CLINICAL INVESTIGATION PLAN (PROTOCOL)

Study Title:	Non-Inferiority Study of the FRESCA Airbox Positive Airway Pressure System versus the (predicate) FRESCA Positive Airway Pressure System for the treatment of Obstructive Sleep Apnea
Investigational Device:	FRESCA Airbox Positive Airway Pressure System
Protocol Number:	18-01
Study Sponsor:	FRESCA Medical 1291 Puerto Del Sol, Suite 200 San Clemente, CA 92673 (949)-542-3535
Study Contact:	Mary Lou Mooney
Phone Number:	(949) 542-3535
Version Number:	C
Release Date:	April 23, 2019

NCT 03999944

1 PROTOCOL SIGNATURES

I have read the attached protocol and hereby agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol to all members of the study team responsible to me who participate in the study. I will discuss this material with them to ensure that all participating staff members are fully informed regarding the investigational device and the conduct of the protocol. Once the Institutional Review Board approves the protocol, I will not modify this protocol without obtaining the prior approval of the Sponsor and of the Institutional Review Board. I will submit the protocol modifications and/or any informed consent modifications to the Sponsor and the Institutional Review Board, and approval will be obtained before any modifications are implemented.

Investigator's Signature	Date
Investigator's Printed Name	

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2 LIST OF ABBREVIATIONS

AE Adverse Event

AHI Apnea-Hypopnea Index

APAP Auto-Adjusting Positive Airway Pressure

BMI Body Mass Index

CI Confidence Interval

CPAP Continuous Positive Airway Pressure

EPAP Expiratory Positive Airway Pressure

EPR Expiratory Pressure Relief

ITT Intent to Treat Population

mITT Modified Intent to Treat Population

ODI Oxygen Desaturation Index

OSA Obstructive Sleep Apnea

PAP Positive Airway Pressure

PSG Polysomnography

RDI Respiratory Disturbance Index

REM Rapid Eye Movement

SAE Serious Adverse Event

UADE Unanticipated Adverse Event Device Effect

3 DEFINITIONS

Apnea	Peak signal excursion (airflow) drops by ≥ 90% of pre-event baseline for ≥ 10 seconds.
Apnea Hypopnea Index (AHI)	The number of apnea and hypopnea events per hour of sleep.
Hypopnea	1. Peak signal excursion (airflow) drops by ≥ 30% of pre-event baseline for ≥ 10 seconds **AND** 2. There is a ≥ 4% oxygen desaturation from pre-event baseline.
ITT Population	Subjects who are enrolled and randomized.
mITT Population	Intent-to-treat subjects who complete a valid PSG Study during randomized sleep nights 1 and 2.
Oxygen Desaturation Index (ODI)	The number of oxygen desaturations ≥ 4% per hour of sleep.
Screen Failures	Subjects who do not meet inclusion/exclusion criteria and are therefore not enrolled in the study.
Subject ID	Assigned number that will uniquely and anonymously identify each subject within the study.
Valid PSG Study	Characterized by at least 4 hours of recorded sleep time with no equipment recording failures and results in analyzable data for AHI and ODI values.

4 PROTOCOL SUMMARY

Title	Non-Inferiority Study of the FRESCA Airbox Positive Airway Pressure System versus the (predicate) FRESCA Positive Airway Pressure System for the treatment of Obstructive Sleep Apnea
Sponsor	FRESCA Medical, Inc. 1291 Puerto Del Sol, Suite 200 San Clemente, CA 92673, USA
Investigational Device	FRESCA Airbox Positive Airway Pressure System
Investigator Study Sites	Up to 6 investigational sites in the United States
Regulatory Status	This is a non-significant risk investigational device exemption (IDE) clinical trial. FDA approval is not required, but IRB review and approval are required.
Study Design	Prospective, open-label, randomized crossover assignment, multi-center study conducted in the United States
Sample Size	Up to fifty (50) subjects will be enrolled to yield a minimum of 38 evaluable subjects (mITT subjects).
Study Objective	To demonstrate that the FRESCA Airbox Positive Airway Pressure System is non-inferior to the (predicate) FRESCA Positive Airway Pressure System.
Subject Population	Inclusion Criteria: 1. Male or female aged 22 – 75 years old. 2. BMI: ≤ 40 kg/m2. 3. Subjects diagnosed with OSA (either newly diagnosed (naive) OSA subjects or current CPAP subjects). 4. Must be able to be fitted properly with FRESCA mask. 5. Must be able to comply with all study requirements as outlined in the protocol. 6. Subject must complete a valid PSG titration night. Exclusion Criteria: 1. Subjects with non-OSA sleep disorders (including periodic limb movement (PLM) disorder and chronic insomnia). 2. Subjects with substantial central or mixed apneas (central and mixed apnea ≥ 5/hr.). 3. Subjects with prior surgical intervention for OSA. 4. Subjects with frequent or sustained episodes of O_2 saturation ≤75%. 5. Subjects with obesity-related hypoventilation. 6. Subjects currently using a CPAP full face mask. 7. Subjects who are medically unstable. 8. Subjects with unstable or severe cardiovascular abnormalities (e.g., heart failure, valvular heart disease). 9. Subjects with atrial fibrillation or other arrhythmias that are not effectively controlled with medication. 10. Subjects with hypotension or uncontrolled HTN. 11. Subjects with chronic lung disease, including COPD.

	12. Subjects with significant cardiopulmonary disease. 13. Subjects with ongoing severe nasal allergies or sinusitis or difficulty breathing through the nose; persistent blockage of one or both nostrils; or any nasal or facial abnormalities that would not allow adequate placement and use of the mask. 14. Subjects with surgery of the upper airway, nose, sinus or middle ear within the previous year. 15. Subjects currently working nights, rotating night shifts or with planned travel during the study period. 16. Subjects on a non-stable dose of medications or other agents that may affect sleep and/or PSG (e.g., sedatives or hypnotics). 17. Subjects who consume > 500 mg caffeine per day (e.g., > 8 cola-type beverages, > 5 cups of coffee). 18. Subjects who consume > 14 alcoholic drinks/week. 19. Subjects who are pregnant (confirmed verbally). 20. Subjects currently enrolled in any other research study.
Study Overview	Study Design/ Duration: This is a prospective, open-label, randomized, crossover assignment non-inferiority study conducted at up to 6 sites. Site participation is expected to be approximately 10 weeks from first subject enrollment until completion of the last study visit. After obtaining informed consent, subjects will attend a screening visit for inclusion/exclusion criteria evaluation. Screening phase Screening visit shall be completed within 90 days of PSG Titration Study • Collect informed consent • Medical history/sleep history • Weight, BMI, vitals • Document medications • Assess inclusion/exclusion criteria • Schedule titration night and two additional sleep nights Successfully screened subjects will undergo a PSG titration study using a standard CPAP device. PSG Titration Night • Perform PSG and adjust pressure to identify effective therapeutic pressure (i.e., AHI < 10). • The PSG titration night will be scored by the study site's authorized personnel. At the conclusion of a valid PSG titration night (i.e., ≥ 4 hours of sleep with no equipment recording failures and results in analyzable data for AHI and

