Study Protocol

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

ClinicalTrials.gov identifier

NCT07444749

Document version

01

Document date

8-Apr-2026

Source document identifier

ER2257120

Public disclosure copy with privacy redactions

Administrative cover; scientific content and document version/date are retained.



Clinical Investigation Plan

Clinical Investigation Plan

Project/Product:
Trillium

Study Title:
A Phase III Randomized Crossover Study to Validate the Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea

Study Identification Number:
SRC-301688-Trillium Pivotal

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

Document Control Page

Author: Sara Garbin

Principal Investigator: See site information below.

Coordinating Investigator: N/A – Coordinating Investigator not needed as this is a single-site study.

Participating Study Site:

Principal Investigator:
Alaa El-Gendy, MD, M.Sc., FCCP

Site Name:
Florida Lung & Sleep Associates

Site Address:
Study Record Storage
2625 Lee Blvd., Suite 100
Lehigh Acres, FL 33971 USA

Study Conduct
14651 Palm Beach Blvd, Suite 105
Fort Myers, FL 33905

Site Telephone Number:
(+1) 239-369-3333

Institutional Review Board or Independent Ethics Committee (IRB/IEC):
Allendale Institutional Review Board
14 Somerset Lane
Old Lyme, CT 06371 USA
(+1) 860-575-0092

Study Monitor:
Name: Kristi Seese
Title: Clinical Study Manager
Phone: [redacted]
Email: [redacted]

Sponsor Safety Event (Adverse Events (AEs), Adverse Device Effects (ADE), and Serious AEs/ADEs) Reporting Contact:
Name: Kristi Seese
Title: Clinical Study Manager
Phone: [redacted]
Email: [redacted]

See Section 15 for details on safety event types, reporting methods, and reporting timelines.

Investigator Agreement

As Investigator of the study entitled "A Phase III Randomized Crossover Study to Validate the Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea"; Protocol ID: SRC-301688-Trillium Pivotal, 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: _____

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1 Clinical Investigation Synopsis

Table 1. Protocol Synopsis

Clinical Investigation Title & ID	A Phase III Randomized Crossover Study to Validate the Clinical Safety, Performance, and Benefit of the Trillium Full Face Mask in Patients with Obstructive Sleep Apnea SRC-301688-Trillium Pivotal
Project Name	Trillium
Sponsor Name and Address	Philips RS North America LLC f/k/a Respironics, Inc. 1010 Murry Ridge Ln Murrysville, PA 15668 USA
Participating Location and Country	Florida Lung & Sleep Associates Study Records Storage: 2625 Lee Blvd., Suite 100, Lehigh Acres, FL 33971 USA Study Conduct: 14651 Palm Beach Blvd, Suite 105, Fort Myers, FL 33905
Investigational Device	Trillium Full Face Mask (FFM)
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 prespecified acceptance criteria among patients with OSA that are already established on PAP therapy.
Clinical Development Stage	Pre-Market Validation Clinical Investigation Using Production-Equivalent Trillium FFM devices

Objectives	This clinical investigation has three objectives: 1. Clinical Safety—To objectively validate the clinical safety profile of the Trillium FFM. 2. Clinical Performance—To objectively and subjectively validate the clinical performance of the Trillium FFM. 3. Clinical Benefit—To objectively and subjectively validate the clinical benefit of the Trillium FFM.
Endpoints	This clinical investigation has following endpoints: 1. 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 2. Clinical Performance ○ Device Detected Unintentional Leak ○ Subjective Patient-Reported Comfort of Breathing 3. 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	<u>Inclusion Criteria</u> 1. Aged 21–85 years (inclusive) 2. Diagnosed with OSA 3. Established on PAP therapy for ≥90 days at the time of consent 4. 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) 5. Able to read, write, speak and understand English 6. Willing and able to provide informed consent 7. Willing and able to follow instructions and complete all activities required by the study 8. Able to remove the mask by themselves 9. Currently using a ResMed PAP therapy device with a connection to ResMed's AirView system 10. Currently using ResMed AirFit F20 <u>Exclusion Criteria</u> 1. Participation in the previous pilot investigation for Trillium FFM 2. Employee or family member who works for Philips or any of its direct competitors in the sleep industry 3. Currently participating in another interventional research study or planned participation in another interventional clinical research study during the trial period 4. Significant risk of aspiration (i.e., active vomiting or taking a prescription drug that induces vomiting) 5. Known allergy to silicone, latex, polyamide (nylon), spandex, polyurethane, acetal, polycarbonate, or polypropylene 6. Active infection or inflammation in an area in contact with the mask 7. Recent head or facial surgery unless cleared by a healthcare provider to resume regular therapy 8. Planned head or facial surgery during the study 9. 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 10. Prescribed oxygen at night or continuously

