedures will take place.

6.2 Recruitment Methods

Participants will be recruited through the site. Recruitment may involve a combination of in-person recruitment during clinical appointments, phone calls, and emails. Study staff will be responsible for assessment of eligibility based on criteria outlined in Section 5.2.2.

Scheduling will be conducted by the site. Participants who are willing to enroll will be scheduled for an in-person visit to provide informed consent and complete study procedures.

6.3 Visit 1 (Baseline Visit)

6.3.1 Informed Consent Process

During the baseline visit, the study site coordinator will review the Informed Consent Form (ICF) with the participant explaining the details of the study and answering any questions the participant may have about the study. If the participant is willing to take part in the study, the ICF will be signed and dated by the participant and the site study representative obtaining consent. A copy of each participant's signed ICF will be given to them for their records.

Those who provide consent will then complete the Eligibility Questionnaire to confirm entry criteria. The participants will then complete the Demographics Questionnaire, which collects information about age, sex, race, and ethnicity.

Participants will be asked to bring their prescribed mask and PAP device to Visit 1.

The enrolled population will consist of all participants who provide informed consent and meet eligibility requirements.

If significant new findings develop during the course of the research study, which may relate to the subject's willingness to continue participation, the subject will be notified. At that time, the subject may be asked to sign a new informed consent form.

6.3.2 Mask Fitting and Use

At the initial visit, participants randomized to the Trillium→ AirFit F20 sequence will undergo a fitting of the Trillium mask. Participants will be fit with mask sizes recommended by the clinician. The clinician may use the provided sizing gauges to aid in the fitting process. Once a mask size is selected, the participant will undergo short trials using his or her own PAP machine at therapeutic pressure for up to 15 minutes, and an assessment of mask fit will be performed. If the participant's PAP device is not available, they will be fitted with the mask and will undergo short trials using a ResMed S9 PAP device provided by the site.

A Mask Information Survey will be used to capture the participant's mask size information (i.e., cushion/frame, headgear). The presence of facial hair will be noted on the form. If the participant is between mask sizes, they may be given an additional size mask and/or cushion to take home and use, if needed.

Participants randomized to the AirFit F20→Trillium sequence will be given a new AirFit F20 mask to take home in the same size that they currently use. Participants will not be fit with the AirFit F20 mask by the clinician or have their therapy pressure applied with their PAP device.

All participants will be instructed to use the mask for the full 15-days of the first trial period. Participants will be instructed to contact the site if they have issues with the recommended cushion and/or headgear sizes as needed. Any change to cushion/frame or headgear during the trial will be documented in EDC.

It is anticipated that the consent, eligibility, baseline/demographic data collection, and mask fitting will take approximately 45–60 minutes to complete.

6.4 Visit 2 (First Follow-Up Visit)

After the first 15-day home use period with the first mask, participants will return to the site for their second study visit. Participants will be instructed to bring their PAP device, the first study mask and any associated parts and/or cushions to return at this visit. The procedure in Section 6.3.2 will be followed for the second mask (i.e., Trillium or AirFit F20, depending on randomization). It is anticipated that the procedures during this visit will take approximately 45–60 minutes to complete. Details of visit procedures are outlined below.

6.4.1 Mask Survey

Participants will be asked to complete a survey providing feedback on attributes of the first mask, including comfort of breathing.

6.4.2 Review of AEs

Refer to Section 15 for Safety Monitoring.

6.4.3 Sleepiness and Health-Related Quality of Life

Participants will be asked to complete the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness for the previous 15 days. Participants will also be asked to complete the EQ-5D-3L, which will assess their health-related quality of life.

6.4.4 Collection of Device Data

Participants will be instructed to bring their therapy device to the visit. The site coordinator will confirm the data has been uploaded into AirView. If data appears to be missing, data can be manually uploaded to AirView. De-identified data from participants' PAP devices will be extracted from the connected ResMed device software, AirView. Extracted data will include average unintentional leak, AHI, usage and pressure data collected during the previous trial period. Data collected outside the trial period (i.e., before Day 1) will not be extracted. The site coordinator will manually enter the extracted device data into the Electronic Data Capture (EDC) system.