	ODI), the subject will be assessed for proper fit to the FRESCA mask. The subject will breathe on the investigational flow generator and mask set to the titrated pressure for a 30-second interval to confirm proper mask fit. Subjects who complete a valid PSG titration night and demonstrate proper FRESCA mask fit will be randomized to one of two sequences of in-lab PSG sleep nights, preferably on consecutive nights. The number of allowable calendar days between the two randomized sleep nights is 0 – 10 days. Sequence 1 Subjects: Night 1: Use of the predicate FRESCA device set to PAP at the PSG-titrated pressure. Night 2: Use of the investigational FRESCA device set to Auto-Adjusting Pressure with EPR. a. The auto-adjusting pressure range will be set with the lower bound at 2 cmH_2O below the PSG-titrated pressure and the upper bound at 5 cmH_2O above the PSG-titrated pressure (not to exceed 20 cmH_2O). b. The EPR setting will be set to 3. Sequence 2 Subjects: Night 1: Use of the investigational FRESCA device set to Auto-Adjusting Pressure with EPR. a. The auto-adjusting pressure range will be set with the lower bound at 2 cmH_2O below the PSG-titrated pressure and the upper bound at 5 cmH_2O above the PSG-titrated pressure (not to exceed 20 cmH_2O). b. The EPR setting will be set to 3. Night 2: Use of the predicate FRESCA device set to PAP at the PSG-titrated pressure. The study will employ a central scorer to score these two randomized PSG sleep nights. The central scorer will be blinded to the randomization sequence.
Primary Effectiveness Outcome Measure	AHI will be used as the primary effectiveness measure with mean AHI being the primary endpoint. The difference in mean AHI between the new and predicate devices will be tested after treatment intervention in this cross-over study design.
Secondary Effectiveness	ODI will be used as a secondary effectiveness measure. Mean ODI by treatment group will be summarized descriptively.

Outcome Measures	
Safety Outcome Measure	Adverse events will be summarized descriptively by treatment group, system organ class, and preferred term. An additional summary will be provided for device and procedure related adverse events by treatment group, system organ class, preferred term and severity. Any SAEs or UADEs will be individually reported.
Statistical Analysis	Primary Endpoint Analysis: The primary endpoint in this study is mean AHI values. It is hypothesized that the new device treatment will be non-inferior to the predicate device treatment in mean AHI. The following 1-sided hypothesis will be tested for AHI: H0: $\mu NEW - \mu PREDICATE \geq 0 + \Delta$ versus HA: $\mu NEW - \mu PREDICATE < 0 + \Delta$ Where μNEW represents the mean AHI for the new device treatment, μPREDICATE represents the mean AHI for the predicate device treatment, and Δ represents the non-inferiority margin. This analysis will assume a non-inferiority (NI) margin of 5 units and a 1-sided alpha level of 2.5%. A 2-sided 95% confidence interval (CI) will also be provided around the difference between treatments, where non-inferiority will also be demonstrated if the upper bound of the 95% CI is less than or equal to the NI margin of 5 units. In this scenario the 2-sided 95% CI equates to testing the 1-sided non-inferiority hypothesis. The hypothesis will be tested using a t-test between treatments from an analysis of variance (ANOVA) model with treatment, sequence, and period as fixed effects and subject as a random effect. This model assumes no carry over effect. The population for this primary analysis is the mITT population. This population consists of the enrolled, intent-to-treat population who had a valid PSG study for both randomized sleep nights. Secondary Effectiveness Analysis: Mean ODI will be summarized descriptively by treatment group.

5 INTRODUCTION

Obstructive Sleep Apnea (OSA) is a common chronic disorder and the most common of all sleep disorders. OSA can occur in any age group, but prevalence increases between middle and older age. Over the last two decades the prevalence of sleep disordered breathing seems to be increasing in both men and women, likely due to increasing rates of obesity. Relative increases reported are between 14% and 55% depending on the subgroup. For men, the current prevalence estimates of moderate to severe sleep-disordered breathing are 10% for 30 to 49 year-olds and 17% for 50 to 70 year-olds. For women, the corresponding prevalence estimates are 3% and 9% **[1]**.

Common consequences of OSA include daytime sleepiness, extreme daytime fatigue, slow reaction time, moodiness, belligerence and vision problems. OSA is also linked to hypertension, increased cardiovascular morbidity, type 2 diabetes, neurocognitive dysfunction and possibly cancer.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of hypopnea and apnea during sleep, as a result of repetitive obstruction of the upper airways. The resulting airflow limitation leads to oxygen desaturation and sleep fragmentation. Patients affected with sleep apnea generally wake up many times during the night when they are unable to breathe or stop breathing intermittently. Clinically, patients will present with loud snoring, daytime hyper somnolence and cognitive impairment.

Continuous positive airways pressure (CPAP) has become the treatment of choice for OSA **[2]**. Performance and safety profiles of CPAP technology have been well documented in published literature encompassing a period of more than thirty years **[3]**.

CPAP machines provide a continuous, high flow stream of pressurized air to patients though a mask worn while sleeping. Positive airway pressure (PAP) provides pneumatic splinting of the upper airway to prevent pauses in breathing and maintain normal oxygen levels. Consistent use of CPAP has been shown to improve ventilatory function **[4]**, objective and subjective measures of daytime somnolence **[5]**, and quality of life **[6**], in patients with moderate to severe OSA.

Despite the proven effectiveness of this therapy, there is often poor patient compliance. Many patients cannot tolerate the CPAP high air flow and, subsequently, only use it intermittently or stop using it completely. Studies report adherence rates ranging from 46 to 80% **[7,8]**. Current CPAP systems incorporate several optional features designed to improve patient comfort. These features include pressure ramping at sleep onset, humidification of inspired air, automatic positive airway pressure (APAP) modes and expiratory pressure relief (EPR) settings. These features have resulted in modest comfort improvements for some patients but have not solved the problem of poor patient compliance, in part because the CPAP devices still rely on continuous, high airflow to delivery therapy.

An opportunity exists to improve the treatment of OSA by increasing comfort and compliance without sacrificing efficacy.

6 DESCRIPTION OF INVESTIGATIONAL DEVICE

6.1 Regulatory History

The first-generation (predicate) FRESCA Positive Airway Pressure System received FDA market clearance in June 2018 via a *de novo* request. The investigational device that is the subject of this clinical study is a modified Positive Airway Pressure System that incorporates additional features such as auto-adjusting pressure and expiratory pressure relief. The results of this clinical study will be used to support a 510(k) submission to obtain FDA market clearance for the investigational device.

6.2 Device Overview

The FRESCA Airbox Positive Airway Pressure System includes a flow generator, hose, mask (nasal mask and nasal pillow configurations), headgear and a proprietary SmartValve™.

Fig. 1: The FRESCA Airbox Positive Airway Pressure System (assembled)

The proprietary SmartValve is seated in the mask and allows positive airway pressure ("PAP") to be generated during expiration but at the same time it (1) significantly reduces the airflow required to provide PAP during inspiration and expiration, and (2) utilizes the patient's own breathing effort during both normal inspiration and expiration. This valve technology allows use of small diameter hose, eliminates the need for a humidifier and prevents CO2 rebreathing, thereby eliminating the need to deliver and vent high airflow for CO2 washout.

The FRESCA Airbox Positive Airway Pressure System also includes a mobile app (Android and IOS) for the display and transfer of device and sleep data and cloud connectivity to allow patients to share their data with their healthcare providers. [NOTE: The mobile app and cloud connectivity will not be used nor evaluated in this study].

6.3 Intended Use, Population and Indications

The FRESCA Positive Airway Pressure System is intended to treat Obstructive Sleep Apnea by delivering a therapeutic breathing pressure to the patient. It is intended for use in the home environment by adult patients weighing more than 66 lbs. (30 kg.).