	11. Prescribed an ASV (adaptive servo-ventilation) device 12. Prescribed mechanical ventilation 13. Pre-existing conditions such as bullous lung disease, pathologically low blood pressure, bypassed upper airway, pneumothorax, pneumocephalus, cerebral spinal fluid (CSF) leaks 14. Any unstable medical condition (e.g., uncontrolled cardiac, lung, or neurological disease) or limitation that would affect the subject's ability to complete trial activities 15. 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 16. Pregnant (self-report) 17. Advised by a health care provider to avoid magnets 18. Patient or anyone in close physical contact during patient's use of the mask with any of the following: ○ Active medical implants that interact with magnets, including but not limited to: ▪ Pacemakers ▪ Implantable cardioverter defibrillators ▪ Neurostimulators (in or around the head or neck) ▪ Cerebrospinal fluid shunts ▪ Insulin/infusion pumps ○ Metallic implants/objects containing ferromagnetic material placed in upper limbs, torso, or higher (i.e., heck and head), including but not limited to: ▪ Aneurysm clips/flow disruption devices ▪ Embolic coils ▪ Stents ▪ Valves ▪ Electrodes ▪ Implants to restore hearing or balance with implanted magnets ▪ Ocular implants or splinters in the eye ▪ Cranial plates ▪ Bone substitute devices ▪ Denture attachments 19. Paralysis of the hemi-diaphragm
Study Design	This will be a Phase III, single-center, two-treatment, two-period, open-label, randomized crossover design pivotal study to validate the clinical safety, clinical performance, and clinical benefits of the Trillium FFM.
Duration of the Clinical Investigation	There are three visits planned for this clinical investigation. The investigation is anticipated to last approximately 30 days for each enrolled subject. The clinical investigation is expected to last 45 days.
Statistical Considerations	<u>Sample Size Determination</u> Based on a previous internal study, with similar subject enrollment criteria, it is assumed that the leak rate for the Trillium mask will be within 13 L/min, with standard deviation of 23. Under these assumptions, a sample size of 37 subjects will provide 80% power to show that the Trillium mask meets the pass criteria of leak rate no more than 24 L/min, at a significance level of α=0.025 using a one-sided one-sample t-test. To account for possible attrition, ~45 subjects will be enrolled in order to complete with the required 37 evaluable subjects. <u>Statistical Analysis</u> 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 subjects 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. For continuous outcomes, linear mixed effect models will be used to estimate treatment effects. The models will account for the crossover design of the study. Adjusted means, standard errors of the means, and 2-sided 95% confidence intervals will be presented for each treatment, and for the difference in treatments.

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

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 Trillium FFM is intended to provide an interface for the application of non-invasive PAP therapy. The mask is intended for single-patient reuse in the home environment and healthcare facilities and/or hospital environments. The mask is to be used by adult patients weighing more than 66lb (30kg) for whom non-invasive PAP therapy has been prescribed for sleep disordered breathing or respiratory diseases (e.g., obstructive pulmonary diseases, restrictive pulmonary diseases, central respiratory diseases, obesity hypoventilation syndrome). The device is not intended for critical care patients.

This study will use a production-equivalent version of the Trillium FFM. For the purposes of this trial, the mask will be labeled with the name "Simplicity".

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

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

Table 2. Technical and Functional Features

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	Built-in exhalation: Anti-asphyxia valves and exhalation (multi holes) are both integral to the elbow. The cushion does not contain any exhalation. Dead space volume: Small Cushion: 198 mL Medium Cushion: 225 mL Large Cushion: 248 mL Small Wide Cushion: 223 mL Total Mask Leak: 16 L/min @ 4 cm H2O 32 L/min @ 13 cm H2O	Built-in exhalation: Multi-hole vent array in elbow assembly - vent holes providing continuous air leak to flush out and minimize the amount of CO_2 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 Dead space volume (Large cushion): 240 mL Total Mask Leak: 19 L/min @ 3 cm H_2O 37 L/min @ 10cm H_2O

<table>
<tr><th>Device Name</th><th>Trillium</th><th>AirFit F20</th></tr>
<tr><td></td><td>44 L/min @ 22 cm H2O
55 L/min @ 31 cm H2O
64 L/min @ 40 cm H2O

Pressure range: 4 cm H_2O to 40 cm H_2O

Anti-asphyxia Feature Activation Pressures:
Closed to Atmosphere: 1.8 cm H_2O
Open to Atmosphere: 1.5 cm H_2O

Total Mask Pressure Drop:
0.2 cm H_2O @ 50 L/min
0.9 cm H_2O @ 100 L/min

Resistance w/Anti-Asphyxia Valve Open to Atmosphere at 50 L/min:
Inspiratory: 1.6 cm H_2O
Expiratory: 1.3 cm H_2O</td><td>48 L/min @ 16 cm H_2O
60 L/min @ 24 cm H_2O
69 L/min @ 30 cm H_2O
82 L/min @ 40 cm H_2O

Pressure range: 3 cm H_2O to 40 cm H_2O

Anti-asphyxia Feature Activation Pressures:
Closed to Atmosphere: ≤ 3 cm H_2O
Open to Atmosphere: ≤ 3 cm H_2O