6.4.5 Mask Fitting and Use

Participants randomized to the AirFit F20→Trillium sequence will undergo a fitting of the Trillium mask. Procedures will be completed as outlined in section 6.3.2 using the mask assigned for period 2 of the trial.

Participants randomized to the Trillium →AirFit F20 sequence will be given a new AirFit F20 mask to take home in the same size that they currently use. Participants will not be fit with the AirFit F20 mask by the clinician or have their therapy pressure applied with their PAP device.

Participants cannot be given a mask for the second period unless they have returned the mask from the first period.

6.5 Visit 3 (Second Follow-Up Visit)

After the second 15-day home use period, participants will return to the site for their third study visit. Participants will be instructed to bring the second study mask and any associated parts and/or cushions to return at this visit. It is anticipated that the procedures during this visit will take approximately 30 minutes to complete. Details of visit procedures are outlined below.

6.5.1 Mask Survey

Participants will be asked to complete a survey providing feedback on attributes of the second mask, including comfort of breathing.

6.5.2 Review of AEs

Refer to Section 15 for Safety Monitoring.

6.5.3 Sleepiness and Health-Related Quality of Life

Participants will be asked to complete the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness for the previous 15 days. Participants will also be asked to complete the EQ-5D-3L, which will assess their health-related quality of life.

6.5.4 Collection of Device Data

Participants will be instructed to bring their therapy device to the visit. The site coordinator will confirm the data has been uploaded into AirView. If data appears to be missing, data can be manually uploaded to AirView. De-identified data from participants' PAP devices will be extracted from the connected ResMed device software, AirView. Extracted data will include average unintentional leak, AHI, usage and pressure data collected during the previous trial period. Data collected outside the trial period (i.e., prior to Visit 2, after study completion) will not be extracted. The site coordinator will manually enter the extracted device data into the Electronic Data Capture (EDC) system.

6.6 Unscheduled Phone Calls

Documentation of unscheduled phone calls will be captured within the EDC.

6.7 Completion

6.7.1 Subject

Once the participant returns the study mask at Visit 3 and completes the required surveys, their participation in the investigation will be complete. Participants will be active in the investigation for up to 36 days after receipt of the first study mask.

6.7.2 Clinical Investigation

The clinical investigation will end when all participants have completed all study procedures.

6.8 Participant Compensation

Participants who complete Visit 3 and return both of their study masks and any associated parts and/or cushions will be compensated with a \$200.00 gift card for their time and participation in the study. Pro-rated compensation will be provided to participants who voluntarily drop out of the study or are withdrawn from the study by the investigators or their designee (i.e., due to an AE). In that scenario, participants will be reimbursed based on the following schedule:

Table 5a. Schedule of Payments for Study Activities for **AirFit F20→Trillium** treatment sequence

Visit	Activity	Timing	Payment Amount
Visit 1	Consent/Eligibility/Surveys Dispense AirFit F20	~30 minutes	\$50
Visit 2 Day 15 (± 3 days)	Surveys/Mask return Mask Fitting (Trillium)	~30 minutes ~30 minutes	\$50 \$50
Visit 3 Day 30 (± 3 days)	Surveys/Mask return	~30 minutes	\$50
Total paid after Visit 3			\$200

Table 5b. Schedule of Payments for Study Activities for **Trillium→AirFit F20** treatment sequence

Visit	Activity	Timing	Payment Amount
Visit 1	Consent/Eligibility/Surveys Mask Fitting (Trillium)	~30 minutes ~30 minutes	\$50 \$50
Visit 2 Day 15 (± 3 days)	Surveys/Mask return Dispense AirFit F20	~30 minutes	\$50
Visit 3 Day 30 (± 3 days)	Surveys/Mask return	~30 minutes	\$50
Total paid after Visit 3			\$200

6.9 Arrangements for Subjects Following Participation

After completion of the clinical investigation, participants will be instructed to return to using their prescribed PAP mask. Each patient's health care provider will be responsible for the ongoing clinical care of each participant. Philips will not make any adjustments or recommendations regarding PAP device settings, beyond troubleshooting aspects of mask fit if necessary.