6.4 Summary of the Necessary Training and Experience Required

The lead investigators at each site will be trained in study methods and device function. Investigators will be responsible for training co-investigators and study staff as needed. FRESCA will provide training and support as necessary prior to study start and throughout the study from a FRESCA representative via on-site visits, telephone and e-mail correspondence.

FRESCA will target selection of investigators who have research experience, experience with the management of sleep apnea patients and experience with CPAP devices and therapy.

7 SUMMARY OF SUPPORTING BENCH AND CLINICAL TESTING

7.1 Bench Testing

Material biocompatibility testing and in-vitro testing are conducted to verify that the physical characteristics, performance and safety requirements detailed in the product design specification are met prior to evaluating the device in human clinical investigations.

7.2 Clinical Testing

A non-inferiority (NI) study was previously completed comparing the FRESCA device patient interface (mask, valve and hose) to a commercially available CPAP device patient interface (mask and hose). The study enrolled subjects diagnosed with obstructive sleep apnea who were compliant users of a commercially-available CPAP mask and hose. This was a prospective, randomized, cross-over multi-site study designed to determine whether treatment with the FRESCA device was non-inferior to treatment with the subject's prescribed CPAP device.

The study met the primary effectiveness endpoint, i.e., the mean AHI and ODI, and confirmed the non-inferiority of the FRESCA device patient interface compared to the CPAP device patient interface in the treatment of OSA. The FRESCA device demonstrated significant improvement in both AHI and ODI (compared to baseline). Most of the device adverse events were asymptomatic or mild and all resolved without the need for any treatment. There were no serious adverse events nor unanticipated adverse device effects. The study results demonstrated the safety and effectiveness of the FRESCA device patient interface.

8 STUDY OBJECTIVES ANDS OUTCOME MEASURES

The objective of this study is to demonstrate that the FRESCA Airbox Positive Airway Pressure System is non-inferior to the existing (predicate) FRESCA Positive Airway Pressure System.

8.1 Efficacy Assessment

AHI will be used as the primary effectiveness measure with mean AHI being the primary endpoint. The difference in mean AHI between the new and predicate devices will be tested after treatment intervention in this cross-over study design.

ODI will be used as the secondary effectiveness measure. Mean ODI by treatment group will be summarized descriptively.

The primary and secondary assessments will be collected for randomized PSG Sleep Nights 1 and 2 based on blinded scoring by a single central scorer using AASM criteria **[9]**.

8.2 Safety Assessments

Adverse events will be summarized descriptively by treatment group, system organ class, and preferred term. An additional summary will be provided for device and procedure related adverse events by treatment group, system organ class, preferred term and severity. Any SAEs or UADEs will be individually reported.

9 STUDY DESIGN

9.1 General

This study is focused on evaluating the efficacy of the FRESCA Airbox Positive Airway Pressure System in subjects with diagnosed obstructive sleep apnea who meet the inclusion and exclusion criteria established in this protocol. Up to fifty (50) subjects will be enrolled at up to six (6) study sites.

The device will be evaluated using polysomnography results and requires each subject's participation in 3 overnight in-lab sleep nights. See Figure 2 and Table 1.

Subjects will undergo one in-lab PSG titration study to identify their therapeutic pressure setting. Subjects who complete a valid PSG titration study that achieves a therapeutic pressure setting (i.e., AHI < 10/hr) will be scheduled for two additional sleep nights, preferably two consecutive nights. The number of allowable calendar days between the two randomized sleep nights is 0 – 10 days. These sleep nights will be randomized to one of two sequences.

> Sequence 1: Original (predicate FRESCA device) set to fixed-pressure on night 1 / FRESCA Airbox device set to auto-adjusting pressure + EPR on night 2
>
> Sequence 2: FRESCA Airbox device set to auto-adjusting pressure + EPR on night 1 / Original (predicate FRESCA device) set to fixed-pressure on night 2

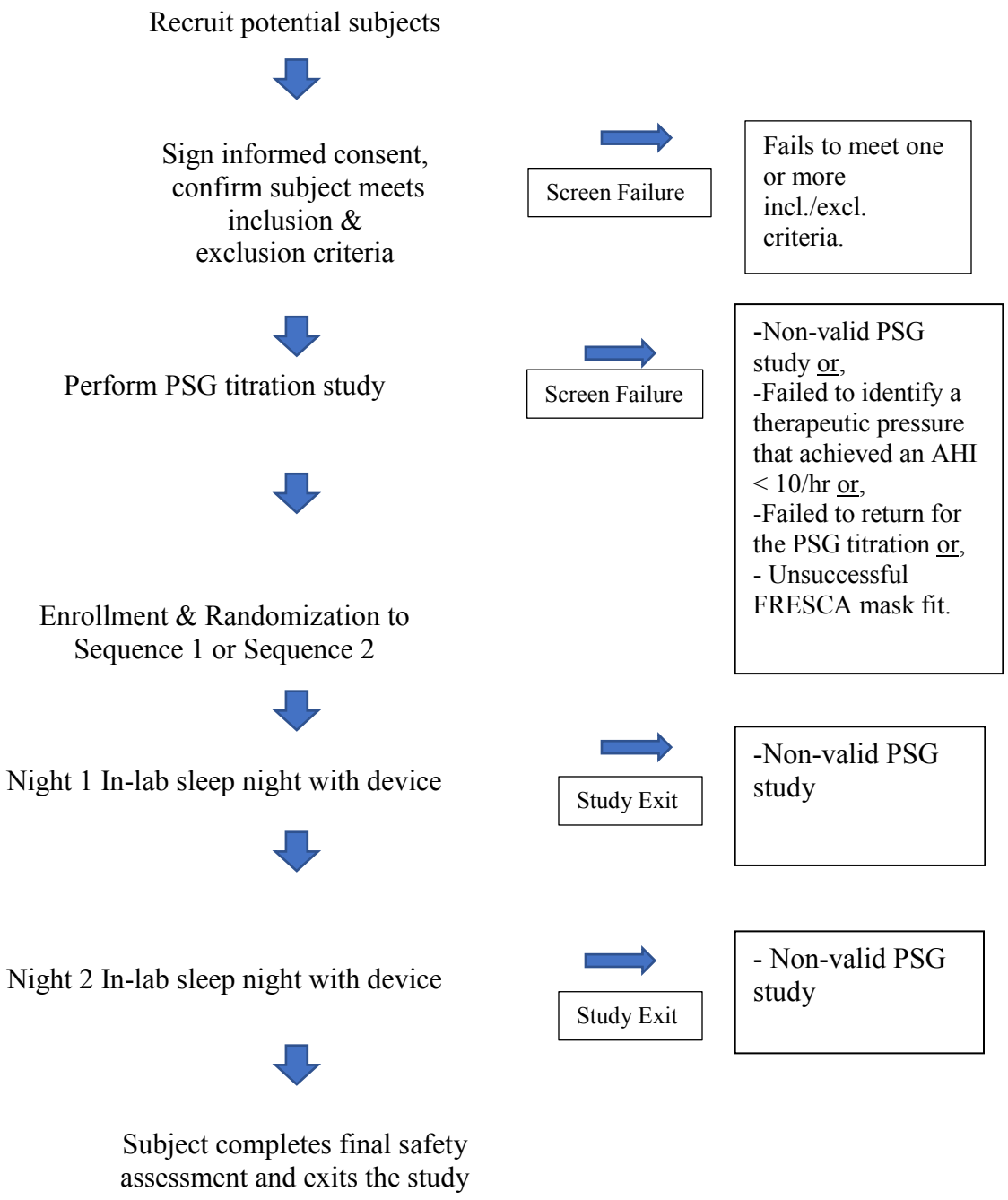

Fig. 2: Study Flow Diagram

Table 1: Schedule of Visits and Procedures

Visit	Screening Visit ≤90 days prior to PSG Titration Night	PSG Titration Night	Night 1	Night 2	Study Exit Visit[1]
Informed Consent	X				
Medical History	X				
OSA History	X				
Weight measure	X				
Height measure	X				
BMI	X				
Vital Signs	X				
Inclusion/Exclusion Review	X				
Confirm eligibility	X	X			
Schedule study nights	X				
Medication Review	X	X	X	X	
Randomization			X		
PSG Procedure		X	X	X	
Sleep Scoring		X	X	X	
Adverse Events		X	X	X	X

[1] Study exit visit can be performed at the conclusion of the final sleep night.