Total Mask Pressure Drop:
0.2 cm H_2O @ 50 L/min
0.6 cm H_2O @ 100 L/min

Resistance w/Anti-Asphyxia Valve Open to Atmosphere at 50 L/min:
Inspiratory: 0.6 cm H_2O
Expiratory: 0.8 cm H_2O</td></tr>
<tr><td>Physical Properties</td><td>Sizes: 4 cushion sizes (small, small wide, medium, large); adjustable frame; 2 headgear sizes (small, standard)

Temperature:
Operating temperature: 5 °C to 40 °C
Storage temperature: –20 °C to 60 °C

Patient Circuit connection: 22 mm</td><td>Sizes: 3 cushion sizes (S, M, L); 3 frame sizes (S, M, L); 3 headgear sizes (S, Std, L)

Temperature:
Operating temperature: 5 °C to 40 °C
Storage temperature: –20 °C to 60 °C

Patient Circuit connection: 22 mm</td></tr>
<tr><td>Chemical Properties</td><td>Materials and biocompatibility: The following materials are used in the Trillium FFM:<table><tr><th>Component</th><th>Material</th></tr><tr><td>Cushion</td><td>Silicone, Polycarbonate</td></tr><tr><td>Frame (w/magnets)</td><td>Polycarbonate, Thermoplastic copolyester elastomer, Polybutylene terephthalate, Nickel coated magnet</td></tr><tr><td>Fabric Sleeves</td><td>Nylon, Spandex</td></tr><tr><td>Elbow</td><td>Polycarbonate, Polyoxymethylene (acetal/ POM), Silicone</td></tr><tr><td>Magnetic Headgear Clips</td><td>Polybutylene terephthalate, Nickel coated magnet</td></tr><tr><td>Headgear</td><td>Nylon, Spandex, Polyurethane foam, polypropylene</td></tr></table></td><td>Materials and biocompatibility:
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.</td></tr>
<tr><td>Software (if applicable)</td><td>N/A – no associated software</td><td>N/A – no associated software</td></tr>
<tr><td>Incorporated Medicinal Substances</td><td>N/A – no incorporated medicinal substances</td><td>N/A – no incorporated medicinal substances</td></tr>
<tr><td>Sterile/Non-Sterile</td><td>Non-sterile</td><td>Non-sterile</td></tr>
<tr><td>Disposable/Reusable</td><td>Reusable</td><td>Reusable</td></tr>
</table>

Device Name	Trillium	AirFit F20
Cleaning and Maintenance	Cleaning: **Daily**: Hand wash the elbow, frame, and cushion **Weekly**: Hand wash the headgear Note: For all cleaning and rinsing steps, use potable (safe to drink), warm water (80–90°F/27–32°C). 1. Disassemble your mask. 2. Create a cleaning solution by mixing 1 teaspoon (5 mL) of mild liquid detergent per 1 gallon (3.8 liters) of water. 3. Fully submerge the mask parts in the cleaning solution and gently wash by hand for at least 1 minute. A soft-bristled brush may be used to remove any buildup in the elbow. Note: Make sure there are no air bubbles inside the mask parts while they are submerged. To release air bubbles trapped in mask parts, gently tap the parts or move them slightly. 4. Remove the mask parts from the cleaning solution. 5. Rinse both fabric and non-fabric parts under running water for at least 1 minute. Remove any remaining dirt or detergent by gently rubbing non-fabric parts and squeezing fabric parts. 6. Inspect mask parts to ensure they are visibly clean and all detergent is removed. If necessary, wash or rinse the mask again. If mask cannot be cleaned, discard and replace it. 7. Air dry mask parts out of direct sunlight. Lay the headgear flat or hang it up to dry. Make sure the entire mask is dry before use. Maintenance: N/A – this is a non-serviceable part	Cleaning: **Daily/After each use**: 1. Disassemble the mask according to the disassembly instructions. 2. Rinse the frame, elbow and cushion under running water. Clean with a soft brush until dirt is removed. 3. Soak the components in warm water (approximately 86°F/30°C) with a mild liquid detergent for up to ten minutes. 4. Shake the components vigorously in the water for at least one minute. 5. Brush the moving parts of the elbow and around the vent holes. 6. Brush the areas of the frame where the arms connect, and inside and outside the frame where the elbow connects. 7. Rinse the components under running water. 8. Leave the components to air dry out of direct sunlight. Make sure to squeeze the arms of the frame to ensure that excess water is removed. **Weekly**: 1. Disassemble the mask. The magnets can remain attached to the headgear during cleaning. 2. Handwash the headgear in warm water (approximately 86°F/30°C) with mild liquid detergent. 3. Rinse the headgear under running water. Inspect to ensure the headgear is clean and detergent free. Wash and rinse again, if necessary. 4. Squeeze the headgear to remove excess water. 5. Leave the headgear to air dry out of direct sunlight. Maintenance: 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	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

Device Name	Trillium	AirFit F20
	frame contacts the cheek, and the headgear wraps around the head.	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	The useful life of the mask depends on the use conditions and maintenance (cleaning, institutional disinfection, and component replacement) of the device. Inspect the mask parts regularly for damage or wear (see Before Use and Mask Care sections of the IFU). Replace components as deemed necessary.	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 products will be used in this study.