6.10 Suspension or Premature Termination

6.10.1 Subject

The term 'discontinuation' refers to the participant's premature withdrawal from the study prior to completing all procedures. Participants may be discontinued from the study for any of the following reasons:

- At the discretion of the PI or his designee, if he/she believes that continuing with the protocol is not in the best interest or may prove harmful to the participant. Such a decision may be precipitated by

adverse events, including fever, nausea, rash, changes in vital signs, or the development of a new medical condition. The investigator will be responsible for making medical/safety decisions regarding the participants continuing in the study.

- At the request of the participant for any reason (or none)
- At the request of the sponsor
- Non-compliance, as defined by failure to respond to phone and/or email contact after three attempts made by a study representative or failure to attend study appointment(s) (lost to follow-up), or being unwilling/unable to consistently use PAP (at least 4 days per week) along with the provided mask
- If the study mask/s provided is/are found to be inadequate for use (e.g., seal, stability, comfort, air flow, etc.)
- If eligibility status changes during the study and the participant no longer meets inclusion or exclusion criteria

The study team will document whether or not each participant completed the study. If, for any participant, study treatment or assessments were discontinued, the reason will be recorded. No further data will be collected following study withdrawal. Each participant's health care provider will be responsible for follow-up care following study withdrawal with communication from research staff.

Participants may withdraw from the study at any time. Withdrawal from the study will not affect their medical treatment or future participation in a research study.

6.10.2 Clinical Investigation

There are no predetermined criteria for suspension or premature termination of the clinical investigation. Should the study be suspended or terminated prematurely, participants will be instructed to return to using their prescribed PAP mask. Participants will receive follow-up care from their health care provider.

7 Statistical Design & Analysis

7.1 Determination of Sample Size

This pilot study will randomize approximately 40 participants in order to complete with 35 evaluable participants.

There are no formal power calculations for this pilot study, however the sample size of 35 participants is expected to provide sufficient estimates of treatment effect and variability. The results will be used for formal power analyses in future studies.

For continuous endpoints, a sample size of 35 will produce a two-sided 95% confidence interval (CI) with a distance from the mean to the limits that is no more than 1.7 when the estimated standard deviation (SD) is at most 4.

For binary endpoints, a sample size of 35 will allow us to estimate the proportion of participants who meet the criteria, and the corresponding two-sided 95% CI with a total width no more than 35%.

This is a crossover study and all participants will be exposed to both treatment groups. Participants will be randomly assigned in a 1:1 manner to one of two treatment sequences.

- Sequence 1: Trillium mask followed by AirFit F20 mask
- Sequence 2: AirFit F20 mask followed by Trillium mask

7.2 General Considerations

A separate Statistical Analysis Plan will provide detailed descriptions of all planned analyses. The Statistical Analysis Plan will be completed prior to database lock.

All variables will be summarized using descriptive statistics. The statistics for continuous variables include the number of non-missing observations, mean, median, SD, minimum, maximum, and 95% CI for the mean. For categorical variables, the number and percentage of participants with the event will be presented.

Unless otherwise specified, all statistical tests will be two sided.

All analyses will be conducted using SAS® software.

All results will be presented in data listings.

7.3 Populations for Analysis

7.3.1 Performance Analysis Set

The Performance Analysis Set will include all randomized participants with sufficient data to conduct analyses of performance endpoints. All analyses of performance endpoints will be conducted on the Performance Analysis Set. Participants will be analyzed according to the actual treatment received.

7.3.2 Safety Analysis Set

The Safety Analysis Set will include all participants who receive treatment. All safety analyses will be conducted on the Safety Analysis Set. Participants will be analyzed according to the actual treatment received.

7.4 Participant Disposition

Participant disposition, including the total number of participants enrolled, randomized, completed and early terminations, will be presented. In addition, a listing will be provided with the reasons for early termination.

7.5 Statistical Analysis

This is the first clinical investigation of the Trillium FFM in patients with OSA. The data will be used to assess the performance and safety of the Trillium FFM, and to assess the appropriateness of acceptance criteria. Accordingly, statistical models may be used, but all analyses will still be considered informative in nature. The details of all analyses will be further described in the Statistical Analysis Plan.

7.5.1 Primary Outcome Analysis

For continuous outcomes, liner mixed effect models will be used to estimate treatment effects. The models will account for the crossover design of the study and may adjust for covariates or other factors deemed relevant and appropriate. Adjusted means, standard errors (SE) of the means, and 2-sided 95% CIs will be presented for each treatment, and for the difference in treatments.