9.2 **Subject Population and Selection**

Study subjects will be recruited from the clinical practices of the investigators. Modest compensation may be provided to enrolled subjects for their participation in the trial.

Data to determine inclusion and exclusion criteria may be obtained from records of prior visits to the study physician and/or sleep center, from documented records obtained from another physician and/or sleep center, or from querying subject's medical history.

9.2.1 **Inclusion Criteria**

Subjects may be included in the study if they meet all of following inclusion criteria:

1. Male or female aged 22 – 75 years old.
2. BMI: ≤ 40 kg/m2.
3. Subjects diagnosed with OSA (either newly diagnosed (naive) OSA subjects or current CPAP subjects).
4. Subject must be able to be fitted properly with a FRESCA mask.

5. Subject must be able to comply with all study requirements as outlined in the protocol.
6. Subject must complete a valid PSG titration study.

9.2.2 **Exclusion Criteria**

Subjects must be excluded from the study if they meet any of the following exclusion criteria:

1. Subjects with non-OSA sleep disorders (including periodic limb movement (PLM) disorder and chronic insomnia).
2. Substantial central or mixed apneas (central and mixed apnea ≥ 5/hr.).
3. Subjects with prior surgical intervention for OSA.
4. Subjects with frequent or sustained episodes of O_2 saturation ≤ 75%.
5. Subjects with obesity-related hypoventilation.
6. Subjects currently using a CPAP full face mask.
7. Subjects who are medically unstable.
8. Subjects with unstable or severe cardiovascular abnormalities (e.g., heart failure, valvular heart disease).
9. Subjects with atrial fibrillation or other arrhythmias that are not effectively controlled with medication.
10. Subjects with hypotension or uncontrolled HTN.
11. Subjects with chronic lung disease, including COPD.
12. Subjects with significant cardiopulmonary disease.
13. Subjects with ongoing severe nasal allergies or sinusitis or difficulty breathing through the nose; persistent blockage of one or both nostrils; or any nasal or facial abnormalities that would not allow adequate placement and use of the mask.
14. Subjects with surgery of the upper airway, nose, sinus or middle ear within the previous year.
15. Subjects currently working nights, rotating night shifts or with planned travel during the study period.
16. Subjects on a non-stable dose of medications or other agents that may affect sleep and/or PSG (e.g., sedatives or hypnotics).
17. Subjects who consume > 500 mg caffeine per day (e.g., > 8 cola-type beverages, > 5 cups of coffee).
18. Subjects who consume > 14 alcoholic drinks/week.
19. Subjects who are pregnant (confirmed verbally).
20. Subjects currently enrolled in any other research study.

9.3 **Study Duration and Number of Subjects**

A total study duration of approximately 10 weeks is anticipated from the time the first subject is enrolled to the completion of the last subject visit at each clinical site. Screening procedures can occur as early as 90 days prior to the scheduled PSG titration study night. Each individual subjects' active participation will require one overnight PSG titration study night and two overnight PSG sleep nights. The number of allowable calendar days between the two randomized PSG sleep nights is 0 – 10 days.

Up to fifty (50) subjects may be enrolled at up to six (6) sites. It is desirable to enroll subjects that are distributed across OSA severity ranges, though stratification will not be employed.

10 STUDY PROCEDURES

10.1 Informed Consent Process

Each subject must document his or her consent by signing an IRB-approved informed consent form. The Investigator or designee will explain the nature, purpose, expected duration, and risks of study participation to the potential subject. Each potential subject will have the opportunity to ask questions and receive answers from personnel conducting the study. The subject must sign a voluntary informed consent prior to undergoing any procedures specifically conducted for the purpose of study enrollment. All subjects will receive a copy of the signed consent form for their records.

10.2 Screening Phase

Screening assessments should be undertaken within 90 days prior to the scheduled PSG titration procedure. Results of standard clinical assessments such as history, physical examination and prior polysomnography testing may be used to identify individuals who may broadly meet trial entry criteria.

Routine clinical evaluations that would be performed as part of the normal clinical care of patients with OSA may be performed prior to informed consent and used as part of the screening assessment; however, no study-related procedures may be performed prior to obtaining full informed consent from the subject. If the subject is subsequently consented and enrolled in the study, the results of standard-of-care tests may be used as study data.

Site personnel will use care in reviewing the subject's clinical status in relation to each inclusion and exclusion criterion and will ensure that appropriately documented results are available prior to concluding that the subject meets trial entry criteria.

Subjects who do not meet the inclusion / exclusion criteria or fail to complete a valid PSG titration study become screen failures and may not be enrolled or participate in any further study procedures.

Once subjects have signed the informed consent document, they must complete screening evaluations within 90 days of the scheduled day of the PSG titration study.

Evaluations will consist of the following:

- Review/ documentation of current medications or agents that may affect sleep or PSG results
- Brief physical examination (Vital signs, Height, Weight, BMI)
- Medical and sleep history

10.3 **PSG Titration Study**

Subjects who meet the inclusion/exclusion criteria will undergo an in-lab PSG titration study to identify the effective therapeutic pressure setting (i.e., AHI < 10/hr.). This PSG titration study will be performed using a commercially-available CPAP mask and hose and will be scored by authorized site personnel.[1]

At the conclusion of a valid PSG titration night (i.e., ≥ 4 hours of sleep with no equipment recording failures and results in analyzable data for AHI and ODI values) and identification of a therapeutic pressure setting, the subject will be assessed for proper fit to the FRESCA mask. The subject will breathe on the investigational device set to the titrated pressure for at least a 30-second interval to determine proper FRESCA mask fit.

10.4 **Randomization**

Each site will be provided a list of subject numbers to be assigned to subjects as they are evaluated at their screening visit. A screening log will record the subject number, subject initials, date of screening, date informed consent was signed, and whether subject was enrolled. A subject is considered enrolled if they sign the informed consent document, meet all inclusion and exclusion criteria, complete a valid PSG titration study that identifies a therapeutic pressure setting (i.e., AHI < 10/hr.) and have a successful FRESCA mask fit. Each enrolled subject will be randomized to one of two sleep night sequences. Randomization assignments will be computer-generated by the study statistician and obtained through the data management system (EDC). A randomization log will be used to record the assigned randomization sequence.