4 Objectives, Endpoints & Hypotheses

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
Clinical Safety Objective: *To objectively evaluate the clinical safety profile of the Trillium FFM.*			
Skin Effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling, localized discomfort at the point of mask contact)	Objective Adverse Events (AEs): • **Negligible/No Harm (S0):** Red marks, indentations and/or discomfort that go away quickly without any treatment. Any AE rate (0–100%) is acceptable. • **Minor (S1):** Red marks, discomfort, irritation or mild peeling that remain after removing mask, but no intervention required. An AE rate of <20% for PAP therapy or <30% for NIV therapy is acceptable. • **Moderate/Major (S2):** Red marks, discomfort, indentations, irritation, 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, pressure necrosis, or scarring. An AE rate of 0% is acceptable.	Number and percentage of subjects with at least one event will be reported by treatment.	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. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Carron et al. 2013[13]; Esquinas et al. 2017[7]; Lemyze et al. 2023[14]; Logger et al. 2020[15]; Ma et al. 2018[16]; Parthasarathy 2008[17]; Ryan et al. 2011[18]; Singh & Pitoyo et al. 2014[6]; Ulander et al. 2014[19]; Van Ryswyk et al. 2019[20]; Yasuda et al. 2021[21]; Zhu et al. 2024[22]
Oronasal Dryness	Objective Adverse Events (AEs): • **Negligible/No Harm (S0):** Temporary discomfort from dryness that resolves when device removed. Any AE rate (0–100%) is acceptable. • **Minor (S1):** Dryness or irritation persists but is treated by patient (i.e.,	Number and percentage of subjects with at least one event will be reported by treatment.	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.

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
	saline spray). May complain of minor cough or sore throat. An AE rate of <50% for PAP therapy or <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.		Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Carron et al. 2013[13]; Ma et al. 2018[16]; Deng et al. 2023[23]; Rotty et al. 2021[11]; Ryan et al. 2011[18]; Ulander et al. 2014[19]; Van Ryswyk et al. 2019[20]; Zhu et al. 2024[22]
Eye-Related Side Effects	Objective Adverse Events (AEs): • **Negligible/No Harm (S0):** Eye dryness resolves when the device is removed and does not impact therapy compliance. Any AE rate (0–100%) is acceptable. • **Minor (S1):** Eye redness, dryness, irritation and/or other eye-related effects that is not relieved by removing the mask. Eye drops may be used by patient for self-treatment. An AE rate of <5% for PAP therapy or <10% for NIV therapy is acceptable. • **Moderate/Major (S2):** Redness, dryness, irritation and/or other eye-related effects that persist and require professional medical treatment. An AE rate of 0% for PAP therapy or <5% for NIV therapy is acceptable.	Number and percentage of subjects with at least one event will be reported by treatment.	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. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Carron et al. 2013[13]; Conde et al. 2022[24]; Deng et al. 2023[23]; Ma et al. 2018[16]; Rotty et al. 2021[11]; Ryan et al. 2011[18]; Ulander et al. 2014[19]; Van Ryswyk et al. 2019[20]; Yasuda et al. 2021[21]; Zhu et al. 2024[22]

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
	• **Critical/Serious (S3):** N/A – This severity rating does not apply to this AE.		
Anxiety	Objective Adverse Events (AEs): • **Negligible/No Harm (S0):** Temporary, able to continue therapy, doesn't impact 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.	Number and percentage of subjects 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 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. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Carron et al. 2013[13]; Deng et al. 2023[23]; Esquinas et al. 2017[7]; Ma et al. 2018[16]; Parthasarathy 2008[17]; Ryan et al. 2011[18]; Ulander et al. 2014[19]; Van Ryswyk et al. 2019[20]
Allergic Reaction	Objective Adverse Events (AEs): • **Negligible/No Harm (S0):** N/A – This severity rating does not apply to this AE. • **Minor (S1):** Minor symptoms that	Number and percentage of subjects with at least one event will be reported by treatment.	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.

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
	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.		Relevant Considerations for Interpretation of Results: 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. Relevant Sources: Felmingham et al. 2019[25]; Ma et al. 2018[16]; Parthasarathy 2008[17]; Prasad & Reeder 2021[26]; Rath & Kaplish 2022[27]; Scalf & Fowler 1999[28]
Headache	Objective Adverse Events (AEs): • **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 percentage of subjects with at least one event will be reported by treatment.	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 Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Bettega et al. 2022[29]; Chang et al. 2022[30]; Deng et al. 2023[23]; Ma et al. 2018[16]; Massongo et al. 2022[31]; Reddy et al. 2022[32]; Ryan et al. 2011[18]
Clinical Performance Objective: *To objectively and subjectively evaluate the clinical performance of the Trillium FFM.*			
Unintentional Leak	Objective Leak via Device Leak Data: • **Device Detected Unintentional Leak:** ≤24 L/min (based on upper bound of the 95% confidence interval)	Descriptive statistics will be presented. Mixed model analyses will be used to estimate	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