For categorical outcomes, results will be summarized using frequency counts and percentages. Shift tables will be used to compare treatment groups.

7.5.2 Pass/Fail Criteria

Preliminary success criteria are presented in Section 4. This pilot study will assess the usability and appropriateness of these criteria.

7.5.3 Subgroup Analysis

If demographic or baseline characteristics show imbalances which may affect interpretation, subgroup analyses accounting for such factors may be conducted.

7.5.4 Multiplicity Control

No adjustments for multiplicity will be made in this pilot study.

7.5.5 Level of Significance

All hypothesis tests will be conducted at an unadjusted significance level of $\alpha = 0.05$.

7.5.6 Multicenter Investigations

This is a single-center study.

7.5.7 Management of Bias

This is conducted as an open-label, crossover study. Due to the nature of the products, the study cannot be blinded.

Participants will be exposed to both treatments in this crossover design. The order of treatment usage will be randomized, which should reduce time-order confounding effects.

Any discrepancies from the planned randomization will be documented as protocol deviations. If the deviations are thought to significantly affect the outcomes, then sensitivity analyses may be conducted excluding such participants.

While there is no wash-out period included in this study, the duration of usage for each treatment is 15 days. This is expected to be sufficient enough time for any subjective carryover effects to dissipate.

Assessment of carryover effects will be considered during the statistical analysis.

7.6 Participant Accountability and Missing Data

Methods for handling missing data will be described in the Statistical Analysis Plan.

7.7 Safety Analysis

Adverse events will be summarized descriptively.

7.8 Interim Analysis

There are no interim analyses planned for this study. The final analysis will occur once all data have been entered and the database is locked.

7.9 Exploratory Analysis

Various exploratory analyses may be performed, including subgrouping, correlation, regression, and text analytics, in order to investigate the relation between baseline factors and study endpoints. These analyses could support algorithm development or aid in future study design, but they are not required for the final study report.

7.10 Deviations from Planned Analysis

Any deviations from the planned statistical analysis will be documented in the clinical investigation report with rationale provided for each.

8 Data Management

8.1 Case Report Forms

Study-related case report forms (CRFs) and source documentation will be collected and maintained by the study site. All such documentation will be kept confidential and stored on a secure server or protected device. Only staff delegated by the PI will have the ability to enter or make changes to the CRFs and source documents. Records will be maintained by the sponsor per trial master file regulations.

The following source/CRFs will be used during the study:

- **Demographics Questionnaire:** Collects information about age, sex, race, and ethnicity.
- **Eligibility Assessment:** Captures self-reported inclusion and exclusion information. The participant will sign and date the consent form attesting that all information noted on the Eligibility Assessment was reported by the participant and true.

- **Mask Information Survey:** Captures the mask (cushion/frame, headgear) sizes and fitting observations.
- **Visit 2 Mask Survey:** Administered at Visit 2 to capture subjective feedback on attributes for the mask used during the prior study period.
- **Visit 3 Mask Survey:** Administered at Visit 3 to capture subjective feedback on attributes for the mask used during the prior study period.
- **Epworth Sleepiness Scale:** Questionnaire used to assess daytime sleepiness
- **EQ-5D-3L:** Questionnaire that measures health-related quality of life
- **Adverse Event:** Captures adverse events
- **Serious Adverse Event:** Captures SAE information
- **Device Data Report:** Captures PAP device data
- **Device Event/Deficiency:** Captures a device event/deficiency
- **Device Tracking and Disposition:** Captures name of device dispensed, device ID, date device dispensed/returned
- **Documentation of Informed Consent:** Captures verification of Informed Consent process
- **Protocol Deviation:** Captures protocol deviation information
- **Subject Disposition:** Captures last visit completed and completion/discontinuation date
- **Unscheduled Call:** Documents an unscheduled call between the participant and study site
- **Disinfection Log:** Captures disinfection process when a site PAP device is used in place of a participant's PAP device
- **Site Personnel Log:** Documents training and delegated tasks for all study staff
- **Site Visitor Log:** Captures sponsor visitor information if sponsor visits the study site

All source/CRFs are provided as a separate package.