10.5 **Baseline Evaluation**

1) Baseline information:
   a) Patient identifier
   b) Date of birth
   c) Gender
   d) Ethnicity
   e) Height (inches)
   f) Weight (pounds)
   g) BMI (calculated from height and weight)
2) Physical Examination:
   a) Vital signs (HR, BP, Oral temperature)
3) Medical history, including but not limited to:
   a) Cardiovascular disease
   b) Cancer
   c) Respiratory disease
   d) Psychiatric illness
   e) Prior surgical intervention for OSA
   f) Non-OSA sleep disorders

[1] Current CPAP users cannot use the same brand and model CPAP mask as they currently use at home.

g) Severe nasal allergies, sinusitis or nasal blockages

4) Listing and dosages of all current prescription medications or other agents that may affect sleep and/or PSG results

10.6 **Detailed Description of Study Procedures**

This study is not blinded, as both the investigator and subject will be aware of the therapy that is being utilized. However, investigators and study staff will minimize discussion about the particular therapy. Since the outcome measures are objective observations of each subject's sleep architecture and respiratory events, and the scoring of the PSGs will be performed by a masked central scorer, bias resulting from the open label nature of this study will be minimized.

Consented subjects who met the inclusion / exclusion criteria and completed a valid PSG titration study will be randomized. Following randomization, subjects are considered enrolled.

Subjects will undergo one in-lab PSG titration study to identify their therapeutic pressure setting. Subjects who complete a valid PSG titration study will be scheduled for two additional sleep nights, preferably two consecutive nights. The number of allowable calendar days between the two randomized sleep nights is 0 – 10 days. These sleep nights will be randomized to one of two sequences.

> Sequence 1: Original (predicate) FRESCA device set to PSG-titrated fixed pressure on night 1 / investigational FRESCA Airbox device set to auto-adjusting pressure + EPR on night 2.
>
> Sequence 2: Investigational FRESCA Airbox device set to auto-adjusting pressure + EPR on night 1 / Original (predicate) FRESCA device set to PSG-titrated fixed pressure on night 2.

If the subject fails to have a valid PSG Study on either night, the subject is considered an early study exit and excluded from the mITT analysis of the primary effectiveness endpoint. These subjects will be analyzed and summarized separately, including the reason(s) they did not complete a valid PSG study.

The following data will be collected for the PSG titration study night and PSG randomized sleep nights 1 and 2:

PSG Titration Study

1) Date of PSG Titration
2) Brand and model of PSG equipment
3) Mask style used during titration
4) Brand and model of CPAP flow generator
5) Brand and model of CPAP mask used[2]
6) Total test time (min)
7) Total sleep time (min)

[2] Current CPAP users cannot use the same brand and model CPAP mask as they currently use at home.

8) AHI (overall)/h
9) ODI (overall)/h
10) Sleep efficiency %
11) Arousal index ((overall)/h
12) Minimum sleep SpO_2 %
13) Mean sleep SpO_2 %
14) Wakefulness (min)
15) Stage N1 (min)
16) Stage N2 (min)
17) Stage N3 (min)
18) REM (min)
19) Prescribed pressure setting (cmH_2O)
20) Adverse event assessment

PSG Sleep Nights 1 and 2

1) Date of sleep night
2) Brand and model of PSG equipment
3) FRESCA mask type (nasal pillow or nasal mask)
4) Device type (predicate or investigational)
5) Device mode (PAP, Auto-adjusting pressure)
6) Fixed pressure (if PAP mode)
7) Auto-adjusting pressure range (if auto-adjusting pressure mode)
8) EPR setting
9) Lights off (24-hr. clock)
10) Lights on (24-hr. clock)
11) Duration of sleep ≥4 hrs (Yes or No)
12) Sleep night notes (i.e., in-room adjustments, equipment technical issues)
13) Medication changes since prior PSG night
14) Adverse event assessment

PSG Central Scoring of Sleep Nights 1 and 2

1) Date EDF File was Scored
2) Date of Sleep Night
3) Sleep Night Number
4) Total test time (min)
5) Total sleep time (min)
6) AHI (overall)/h
7) ODI (overall)/h
8) Sleep efficiency %
9) Arousal index ((overall)/h
10) Minimum sleep SpO_2 %
11) Mean sleep SpO_2 %
12) Wakefulness (min)
13) Stage N1 (min)
14) Stage N2 (min)

15) Stage N3 (min)
16) REM (min)
17) Comments/notes

10.7 **Study Withdrawal Criteria**

An enrolled subject will be exited from the study when any of the following occurs:

1. Subject withdraws consent.
2. The investigator removes them from the study for their welfare.
3. Subject is non-compliant with study procedures.
4. Subject fails to return for a study visit and does not respond to 3 documented contact attempts.

11 STATISTICAL CONSIDERATIONS

11.1 **General Considerations**

All data collected will be listed and summarized descriptively. All analyses will be pooled across the enrolling sites, unless otherwise specified, and conducted using SAS v9.4 or higher. All summary tables will include each treatment group and all subjects combined.

Descriptive statistics for categorical variables will be summarized with frequencies and percentages, while continuous variables will be summarized with n, mean, median, standard deviation, and range.

Further details will be provided in the Statistical Analysis Plan.

11.2 **Analysis Populations**

The enrolled population will include all subjects who sign the informed consent document, meet all inclusion and exclusion criteria, complete a valid PSG titration study that identifies a therapeutic pressure setting (i.e., AHI < 10/hr). and have a successful FRESCA mask fit.

The intent-to-treat (ITT) population will include all subjects who are considered enrolled and randomized. The ITT population will be used to determine any adverse event outcomes and assess study safety outcomes.

The modified intent-to-treat (mITT) population will include all intent-to-treat subjects who complete a valid PSG Study during randomized sleep nights 1 and 2. The mITT population will be used to assess study effectiveness outcomes.

11.3 **Sample Size**

A sample size calculation was performed for the primary analysis of demonstrating non-inferiority of FRESCA Airbox treatment against the predicate (control) FRESCA treatment. It is planned to enroll up to 50 subjects across up to 6 study sites to yield at least 38 evaluable (mITT) subjects. Using 38 evaluable subjects for the primary analysis will provide 85% power to

demonstrate non-inferiority assuming the mean difference between treatments is 0. These calculations also assume a 1-sided alpha level of 0.025%, standard deviation of 5 units, and a NI margin of 5 units. Sample size calculations were performed using the POWER procedure in SASv9.4, assuming a 2-group t-test between treatments, assuming a period effect in the ANOVA model as described in Section 11.4.

11.4 **Statistical Analyses**

11.4.1 **Primary Endpoint Analysis**

The primary endpoint in this study is mean AHI values. It is hypothesized that the new device treatment will be non-inferior to the predicate device treatment in mean AHI. The following 1-sided hypothesis will be tested for AHI:

H0: $\mu NEW - \mu PREDICATE \geq 0 + \Delta$

versus

HA: $\mu NEW - \mu PREDICATE < 0 + \Delta$

Where μNEW represents the mean AHI for the new device treatment, $\mu PREDICATE$ represents the mean AHI for the predicate device treatment, and Δ represents the non-inferiority margin. This analysis will assume a non-inferiority (NI) margin of 5 units and a 1-sided alpha level of 2.5%. A 2-sided 95% confidence interval (CI) will also be provided around the difference between treatments, where non-inferiority will also be demonstrated if the upper bound of the 95% CI is less than or equal to the NI margin of 5 units. In this scenario the 2-sided 95% CI equates to testing the 1-sided non-inferiority hypothesis.