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
		the mean leak per treatment, and the treatment difference.	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. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: BaHammam et al. 2017[12]; Carron et al. 2013[13]; Chihara et al. 2013[33]; Deng et al. 2023[23]; Donovan et al. 2015[34]; Esquinas et al. 2017[7]; Kang et al. 2022[35]; Lebret et al. 2017[36]; Ma et al. 2018[16]; Preutthipan 2015[37]; Rossetto et al. 2023[38]; Rotty et al. 2021[11]; Ryan et al. 2011[18]; Shrivastava 2013[39]; Ulander et al. 2014[19]; Van Ryswyk et al. 2019[20]; Zhu et al. 2024[22]
Comfort of Breathing	Subjective Patient-Reported Outcomes (PRO): • **Comfort of Breathing:** Average satisfaction rating ≥7.0 on a 0–10 scale (0 indicating extremely dissatisfied, 5 neutral, 10 extremely satisfied) based	Descriptive statistics will be presented. 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

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
	on lower bound of the 95% confidence interval.		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, dysosmiais, 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. The acceptance criterion of 7.0 is selected as it is the minimum value on an 11-point Likert scale could be considered satisfied. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: Atwood et al. 2013[40]; Carron et al. 2013[13]; Donovan et al. 2015[34]; Deng et al. 2023[23]; Esquinas et al. 2017[7]; Lebret et al. 2021[41]; Ma et al. 2018[16]; Marini, 2013[42]; Parthasarathy 2008[17]; Ryan et al. 2011[18]; Ulander et al. 2014[19];Wu et al. 2022[43]
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)	Descriptive statistics will be presented. Mixed model analyses will be used to estimate the mean AHI per	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

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
		treatment, and the treatment difference.	• 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. Relevant Considerations for Interpretation of Results: • **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. • **Leak:** If AHI results do not meet acceptability criteria and leak is high (i.e., unintentional leak >24 L/min), 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. Relevant Sources: BaHammam et al. 2017[12]; Barnes et al 2017[44]; Bartolucci et al. 2023[45]; Benoist et al. 2017[46]; Certal et al, 2015[47]; Chen et al. 2019[48]; Cowie et al. 2015[49]; Cowie et al. 2017[50]; Deng et al. 2023[23]; Fu S et al. 2023[51] ; Gao et al. 2019[52]; Hernandez et al. 2020[53]; Hsu et al. 2020[54]; Iftikhar et al. 2023[55]; Kim et al. 2017[56]; Lee et al. 2023[57]; Li Y, Du J et al. 2023[58]; Liu Z et al. 2023[59]; Ma et al. 2018[16]; Meghpara et al. 2022[60]; Neruntarat et al. 2021[61]; Patil et al. 2019[5]; Randerath et al. 2021[62]; Reddy et al. 2022[32]; Rossetto et al. 2023[38]; Rueda et al. 2020[63]; Ryan et al. 2011[18]; Sawunyavisuth et al. 2023[64]; Silva de Sousa et al. 2023[65]; Srijithesh et al. 2019[66]; Strollo et al. 2014[67]; Trindade et al. 2023[68]; Trzepizur et al. 2021[69]; Van Ryswyk et al. 2019[20]; Wang Y et al. 2023[70]; Woo et al 2020[71]; Xu J et al. 2022[72]; Zhang F et al. 2022[73]; Zonato et al. 2021[74]; Zonato et al. 2022[75]

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
Adherence	Objective Adherence via Device Use Data: • **Established Patients:** No clinically meaningful decrease in usage in patients already established on therapy (non-inferiority margin = 0.5 hours device use per night)	Descriptive statistics will be presented. For continuous adherence parameters, mixed model analyses will be used to estimate the mean response per treatment, and the treatment difference.	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 • daily use (actual use 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. 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. Relevant Considerations for Interpretation of Results: • **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.

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
			Relevant Sources: BaHammam et al. 2017[12]; Chen et al. 2022[8]; Deng et al. 2023[23]; Engleman et al. 2003[76]; Lajoie et al 2023[77]; Lebret et al. 2021[41]; Ma et al. 2018[16]; Patil et al. 2019[5]; Rotty et al. 2021[11]; Ryan et al. 2011[18]; Sawunyavisuth et al. 2023[64]; Van Ryswyk et al. 2019[20]; Wu et al. 2022[43]; Yi et al. 2022[78]; Zhu et al. 2024[22]
Sleepiness	Subjective Sleepiness Outcomes: • **Epworth Sleepiness Scale (ESS):** No clinically meaningful increase in ESS score in patients already established on therapy (non-inferiority margin = 2 points)	Descriptive statistics will be presented. 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. Relevant Considerations for Interpretation of Results: • **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 L/min), then this may suggest patients are not getting effective therapy even though they are wearing the mask. Relevant Sources: Afshar et al. 2020[79]; Gao et al. 2019[52]; Kryger & Malholtra 2019[80]; Lajoie et al. 2023[77]; Li et al. 2022[81]; Mangione et al. 2022[82]; Patil et al. 2019[5]; Rotty et al. 2021[11]; Ryan et al. 2011[18]; Stajic et al 2022[83]; Trzepizur et al. 2021[69]; Weaver et al. 2023[84]
Quality of Life	Subjective QOL Instruments: • **European Quality of Life-5D (EQ-5D):** No clinically meaningful increase in EQ-5D index score in patients already established on therapy (non-inferiority margin = 0.08 points)	Each EQ-5D item will be summarized descriptively using frequency counts and percentages. For the continuous parameters (EQ VAS	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,