8.2 Documentation Collection and Maintenance

Data and source documentation collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. All data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system provided by the Sponsor. The data will be housed within a secure server and accessible only to the sponsor, study personnel, and investigators. Access to the EDC system will be secured through logins managed by a system administrator and appropriate training will be provided. The EDC system provides the capability to perform data management activities within a consistent, auditable, and integrated electronic environment (data security, data entry, data validation). Data entries and modifications will be recorded via an audit trail. If the data manager or study monitors identify data errors or inconsistencies, they will generate queries that will be sent to the Principal Investigators and study staff. After queries are resolved, the database will be locked, and the data will be imported into statistical software and analyzed by biostatisticians. After completion of the study, all study data will be monitored by the study team in partnership with the clinical trial staff and site investigator as outlined in the Monitoring Plan.

Hard copies of study documents, if required, will be kept on site for at least two years after study completion. The sponsor will maintain study records until the study product's end of life (EOL) + 15 years. Records will be stored at Iron Mountain, a secure information management services company.

9 Quality Assurance/Quality Control

9.1 Monitoring Plan

Onsite and/or remote monitoring will be conducted for this study. Monitoring details will be outlined in the monitoring plan. The monitoring plan will be maintained and updated as needed by the study team.

This clinical study will be monitored by Philips (Sponsor) in compliance with the Code of Federal Regulations (CFR) for clinical research, ISO 14155 and MDR as applicable. The purpose of such monitoring is to ensure the study remains in compliance with the approved protocol, investigator agreement and regulatory requirements, to verify the completeness, reliability, accuracy of study data and to resolve any issues that arise during the conduction of the study.

9.2 Training

The PI and study personnel will be trained to the study protocol, study product, trial master file (TMF) documents, monitoring plan, CRFs and/or eCRFs, direct data entry (see associated task), and all Sponsor expectations, as applicable. Once complete, training and delegations will be documented for PI and study personnel.

10 Benefits & Risks

10.1 Benefits

Effective treatment of OSA enhances sleep quality, boosts cognitive function, improves mood and elevates overall quality of life. Long-term compliance can also reduce the risk of health complications associated with untreated OSA including cardiovascular diseases, stroke, hypertension, and diabetes.

Trillium mask is designed to be user friendly and reduce pressure points of the mask. The Trillium mask is designed to be user-friendly and minimize pressure points, providing greater comfort. This study will introduce participants to additional mask options in terms of size, style, and fit, tailored to accommodate individual preferences and facial anatomy. Improved patient comfort with these new mask options may lead to increased compliance.

Participants in the study are already on therapy and maintaining compliance. While they may experience improved comfort and potentially increase their mask wear time, they will not gain the benefit of transitioning to initial compliance, as they are already compliant.

10.2 Risks

Participants may encounter various side effects such as redness, marks, indentations, pressure, skin irritation, skin breakdown, bruising, blistering, discomfort or irritation of the eyes (itchiness, excessive tearing, burning, dryness, puffiness, infection, blurred vision), dry mouth, dry upper airway, nasal irritation, nose bleeds, excessive running of the nose, claustrophobia, anxiety, chest discomfort, shortness of breath, headaches, increased drowsiness, tooth/gum/jaw soreness, aggravation of an existing dental conditions, pain/ pressure in the ears, temporary sleep disturbances, aerophagia, or allergic reactions. There is also a risk of loss of patient confidentiality.

Study masks that contain magnets can interfere with implants or the participant or bed partner. The harms associated with interference would vary depending on the implant. Study participants would be excluded from participating if they or their bed partner have impacted implants or have been advised to avoid magnets.

Careful mask application, sizing, and adjustment should mitigate many of the mask related risks including skin related harms, headaches, and irritation of the eyes. Breathing discomfort should be transient or can be addressed with counselling. Participants will be able to discontinue use of the study mask at any time. They will have access to their original mask, ensuring no prolonged interruption in therapy.

The study materials provided to the participants, including mask instructions for use, list contraindications and warnings.

The exclusion criteria rule out patients with known allergies to mask materials, abnormalities that could affect proper fit, as well as those considered high-risk.