The hypothesis will be tested using a t-test between treatments from an analysis of variance (ANOVA) model with treatment, sequence, and period as fixed effects and subject as a random effect. This model assumes no carry over effect.

The population for this primary endpoint analysis is the mITT population. The mITT population, by definition, will not have any missing data and hence, there will not be any imputation methods applied.

11.4.2 **Sensitivity Analyses for Primary Endpoint**

A sensitivity analysis will be conducted on the primary endpoint to assess a site effect. This sensitivity analysis will be conducted in a similar manner as for the primary endpoint. The model described for the primary endpoint will also include a term for site in the ANOVA model. If the term for site is significant at the 2-sided alpha of 5% then it will be concluded that a site effect exists. Sites having less than 2 subjects in either treatment group will be pooled together into one site.

The primary analysis will also be conducted for the ITT population. There will be two sensitivity analyses using the ITT population, the first will use all ITT subjects and apply a multiple imputation method for missing AHI values. Missing values will be imputed based on baseline

characteristics of sex, age, and baseline AHI value. The second sensitivity analysis will include all ITT subjects with observed data collected.

11.4.3 **Secondary Effectiveness Analysis**

Mean ODI will be summarized descriptively by treatment group. The population for this secondary analysis is the mITT population.

11.4.4 **Safety Analysis**

Adverse events will be summarized descriptively by treatment group, system organ class, and preferred term. An additional summary will be provided for device and procedure related adverse events by treatment group, system organ class, preferred term and severity. Any SAEs or UADEs will be individually reported. A listing of all adverse events will be generated.

11.4.5 **Subgroup Analysis**

Descriptive statistics of the primary endpoint will be provided for the following subgroups using the mITT population:

- Gender (Female, Male)
- BMI (<30, 30-40)
- Investigational Study Site

12 DATA COLLECTION, QUALITY ASSURANCE AND MANAGEMENT

12.1 **Source Documents**

Source documents include, but are not limited to, hospital records, clinical and office charts, laboratory notes/reports, memorandums, subjects' evaluation checklists, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate copies, and source document worksheets. Investigators are to maintain all source documents as required by the protocol, including subject source document worksheets, supporting medical records, and informed consents. The source documents will be used at the regular monitoring visits to verify information recorded on the eCRF.

12.2 **Recording of Data**

Data will be recorded electronically on electronic case report forms (eCRFs).

Clinical data generated in the study will be submitted to the Sponsor or its designee for quality assurance review and statistical analysis. Incoming data will be reviewed to identify inconsistent or missing data and Unanticipated Adverse Device Effects. Data queries will be issued to address data issues and will be followed up with calls or emails to the investigational sites and during site visits by site monitors. Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that adverse events and adverse device effects are detected, managed and reported as required.

12.3 **Data Processing**

Data processing will be performed according to FRESCA's SOPs or those of its delegated vendors, ensuring adherence to GCPs. Audits may be performed for quality assurance of data handling.

13 RISK AND BENEFIT OF THE INVESTIGATIONAL DEVICE

13.1 **Potential Benefits**

There are no direct benefits anticipated to study subjects for participation, other than possible knowledge gained about their current condition during the sleep studies. Indirect benefit to patients with OSA will be gained from the data arising from the study, and the demonstration of potential benefits of the FRESCA Airbox Positive Airway Pressure System.

13.2 **Risk Assessment**

Limiting device use to three, discreet sleep nights is unlikely to have long-term risk of any kind. Possible short-term risk is limited to undergoing a poor night's rest if the device does not reduce symptoms of sleep disordered breathing. The anticipated adverse events for this study are listed in Section 14 below.

13.3 **Risk-Benefit Assessment and Risk Mitigation**

Both social benefit and subject-level benefit appear to exceed the risks associated with performing the trial. This favorable risk-benefit profile confirms that it is appropriate to perform this clinical trial to demonstrate the non-inferiority of the FRESCA Airbox System compared to the predicate (control) FRESCA System in the treatment of OSA.

Risk mitigation measures that will be implemented in this trial include:

- Full informed consent.
- Consistent implementation of a well-designed protocol.
- Inclusion and exclusion criteria designed in part to screen out subjects at any elevated risk.
- Selection of well-qualified Investigators and staff.
- Proper training and preparation of investigational sites and personnel.
- Continuous observation of study subjects by clinical staff during device use.

13.4 **Non-Significant Risk Determination**

The FRESCA Airbox Positive Airway Pressure System described in this protocol does not meet the definition of a significant risk device as defined in 21 CFR 812.3(m), specifically:

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

- Purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- For use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The following information supports a non-significant risk determination for the FRESCA Airbox System:

- There are no invasive procedures involved in the study.
- None of the expected adverse events as defined in the protocol would be life-threatening or would result in any permanent impairment of a body function or permanent damage to a body structure.
- The investigational device is a modification to a Positive Airway Pressure System previously cleared for market by the FDA for the treatment of OSA.
- If the subject feels any discomfort during the study, he/she will be able to remove the device immediately.
- The investigational device will be used during a laboratory-based PSG evaluation monitored by a respiratory technician.

14 ADVERSE EVENTS

14.1 Listing of Possible Adverse Events

Adverse events which might occur or have been known to occur with Positive Airway Pressure treatment include but are not limited to the following:

- Irritations from PSG equipment sensor interfaces
- Skin / nose irritation from the mask
- Facial marks from the mask
- Eye irritation
- Runny or stuffy nose
- Difficulty breathing
- Difficulty sleeping
- Dry mouth
- Nosebleeds
- Headache
- Claustrophobia
- Shortness of breath
- Dizziness
- Tiredness
- Panicky feeling

However, because this is an investigational device, there may be additional risks and discomforts associated with the device that are not known at this time.

Any clinically significant, undesirable experience (sign, symptom, illness, or other medical event) occurring or worsening during the study period should be considered an adverse event. A clinically significant event is any event (sign, symptom, lab/imaging abnormality, or diagnosis) that is noteworthy enough to merit documentation in standard medical records (e.g. History and Physical, Progress notes, clinic visit notes, etc.) or require medical intervention to correct. Events and findings that would otherwise be termed adverse events, but are not new onset or worsening events, will be defined as pre-existing conditions and will not be analyzed as adverse events for this study.

Throughout the course of the proposed study, all efforts will be made to remain alert to possible adverse experiences or untoward findings. Any adverse events, complications, and suspected device deficiencies observed by the investigator or reported by the subjects, whether or not ascribed to the procedure or investigational device, will be recorded in the appropriate section of the subject's case report form. All adverse events will be monitored until adequately resolved or the subject exits from the study.

14.2 **Severity of Adverse Events**

The following definitions for rating severity of Adverse Events will be used by Investigators and study monitors:

- Asymptomatic: An adverse event that is not noticed by the subject and does not require additional therapy.
- Mild: An adverse event that is noticeable to the subject and may require additional therapy.
- Moderate: An adverse event that interferes with the subject's activities and requires intervention or additional therapies.
- Severe: An adverse event that is intolerable or incapacitating and necessitates additional therapy or places the subject at immediate risk of harm.

14.3 **Relationship of Adverse Event to the Study Device**

The relationship of the adverse event to the device will be determined by the Investigator based on his or her clinical judgment and the following definitions:

Definitely Not Related: An adverse event for which sufficient information exists to determine that it is unrelated to device use.

Unlikely Related: An adverse event that occurs during or after device use that could also have been produced by the subject's clinical state or by other therapies. The Investigator determines that the adverse event is unlikely to have been related to the device.