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

Outcomes	Acceptance Criteria	High-Level Analyses	Supporting Information
	• **Established Patients:** No significant change in QOL score in patients already established on therapy	and Index Score), mixed model analyses will be used to estimate the mean response per treatment, and the treatment difference.	neuromuscular disease, spinal injury), they also may have a broad range of comorbidities that may also independently influence patients' perceptions of QOL. Relevant Considerations for Interpretation of Results: • **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. Relevant Sources: Afshar et al. 2020[79]; Albalawi et al. 2022[85]; Breen et al. 2023[86]; Chen et al. 2019[48]; Diaz de Teran et al. 2019[87]; Hannan et al. 2014[88]; Hull et al. 2014[89]; Kryger & Malhotra 2018[80]; Patil et al. 2019[5]; Rochwerg et al. 2017[90]; Ryan et al. 2011[18]; Simonds et al. 2016[91]; Shaughnessy et al. 2019[92]; Trzepizur et al. 2021[69]; Weaver at al. 2021[84]; Windisch et al. 2018[93]; Zhang et al. 2020[94]; Zhu et al. 2024[22]

5 Design of the Clinical Investigation

5.1 General Information

This will be a Phase III, single-center, two-treatment, two-period, open-label, randomized crossover design pivotal study to validate the clinical safety, clinical performance, and clinical benefits 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 study.

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 subject. 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 CIP. 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 and methods selected for this trial are sufficiently representative of the product's intended OSA users in normal use conditions for the device (i.e., at-home nightly use). 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.

Up to 45 subjects will be enrolled and randomized, with approximately 37 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

1. Aged 21–85 years (inclusive)
2. Diagnosed with OSA
3. Established on PAP therapy for ≥90 days at the time of consent
4. 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)
5. Able to read, write, speak and understand English
6. Willing and able to provide informed consent
7. Willing and able to follow instructions and complete all activities required by the study
8. Able to remove the mask by themselves
9. Currently using a ResMed PAP therapy device with a connection to ResMed's AirView system

10. Currently using ResMed AirFit F20

Exclusion Criteria

1. Participation in the previous pilot investigation for Trillium FFM
2. Employee or family member who works for Philips or any of its direct competitors in the sleep industry
3. Currently participating in another interventional research study or planned participation in another interventional clinical research study during the trial period
4. Significant risk of aspiration (i.e., active vomiting or taking a prescription drug that induces vomiting)
5. Known allergy to silicone, latex, polyamide (nylon), spandex, polyurethane, acetal, polycarbonate, or polypropylene
6. Active infection or inflammation in an area in contact with the mask
7. Recent head or facial surgery unless cleared by a healthcare provider to resume regular therapy
8. Planned head or facial surgery during the study
9. 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
10. Prescribed oxygen at night or continuously
11. Prescribed an ASV (adaptive servo-ventilation) device
12. Prescribed mechanical ventilation
13. Pre-existing conditions such as bullous lung disease, pathologically low blood pressure, bypassed upper airway, pneumothorax, pneumocephalus, cerebral spinal fluid (CSF) leaks
14. Any unstable medical condition (e.g., uncontrolled cardiac, lung, or neurological disease) or limitation that would affect the subject's ability to complete trial activities
15. 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
16. Pregnant (self-report)
17. Advised by a health care provider to avoid magnets
18. Patient or anyone in close physical contact during patient's use of the mask with any of the following:
    a) Active medical implants that interact with magnets, including but not limited to:
        - Pacemakers
        - Implantable cardioverter defibrillators
        - Neurostimulators (in or around the head or neck)
        - Cerebrospinal fluid shunts
        - Insulin/infusion pumps
    b) Metallic implants/objects containing ferromagnetic material placed in upper limbs, torso, or higher (i.e., heck and head), including but not limited to:
        - Aneurysm clips/flow disruption devices
        - Embolic coils
        - Stents
        - Valves
        - Electrodes
        - Implants to restore hearing or balance with implanted magnets
        - Ocular implants or splinters in the eye
        - Cranial plates

- Bone substitute devices
- Denture attachments

19. 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. Subjects will be randomly assigned in a 1:1 manner to one of two treatment sequences:

- Sequence 1: Trillium mask followed by AirFit F20 mask (Trillium→AirFit F20)
- Sequence 2: AirFit F20 mask followed by Trillium mask (AirFit F20→Trillium)

By randomizing the order in which subjects 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.

Subjects 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 subject, 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 subjects 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 subjects based on available information. Patients will be contacted based on their potential eligibility. No additional pre-screening procedures will take place.