Many of the risks associated with the study stem from PAP therapy and not masks specifically. These risks are mitigated by only including patients who are already established on therapy. Being established on therapy means that participants already have acclimated to the therapy pressure and have determined appropriate comfort settings. Acclimation to the delivered therapy pressure would lead to a reduced risk of ear pain/pressure, and anxiety. Establish therapy participants would have humidifier settings optimized decreasing the risk of oronasal dryness and the harms associated.

10.3 Benefit–Risk Ratio

Participants in the study are already receiving established therapy and are not considered a high-risk population. Many of the risks associated with the study are self-limiting and have mitigations in place to minimize their occurrence and severity. Providing participants with a mask option that provides increased comfort may increase therapy compliance among users. The criteria for participant selection, mask design, and study design reduce risk as low as possible. Given these findings, the benefits of study participation outweigh the associated risks of use of the study product.

11 CIP Modifications/Amendments & Deviations

11.1 Modifications/Amendments

The IRB will be notified of all changes made to the CIP, including changes that are likely to have a substantial impact on the safety, health or rights of the participants or on the robustness or reliability of the clinical data generated by the investigation, as well as non-substantial modification. Any changes made will require resubmission to the IRB and reapproval of the CIP. The changes will only be implemented to the study procedures once approval has been obtained from the IRB.

11.2 Deviations

A protocol deviation is defined as the instance of failure to follow, intentionally or unintentionally, the requirements of the protocol. There will be no intentional deviations from the procedures outlined in the CIP, except if to protect the rights, safety and well-being of the human subjects under emergency circumstances. Any changes or updates made to the CIP will be reapproved through the IRB from where the CIP was initially approved. Waivers from the CIP will not be permitted.

Deviations from the procedures outlined in the CIP will be considered acceptable to protect the rights, safety and well-being of human subjects under emergency circumstances, when the investigator may deviate without prior approval of the sponsor.

The non-compliance may be either on the part of the participant, the investigator, or research staff. The PI or designee shall document and explain any deviation from the approved protocol that occurs during the study. These deviations may be major or minor/administrative in nature. The principal investigator will determine the cause and implement appropriate corrective and preventative actions for any major deviations. Please see the table below for description and reporting requirements for each type. Protocol deviations will be reported to IRB per their policy, by the site or Sponsor, as applicable. All deviations will be reviewed by the sponsor. If evidence of systemic deviations are found, the principal investigator may be disqualified from future investigations.

Table 6. Description and Reporting Requirements of Deviation Types

Type	Description	Reporting Requirements
Minor Deviation	Deviation does not have a significant effect on participant safety/rights or the scientific soundness of the study plan	Document on appropriate (e)CRF
Major Deviation	Deviation does have a significant effect on participant safety/rights and/or the scientific soundness of the study plan, or significantly impact the integrity of research data	Document on appropriate (e)CRF and report to sponsor within 7 calendar days from site awareness.

12 Product Accountability

All investigational and released products will be shipped directly to the site. The investigational products will be tracked with serial numbers. The study team will confirm with the site receipt of all products, and that it matches the records from the study team of the products shipped. Product information, including serial numbers for investigational product, will be recorded for each participant. Product use will be tracked throughout the study for each participant, including when the product was issued, the length of use, and the return date of all products. After conclusion of the study, all investigational products (used and unused) and unused released products will be collected from the site and returned to Philips. The date of receipt of the study products to Philips will be recorded and inventoried by the study team to ensure this study product has been returned. The used released product may be destroyed at the site. An inventory of products will be maintained. Following inspection of the investigational products at Philips, used investigational products will be destroyed. Unused investigational products may be used for another study, if applicable.

13 Confidentiality

Participant confidentiality and privacy will be held strictly in trust by the participating investigators, their staff, and the sponsor at all times throughout the clinical study. All data and records generated during this study will be kept confidential in compliance with all applicable local, national, and international laws and regulations governing confidentiality and data protection. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the Sponsor's requirements.

Except when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records. All participants and their research data will be assigned a unique identifier that is not derived from the participant's name or contact information. A code list linking the participants to their codes will be maintained by the Investigator. A unique source record will be available for each participant, including documentation of the ICF review process, review of Philips Privacy Policy by means of the ICF, and medical history, as applicable.