Likely Related: An adverse event that occurs during or after device use that could also have been produced by the subject's clinical state or by other therapies. The Investigator determines that the adverse event is likely to have been related to the device.

Definitely Related: An adverse event that occurs during or after device use and is known to be a complication of the device for which no other reasonable explanation can be determined.

14.4 **Relationship of Adverse Event to the Study Procedures**

The relationship of the adverse event to the procedure will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

Definitely Not Related: An adverse event for which sufficient information exists to indicate that it is unrelated to the study procedure.

Unlikely Related: An adverse event that occurs during or after the procedure that could also have been produced by the subject's clinical state or by other therapies. The Investigator determines that the adverse event is unlikely to have been related to the study procedure.

Likely Related: An adverse event that occurs during or after the procedure that could also have been produced by the subject's clinical state or by other therapies. The Investigator determines that the adverse event is likely to have been related to the study procedure.

Definitely Related: An adverse event that occurs during or after the procedure and is known to be a complication of the procedure for which no other reasonable explanation can be determined.

14.5 **Definition of Adverse Event**

Serious Adverse Event (SAE)

An SAE includes any of the following events which may or may not be considered related to the investigational device or procedures:

For the purposes of ascertaining these terms, the following definitions will be applied:

- Any adverse event resulting in death.
- Any adverse event which is life-threatening3
- Any adverse event resulting in hospitalization, or significant prolongation of an existing hospitalization.4
- Any adverse event resulting in a persistent, significant impairment.5

[3] "Life threatening" means that the study subject was at a substantial and immediate risk of dying due to that adverse event as it occurred. "Life threatening" adverse events do not include an adverse event that had it occurred in a more severe form, might have caused death.
[4] "Hospitalization" includes any ER admission. A "significant" prolongation is related to the adverse event, is medically necessary and nontrivial in duration, but excludes delays waiting for diagnostic results.
[5] "Significant impairment" is defined for this protocol as a substantial disruption of a person's ability to conduct normal life functions.

- Any adverse event requiring significant medical or surgical intervention 6 to prevent a significant impairment. 3
- Any adverse event resulting in a congenital anomaly or birth defect.

ALL SERIOUS ADVERSE EVENTS OCCURRING DURING THE STUDY

MUST BE COMMUNICATED TO THE SPONSOR OR ENTERED INTO THE EDC

WITHIN 24 HOURS.

Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an investigational device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; or any other unanticipated serious problem associated with an investigational device that relates to the rights, safety, or welfare of subjects.

The Investigator must report any UADE to the Sponsor and the reviewing IRB as soon as possible but not later than 10 working days.

The Sponsor must promptly conduct an evaluation of any UADE. A confirmed UADE will be reported to the FDA and all reviewing IRB's and Investigators within 10 working days after receiving notice of the adverse effect. If it is determined that an unanticipated adverse device effect presents an unreasonable risk to subjects, this study, or those parts of the study presenting that risk, will be terminated as soon as possible. Such termination shall occur not later than 5 working days after the determination is made and not later than 15 working days after the Sponsor first received notice of the effect.

15 STUDY MONITORING

A representative of FRESCA Medical or a contracted representative of FRESCA Medical will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with Good Clinical Practices, 21CFR 812, and FRESCA Medical's internal monitoring procedures. It is the responsibility of the Investigator to be present or available for consultation during such scheduled monitoring visits, if requested. Direct access to all data and source documentation pertaining to a subject's participation in this clinical investigation must be made available to the Clinical Monitor during these routine visits.

Study monitoring involves the following elements:

- A representative of FRESCA Medical may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment

[6] A "significant medical or surgical intervention" generally indicates a procedure or therapy with significant novel risk, delay or subject discomfort, that results from the adverse event. A "significant medical or surgical intervention" does not include oral medication, noninvasive diagnostic testing or blood testing, routine intravenous fluids or the administration of antibiotics or antiemetics.

with respect to the needs of the study, to familiarize the investigator with the study protocol, and to ensure the staff is trained to the study requirements.

- A representative of FRESCA Medical may meet with the investigators at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, and that study data are being correctly recorded.
- A representative of FRESCA Medical may visit the clinical site at any time during the study to review the relevant source documentation to confirm completeness and accuracy of the data recorded on the eCRFs. Additionally, telephone consultation will occur as necessary to ensure the proper progress and documentation of the study findings.
- A representative of FRESCA Medical may visit the clinical site at the end of the study to review and/or collect final completed case report forms, resolve any corrections and/or data clarifications and ensure all logs and regulatory documents are completed and finalized.

Study monitoring will be performed by an adequate number of personnel, who are appropriately qualified by education and /or experience to perform all specified and necessary monitoring tasks.

16 AMENDMENTS TO THE CLINICAL INVESTIGATION PROTOCOL

No change in the study procedures shall be implemented without the mutual agreement of the Investigator and FRESCA Medical. All changes which require IRB approval will be submitted per the IRBs process. All changes must be documented by signed protocol amendments.

17 INVESTIGATIONAL DEVICE ACCOUNTABILITY

FRESCA Medical will provide to the study investigator and clinical site all investigational and predicate (control) devices required for the conduct of the study.

The Investigator is responsible for ensuring that investigational devices and supplies are maintained under controlled access storage conditions. The Investigator shall segregate any device patient interface or component removed from its package and not used. These items are intended for single subject use and must not be used on multiple subjects.

The investigator must maintain accurate records of the receipt of all investigational devices shipped by the sponsor, including the date and lot numbers received, date of use and/or return. Investigational material accounting procedures must be completed by the study site and sponsor before the study is considered terminated.

Investigational devices and supplies will be inspected upon receipt at the investigational site. Once accepted, these are entered onto the Device Accountability Form by authorized study site personnel. When a device is used, the study ID number for that subject is entered on the Device Accountability Form. The Device Accountability Log will be verified by the site monitor against the Device Return Forms and packing slips.

At the end of the study or upon request by the site monitor, any remaining investigational devices, used or unused, will be returned to Sponsor according to the provided instructions.

18 PUBLICATION POLICY

All information obtained during the conduct of this study will be regarded, as property of FRESCA Medical and confidential. Written permission from FRESCA Medical is required prior to disclosing any information relative to this study. Manuscripts prepared for publication will be in accordance with the policy established and agreed to between the Investigator and FRESCA Medical. Submission to the Sponsor for review and comment prior to submission to the publisher will be required. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware**.**

19 CONFIDENTIALITY

All records containing personal identification or information that identifies a study subject will be handled confidentially within the law. No individual identities will be used in any reports or any publications resulting from this study.

20 INVESTIGATOR RESPONSIBILITIES

20.1 Clinical Investigator Qualifications

The Investigator, approved co-Investigators, Study Coordinator and all supporting staff at the Investigator's site must be appropriately qualified by education and / or experience to perform their tasks.

20.2 Ethics Approval

Each investigational site must obtain initial and at least annual re-approval from the governing Institutional Review Board (IRB). Furthermore, the study must not begin until the ethics approval letter is received by FRESCA Medical. In addition, a copy of the ethics approval letter must be filed on site in the Investigator's study binder.

20.3 Informed Consent and Authorization for Use of Protected Health Information (PHI)

To protect the rights and welfare of Study subjects, this study will adhere to regulations and guidelines and the Declaration of Helsinki. All subjects enrolling in the study will be informed of the investigational nature of the study and will be required to sign an Informed Consent document. Authorization of use and disclosure of PHI must be obtained from each subject (or the subject's legal representative) prior to enrolling in the study. Written authorization for use and disclosure of Protected Health Information under the HIPAA rules will be obtained for all subjects either through use of a HIPAA authorization provision or inclusion of the authorization provision into the ICF.