6.2 Recruitment Methods

Subjects 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. Subjects who are willing to enroll will be scheduled for an in-person visit to provide informed consent and complete study procedures.

6.3 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 subject explaining the details of the study and answering any questions the subject may have about the study. If the subject is willing to take part in the study, the ICF will be signed and dated by the subject and the site study representative obtaining consent. A copy of each subject'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 subjects will then complete the Demographics Questionnaire, which collects information about age, sex, race, and ethnicity.

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

The enrolled population will consist of all subjects 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 ICF.

6.3.2 Mask Fitting and Use

At the initial visit, subjects randomized to the Trillium→AirFit F20 sequence will undergo a fitting of the Trillium mask. Subjects 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 subject 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 subject'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 subject's mask size information (i.e., cushion/frame, headgear). The presence of facial hair will be noted on the form. If the subject is between mask sizes, they may be given an additional size mask and/or cushion to take home and use, if needed.

Subjects 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. Subjects will not be fit with the AirFit F20 mask by the clinician or have their therapy pressure applied with their PAP device.

All subjects will be instructed to use the mask for the full 15-days of the first trial period. Subjects 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, subjects will return to the site for their second study visit. Subjects 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

Subjects 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

Subjects will be asked to complete the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness for the previous 15 days. Subjects 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

Subjects 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 subjects' 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

Subjects 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.

Subjects 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. Subjects will not be fit with the AirFit F20 mask by the clinician or have their therapy pressure applied with their PAP device.

Subjects 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, subjects will return to the site for their third study visit. Subjects 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

Subjects 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

Subjects will be asked to complete the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness for the previous 15 days. Subjects 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

Subjects 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 subjects' 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 EDC.

6.7 Completion

6.7.1 Subject

Once the subject returns the study mask at Visit 3 and completes the required surveys, their participation in the investigation will be complete. Subjects 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 subjects have completed all study procedures.

6.8 Subject Compensation

Subjects 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 subjects 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, subjects 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, subjects 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 subject. 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 subject's premature withdrawal from the study prior to completing all procedures. Subjects 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 subject. 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 subjects continuing in the study.
- At the request of the subject 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 subject no longer meets inclusion or exclusion criteria

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

Subjects 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, subjects will be instructed to return to using their prescribed PAP mask. Subjects will receive follow-up care from their health care provider.

7 Statistical Design & Analysis

7.1 Determination of Sample Size

This study will randomize ~45 subjects in order to complete with 37 evaluable subjects.

The sample size for this study is based on the primary endpoint of Leak rate (L/min).

The hypothesis we wish to test is:

H_0: $\mu_{Trillium} = \mu_{Pass}$

H_A: $\mu_{Trillium} < \mu_{Pass}$

Where

$\mu_{Trillium}$ = Mean Leak rate for the Trillium mask

μ_{Pass} = Pass Criteria value = 24 L/min.

The sample size is selected based results of a pilot study, with similar subject enrollment criteria.

Assuming a mean leak rate of 13 L/min, and a SD of 23, a sample size of 37 subjects will provide 80% power to show that the Trillium mask does not exceed a leak rate of 24 L/min, with a one-sided significance level of α=0.025 using a one-sample t-test.

This sample size will also provide over 80% power to show that the Trillium mask has a mean comfort of breathing score of at least 7; assuming a mean comfort of breathing score of at least 8.3 and SD no more than 2.25 with a one-sided significance level of α=0.025 using a one-sample t-test.

To account for possible attrition, ~45 subjects will be enrolled in order to complete with the required 37 evaluable subjects.

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

- Sequence 1: Trillium mask followed by AirFit F20 mask (Trillium→AirFit F20)
- Sequence 2: AirFit F20 mask followed by Trillium mask (AirFit F20→Trillium)

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 subjects 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 Demographics

Demographic characteristics include age, sex, race, and ethnicity.

Results will be summarized using descriptive statistics.

7.4 Population for Analysis

7.4.1 Performance Analysis Set

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

7.4.2 Safety Analysis Set

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

7.5 Subject Disposition

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

7.6 Statistical Analysis

The details of all analyses will be further described in the Statistical Analysis Plan.

7.6.1 Primary Outcome Analysis

For continuous outcomes, linear mixed effect models will be used to estimate treatment effects. The models will account for the crossover design of the study. 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.

7.6.2 Pass/Fail Criteria

Success criteria are presented in Section 4.

The Trillium leak rate will be considered successful if the mean leak rate is no more than 24 L/min. This will be based on the linear mixed model analysis.

The hypothesis is:

H_0: $\mu_{Trillium} = \mu_{Pass}$

H_A: $\mu_{Trillium} < \mu_{Pass}$

Where

$\mu_{Trillium}$ = Mean Leak rate for the Trillium mask

μ_{Pass} = Pass Criteria value = 24 L/min

If the upper bound of the 2-sided 95% CI is no more than 24, then the Trillium mask leak rate will be considered successful.

The Trillium comfort of breathing will be considered successful if the mean comfort of breathing is at least 7, based on 0-10 scale. This will be based on the linear mixed model analysis.