Physical documents containing participant information will be stored in locked, access-restricted areas at the site. Access will be restricted to study personnel directly involved in the research. Coded data will be stored securely on password-protected electronic systems and encrypted devices maintained by the Sponsor. The Sponsor will analyze the coded data and utilize the results for research purposes to support scientific and marketing objectives as outlined in this protocol.

The study monitor, other authorized representatives of the Sponsor, IRB, and regulatory agencies may inspect all documents and records pertaining to the study. The investigator site must provide direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection.

The data collected during this study may be reanalyzed at a later date and may be combined with the results of other studies. This possibility will be captured in the consent form. The Sponsor and third parties approved by the Sponsor may use the results of this study for other research and commercial purposes, including:

- Reviewing the safety or effectiveness of the study device and other products or therapies
- Evaluating other products or therapies for patients
- Developing a better understanding of disease
- Identifying trends within the data

No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor. The privacy of each subject and confidentiality of data shall be preserved in reports and when publishing any data.

14 Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have been outlined in the Declaration of Helsinki. The clinical investigation will also be conducted in compliance with the United States Code of Federal Regulations and international standards outlined in ISO 14155.

The clinical investigation will not begin until the required regulatory and ethical assessments have been completed with non-negative outcomes, in accordance with MDR and national legislation. Any additional requirements imposed by the IRB or regulatory authority will be followed.

15 Safety Monitoring

15.1 Definitions of Reportable Events

15.1.1 Definition of Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study product.

15.1.2 Definition of Serious Adverse Event (SAE)

An SAE is any adverse event that led to any of the following:

- a. death
- b. serious deterioration in the health of the subject that resulted in any of the following:
 - i. life-threatening illness or injury,
 - ii. permanent impairment of a body structure or a body function
 - iii. hospitalization or prolongation of patient hospitalization
 - iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
 - v. chronic disease
- c. fetal distress, fetal death or a congenital physical or mental impairment or birth defect

15.1.3 Definition of Adverse Device Effects (ADE)

An ADE is defined as any adverse event related to the use of an investigational medical device or a comparator.

15.1.4 Definition of Serious Adverse Device Effects (SADE)

Any adverse device effect that has resulted in any of the consequences characteristic of an SAE (see section 15.1.2).

15.1.5 Definition of Device Deficiencies (DD)

A DD is defined as any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunctions, use errors or inadequacy in information supplied by the manufacturer.

15.2 Foreseeable Adverse Events

Expected adverse device effects are:

- Skin effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling)
- Oronasal dryness

- Eye-related side effects
- Anxiety
- Allergic reaction
- Headache

15.3 Adverse Event Classification

15.3.1 Expected Side Effects

The severity/intensity of expected side effects will be assessed by the PI or designee using the following guidelines:

Skin Effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling)

- *Negligible/No Harm (S0)*: Red marks that go away quickly without any treatment.
- *Minor (S1)*: Red marks that remain but no intervention required. Mild peeling.
- *Moderate/Major (S2)*: Red marks, peeling or breakdown that require professional medical intervention
- *Critical/Serious (S3)*: Serious breakdown or pressure necrosis- may cause scarring

Oronasal Dryness

- *Negligible/No Harm (S0)*: Temporary discomfort that resolves when device removed.
- *Minor (S1)*: Dryness or irritation persists but is treated by patient (i.e., saline spray). May complain of minor cough or sore throat
- *Moderate/Major (S2)*: Chronic nose bleeds or cough. Requires professional medical intervention

Eye-Related Side Effects

- *Negligible/No Harm (S0)*: Dryness resolves when mask removed and does not impact therapy compliance.
- *Minor (S1)*: Eye redness/ dryness. Eye drops may be used by patient to treat.
- *Moderate/Major (S2)*: Redness, dryness and/or irritation that persist and require professional medical treatment.

Anxiety

- *Negligible/No Harm (S0)*: Temporary, able to continue therapy, doesn't impact sleep.
- *Minor (S1)*: Persist throughout night, impact to sleep or therapy
- *Moderate/Major (S2)*: Professional medical intervention needed to continue therapy

Allergic Reaction

- *Minor (S1)*: Minor symptoms that resolve without treatment or with self-treatment
- *Moderate/Major (S2)*: Require professional medical intervention
- *Critical/Serious (S3)*: Anaphylaxis

Headache

- *Negligible/No Harm (S0)*: Resolves after mask is removed.
- *Minor (S1)*: Resolves with self-treatment.