20.4 Regulatory Compliance

It is the responsibility of the Investigator(s) to conduct this study in accordance with the signed Investigator Agreement, the investigational plan, 21 CFR Part 812, and other applicable FDA

regulations (including regulations for the protection of the rights, safety and welfare of subjects, and for the control of devices under investigation), and relevant FDA guidance documents, and to ensure that all subjects enrolled in the study:

- Have been given a copy of the IRB-approved Informed Consent Form.
- Have been given the opportunity to ask any questions regarding the study procedures.
- Have voluntarily and willingly signed the IRB-approved Informed Consent Form prior to study participation.

20.5 **Financial Disclosure**

A clinical Investigator shall disclose to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification or disclosure statements required by the regulations. The Investigator shall promptly update this information if any relevant changes occur during the study.

20.6 **Specific Investigator Responsibilities**

The Investigator(s) agrees to conduct the study in accordance with this protocol. Prior to beginning the study, the Investigator(s) must sign the Investigator Agreement, furnish associated documentation (CV, statement of relevant education/experience and qualifications, financial disclosure form) and submit a signed protocol signature page to the Sponsor.

An Investigator must not make any changes in a study without first receiving approval from the Sponsor and IRB, except when necessary to eliminate apparent immediate hazards to a subject.

The Investigator agrees that the Study monitors, Sponsor’s employees, contractors or designees, as well as any regulatory bodies as required, will have the right to audit and review pertinent medical and study records relating to this clinical trial. The Investigator and staff will assist with the production, review, interpretation and/or correction of such records as required.

Clinical records will be marked according to hospital procedures regarding the subject’s participation in this clinical research study.

Investigator responsibilities relating to device accountability include maintaining an accurate Device Accountability Record, returning used and unused devices as instructed, and using study supplies only for the treatment of study subjects.

An Investigator shall permit an investigational device to be used only with subjects under the Investigator's supervision. An Investigator shall not supply an investigational device to any person not authorized to receive it.

All data will be recorded on case report form worksheets and/or other source documents for each subject that is enrolled in the study. The Investigator(s) will ensure that the medical records and other study documents are maintained in a secure and confidential manner.

The Investigator(s) will ensure that the medical records and other study documents are made available for review by the study monitor and any government regulatory bodies as required.

All subject study records are to be maintained in a secure location until notified by the Sponsor that the forms may be discarded or transferred. In any event, all study records must be maintained during the investigation and for a period of 2 years after the latter of the following two dates: (1) the date on which the investigation is terminated / completed, or (2) the date that the records are no longer required for purposes of supporting the premarket notification application. The Sponsor will notify the investigator of applicable date and circumstance at a later time. Study records to be retained include the following:

1. Subject Case Report Forms, Informed Consents, Screening/Enrollment Logs and Subject Accountability Logs.
2. Device Accountability Records and records of device shipment receipt, use or disposition for all devices shipped to the center.
3. Correspondence with the IRB, Sponsor, any government regulatory bodies, monitor, or other Investigators, including required reports.
4. Study protocol and any amendments issued with signature pages.
5. Protocol and informed consent approvals from the IRB.
6. Clinical trial agreements and curricula vitae of Investigator(s), and the site personnel signature form.
7. All other records that may be required by the FDA or the Sponsor during the conduct of the trial.

20.7 **Investigator Reports**

Investigator reports include the following:

1. Unanticipated ADE's: The Investigator shall report any UADE to the Sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the Effect.
2. Withdrawal of IRB Approval: The Investigator shall report to Sponsor within 5 working days if, for any reason, the IRB withdraws approval to conduct the investigation, including a complete description of the reason(s) for which approval was withdrawn.
3. Deviation from the Investigational Plan: The Investigator shall notify Sponsor and the reviewing IRB of any changes in, or deviations from, the Protocol to protect the life or physical wellbeing of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurs. Except in such emergency, prior approval by Sponsor is required for changes in or deviations from

the investigational plan; and if such changes or deviations may affect the scientific soundness of the plan, or the rights, safety or welfare of the study subjects, then IRB approval is also required.

4. Use of Device without Informed Consent: No subject may be treated with the investigational device without prior written Informed Consent. If the Investigator does so proceed, the Investigator must report this use to the Sponsor and the reviewing IRB within 5 working days after it occurs.

21 SPONSOR RESPONSIBILITIES

The Sponsor is responsible for selecting qualified Investigators and providing them with the information needed to conduct the investigation properly. The Sponsor will ensure proper monitoring of the investigation and that IRB approval has been obtained prior to the Investigator commencing study-related activities. The Sponsor is also responsible for ensuring that the reviewing IRBs are promptly informed of significant new information related to this study. The Sponsor will be directly responsible for or will ensure through the Clinical Trial Agreement with Investigators that all records pertaining to this study will be retained per requirements outlined in the Retention Period section of 21CFR812.140.

21.1 Sponsor Qualifications

The Sponsor's Clinical Operations employees and contractors, including site and medical monitors, shall be appropriately qualified by education and / or experience to perform their tasks. Resources, systems, standard operating procedures and training adequate to oversee the scientific, ethical and regulatory aspects of the clinical study will be maintained throughout the period of the clinical investigation.

21.2 Study Conduct

Sponsor shall select Investigators qualified by training and experience and provide Investigators with the information and training that they need to conduct the investigation. Sponsor shall select monitor(s) qualified by training and experience to monitor the progress of the investigation.

21.3 Serious Adverse Events

Sponsor must conduct an investigation of any serious adverse events, including any UADEs. If Sponsor determines that the UADE presents an unreasonable risk to subjects, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible. This termination shall occur no later than 5 working days after Sponsor makes the determination and no later than 15 working days after Sponsor first received notice of the effect.

21.4 Securing Compliance

Sponsor must ensure that the Investigator continues to comply with the signed agreement, the investigational plan, other applicable FDA regulations and other conditions imposed by the IRB/FDA, or discontinue shipments of device to the Investigator, terminate the Investigator's

participation in the investigation and require such an Investigator to return device, unless this action would jeopardize the rights, safety or welfare of a subject.

21.5 **Records**

Sponsor or delegate shall maintain the following accurate, complete, and current study

documentation. These records must be maintained during the investigation and for a period of 2 years after the latter of the following two dates: (1) the date on which the investigation is terminated/completed, or (2) the date that the records are no longer required for purposes of supporting the premarket approval application. The applicable date and circumstance will be identified during the study.

1. Correspondence (including reports) with another Sponsor, Study Monitor, Investigators, an IRB or regulatory body.
2. Records of shipment, including: name and address of consignee, type and quantity of device, date of shipment and lot and/or serial numbers.
3. Records of disposition, describing: Lot and/or serial numbers of devices returned or disposed of by the Investigator or other persons and reasons for and method of disposal.
4. Signed Investigator Agreements, including financial disclosure information.
5. Current, signed and dated CV of each of the Investigators.
6. A listing of the names of the institutions at which the investigation will be conducted.
7. A listing of the names and contact information for site and medical monitors.
8. Documentation of each IRB approval.
9. Each approved version of the clinical protocol, Informed Consent document.
10. Statistical records and analyses, and interim and / or final study report(s).

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