The hypothesis is:

H_0: $\mu_{Trillium} = \mu_{Pass}$

H_A: $\mu_{Trillium} > \mu_{Pass}$

Where

$\mu_{Trillium}$ = Mean comfort of breathing score for the Trillium mask

μ_{Pass} = Pass Criteria value = 7

If the lower bound of the 2-sided 95% CI is at least 7, then the Trillium mask leak rate will be considered successful.

Additional endpoints will be analyzed similarly and will be detailed in the Statistical Analysis Plan.

7.6.3 Subgroup Analysis

No subgroup analyses are planned. If demographic or baseline characteristics show imbalances which may affect interpretation, subgroup analyses accounting for such factors may be conducted in an exploratory manner.

7.6.4 Multiplicity Control

No adjustments for multiplicity will be made in this study.

7.6.5 Level of Significance

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

7.6.6 Multicenter Investigations

This is a single-center study.

7.6.7 Management of Bias

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

Subjects 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 subjects.

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.

7.7 Subject Accountability and Missing Data

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

7.8 Safety Analysis

Adverse events will be summarized descriptively.

7.9 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.

7.10 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.

7.11 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 subject will sign and date the consent form attesting that all information noted on the Eligibility Assessment was reported by the subject 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 subject and study site
- **Disinfection Log**: Captures disinfection process when a site PAP device is used in place of a subject'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 system (EDC) 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/termination. 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 assure 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 subjects 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.

Subjects 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

Subjects 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 subject or bed partner. The harms associated with interference would vary depending on the implant. Study subjects 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. Subjects 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 subjects, 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 subjects 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 subjects would have humidifier settings optimized decreasing the risk of oronasal dryness and the harms associated.

10.3 Benefit–Risk Ratio

Subjects 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 subjects with a mask option that provides increased comfort may increase therapy compliance among users. The criteria for subject 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 subjects 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 competent authority 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. Any changes or updates made to the CIP will be reapproved through the IRB or EC 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 subject, 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. 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.

Table 6. Description and Reporting Requirements of Deviation Types

Type	Description	Reporting Requirements
Minor Deviation	Deviation does not have a significant effect on subject safety/rights or the scientific soundness of the study plan	Document on appropriate (e)CRF
Major Deviation	Deviation does have a significant effect on subject 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 subject. Product use will be tracked throughout the study for each subject, 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

Subject 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 (See Section 8.2).

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

Physical documents containing subject 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 MDR 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 investigational device.

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 AE 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 malfunction, use errors or inadequacy in information supplied by the manufacturer.

15.2 Foreseeable Adverse Events and Anticipated Device Defects

Expected adverse device effects are:

- Skin effects (i.e., localized red marks/skin irritation, breakdown, and/or peeling, localized discomfort at the point of mask contact)
- 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, localized discomfort at the point of mask contact)

- *Negligible/No Harm (S0)*: Red marks, indentations and/or discomfort that go away quickly without any treatment.
- *Minor (S1)*: Red marks, discomfort, irritation or mild peeling that remain after removing mask, but no intervention required.
- *Moderate/Major (S2)*: Red marks, discomfort, indentations, irritation, peeling or breakdown that require professional medical intervention.
- *Critical/Serious (S3)*: Serious breakdown, pressure necrosis, or scarring

Oronasal Dryness

- *Negligible/No Harm (S0)*: Temporary discomfort from dryness 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)*: Eye dryness resolves when mask removed and does not impact therapy compliance.

- *Minor (S1)*: Eye redness, dryness, irritation and/or other eye-related effects that is not relieved by removing the mask. Eye drops may be used by patient for self-treatment.
- *Moderate/Major (S2)*: Redness, dryness, irritation and/or other eye-related effects that persist and require professional medical treatment.

Anxiety

- *Negligible/No Harm (S0)*: Temporary, able to continue therapy, doesn't impact sleep.
- *Minor (S1)*: Persists 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)*: Requires 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

The occurrence of an adverse event (AE), serious adverse event (SAE), Adverse Device Defect (ADE), Serious Adverse Device Defect (SADE), or Device Deficiency (DD) may come to the attention of the study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

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 and Serious Adverse Device Defect Reporting

If an SAE or SADE occurs, the PI or designee completes both the appropriate (e)CRF 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 subjects included in this investigation are existing PAP users and this investigation poses minimal risk and minimal burden on the subject in comparison with the standard of care treatment of the patient's condition.

16 Publication Policy

Results of this validation study may be submitted for publication. This Phase III study is intended to support claims validation and will be registered on ClinicalTrials.gov as an applicable clinical trial.

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18 Appendices

Appendix 1 – Instructions for Use

19 Record Version History

Version	Author	Section	Description of Change(s)
00	[REDACTED]	All	Initial release
01	[REDACTED]	3.3	Updated mechanical characteristics, cleaning instructions and maximum repeat applications. Chemical properties (i.e., product materials) were reformatted to clarify component-level materials, including updated elbow material.

See EDMS for signatures and version dates