- *Moderate/Major (S2)*: Chronic or severe enough that requires professional medical intervention.

15.3.2 Other Adverse Events

The severity/intensity of all other AEs (i.e., those not described in section 15.3.1) will be assessed by the PI or designee using the following guidelines:

- *Negligible/No Harm (S0)*: Events that do not warrant treatment and do not interfere with the subject's daily activities
- *Minor (S1)*: Events result in a low level of inconvenience or concern. Events may cause some interference with functioning and may require self-treatment.
- *Moderate/Major (S2)*: Events interrupt a subject's usual daily activity and may require systemic drug therapy or other professional medical intervention
- *Critical/Serious (S3)*: Meets the definition of SAE as outlined in Section 15.1.2

15.4 Relationship of Adverse Event to the Study Product

All AEs must have their relationship to the study product assessed by the PI or designee who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality may be classified using the categories below. In a clinical trial, the study product must always be suspect.

- *Not Related*: The event is not known to be an effect of the study product. There is no temporal relationship between the study product and the event onset. An alternate etiology has been established. The subject never received the study product.
- *Possibly Related*: The event is a lesser known or possible effect of the study product. There is some evidence to suggest a causal relationship and a reasonable temporal relationship between the study product and the event onset. However, other factors may have contributed to the event.
- *Causally Related*: The event is a known effect of the study product (e.g., listed in Section 15.3.1). There is a temporal relationship between the study product and the event onset. The event stops or improves with discontinuation of the study product (and reoccurs on restarting).

15.5 Reporting Process

15.5.1 Adverse Event, Adverse Device Defect, and Device Deficiencies Reporting

All AEs, ADEs, and DDs will be captured on the appropriate (e)CRF as soon as possible after site's awareness. The (e)CRF may include but is not limited to the following data elements: event description, dates of onset, resolution, and site awareness, event status (e.g., ongoing), assessment of severity (intensity) and seriousness, relationship to study product or study activity, action taken, and outcome. All AEs, ADEs, and DDs occurring while on study must be documented appropriately regardless of relationship or expectedness. All AEs, ADEs, and DDs will be followed to adequate resolution.

PI or designee will record all events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the PI or designee will inquire about the occurrence of AEs, ADEs, and DDs since the last visit. Changes in the severity of an AE, ADE, and DD will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

Device deficiencies for Trillium FFM will be reported through to the Philips product development team.

15.5.2 Serious Adverse Event or Serious Adverse Device Effect

If an SAE or SADE occurs, the PI or designee completes the appropriate (e)CRF(s) for AEs, ADEs and the SAE Report ("SAE form"). The SAE form is submitted to the study sponsor as soon as possible (e.g., within 24 hours of awareness) and no later than 3 calendar days after site personnel's awareness of event. As the site gains more information (i.e., admission records, hospital discharge summaries), a new SAE form with the new information should be submitted to the Sponsor. The study sponsor is responsible for conducting an evaluation of the SAE or SADE and shall report the results of such evaluation to the reviewing IRB and other relevant parties as applicable.

15.6 Data Safety Monitoring

It has been determined that this study does not require a data safety monitoring board (DSMB). The participants included in this investigation are existing PAP users and this investigation poses minimal risk and minimal burden on the participant in comparison with the standard of care treatment of the patient's condition.

16 Publication Policy

Results of this pilot study will not be submitted for publication. This study is not intended to support claims validation or regulatory submissions; however, it is a Phase II clinical investigation and will be registered on ClinicalTrials.gov as an applicable clinical trial.

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18 Choice of Evaluators

The qualifications of the evaluators of this Clinical Investigation Plan are provided in **Table 7**.

Table 7. Evaluator Qualifications

Name, Title	Education	Relevant Experience	Role/Responsibility
[EVALUATOR NAMES AND PROFESSIONAL DETAILS REDACTED]			

19 Appendices

Appendix 1 – Instructions for Use

20 Record Version History

Version	Author	Section	Description of Change(s)
00	[REDACTED]	All	Initial version.
01		Document Control page	Administrative change: updated IRB information
02		15.3.2	Updated Minor (S1) severity definition
[REDACTED] See current EDMS for Approvals and Validity Date			