Title Page

Protocol Title: A Prospective, Randomized, Crossover Study of Therapy Adherence with TheraPAP Compared to Automatic Adjusting Positive Airway Pressure (APAP) for the Treatment of Obstructive Sleep Apnea (OSA)

Protocol Name: TheraPAP Adherence 1

Sponsor Protocol #: Home 0001

Version Number: 0.2

Compound Number: TheraPAP

Short Title: TheraPAP Adherence Crossover Study

Sponsor Name and Legal Registered Address:

SleepRes, PLLC

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Regulatory Agency Identifying Number: Exempt

Approval Date: 05/02/2024

Date and Version of Previous Protocol: na

Sponsor Signatory:

William Noah, MD	Date

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Prospective, Randomized, Crossover Study of the TheraPAP Compared to Automatic Adjusting Positive Airway Pressure (APAP) for the Treatment of Obstructive Sleep Apnea (OSA)

Protocol Name/Number: TheraPAP Adherence 1

Sponsor: SleepRes, PLLC

Rationale: TheraPAP is a prototype device (with full documented electrical and isolation safety) being developed by SleepRes for the treatment of obstructive sleep apnea (OSA) that can deliver either standard CPAP at a set pressure or what is called TPAP[1]. TPAP is a pressure control algorithm that lowers the pressure from the set pressure at the beginning of inspiration and does not return the pressure to the full set level until about halfway through expiration. The present study, TheraPAP Adherence 1, is a randomized crossover study designed to examine the difference in therapy adherence between TPAP vs. CPAP alone in the treatment of OSA.

Overall Design:

The TheraPAP Adherence Study is a randomized, crossover study in treatment naive participants with OSA in which the adherence to therapy will be compared between TPAP and standard APAP. Because all participants will breathe on both therapy types and those therapy types are individually unique in feel, blinding is not possible. Participants will be chosen from a pool of patients who are PAP-naïve and who have received either a PSG (in-lab polysomnogram), split-night study (in-lab PSG and pressure titration) or home sleep study (HST) within the previous 3 months.

Upon signing an informed consent, participants will be randomly assigned to start on either the TPAP or APAP arms when they arrive at the office to pick up their Sefam S.Box with TheraPAP algorithms integrated. Each participant will then be given their new equipment and will be trained in proper use for both arms of the study so that they will not need to appear at the office again until the study is completed. In both the APAP and TPAP arms, participants will have their therapy set to 5-20 cmH_2O for three nights. The pressure range will then be narrowed to ± 2 cmH_2O around their 95% pressure level as assessed during the third night. This same pressure range will be used during the second arm for each patient.

[1] TPAP will be used herein to refer to the active treatment.

Within the TPAP arm, participants will be set to a double Comfort Setting drop according to the following table. This drop schedule will be implemented even while the TPAP device is operating with automatic pressure adjustment.

P_{set} (cmH_2O)	Pressure Drop 1 (cmH_2O)	Pressure Drop 2 (cmH_2O)
5.0 - 5.9	0	0
6.0 – 6.9	1	0
7.0 – 7.9	2	0
8.0 – 8.9	2	1
9.0 – 9.9	2	2
10.0 – 20.0	2	3

Table 1: Comfort Setting Pressure Drops 1 and 2 to be used at the specified target set pressure to the patient.

Participants will use their starting therapy nightly at home for 6 weeks after which time they will undergo a washout period of 1 week where no therapy will be used. Following the washout period, they will initiate another 6-week usage with the second therapy. Afterward, they will return to the office to receive their permanent equipment. Phone calls as reminders to end the first arm, start the washout period, then to start the second arm will be made.

Immediately after both arms of the study are completed, the following will occur:

- Eligibility criteria will be reviewed and confirmed
- Participants will be asked to respond to the following
    - ESS (Epworth Sleepiness Scale)
    - FOSQ (Functional Outcomes of Sleep Questionnaire)

During the home use period, subjects will be called at the following time points during each arm of the study. At each time point, adverse events and compliance with the device will be assessed. Subjects using the device less than an average of 5 hours per night during the first week will be contacted on a more regular basis (weekly until 5 hour per night use is achieved) to address any problems and encourage use. If patients discontinue use of the device during the home use period, they will still be encouraged to return for all testing per protocol. If a patient refuses to come in for further testing, they will be considered a lost to follow up and excluded from efficacy analysis.

- 1 Day Phone Call (+2 days)
- 7 Day Phone Call (+/- 3 days)
- 14 Day Phone Call (+/- 3 days) IF deemed necessary per 7 Day compliance
- 28 Day Phone Call (+/- 3 days) Check-in

- Week 6 Phone Call (+/- 3 days) – End first arm, fill out questionnaires, start Washout Period
- Week 7 Phone Call (+/- 3 days) - Review protocol, start 2nd arm
- Week 12 (+/- 3 days) - Equipment Return

Data collected from the therapy device will include the following:

- Usage averaged over the 6-week period and nightly
- Leak averaged over the 6-week period and nightly
- P95 averaged over the 6-week period and nightly (for the CPAP/APAP arm only)
- Sleep events averaged over the 6-week period and nightly

Number of Participants:

A total of 32 participants will be enrolled.

Study Duration:

Per subject study duration will be approximately 4 months (screening plus 90 days of home use). Total study duration will be approximately 9 months (6-month enrollment plus 35 days of home use).

1.2 Schedule of Activities (SoA)

Schedule of Activities

Procedures	Screening	Office	Home
Telephone or outpatient contacts with participant	X		
Informed consent when patient comes to office		X	
Analysis of CPAP compliance data		X	
Demographics		X	
Medical history & medications		X	
Height		X	
Weight		X	
Randomization		X	
Provide equipment and training		X	
1st Post- 6-Week Activity			
Review and confirm eligibility criteria	X		
ESS			X
FOSQ			X
AE/SAE Monitoring			X

2nd Post- 6-Week Activity			
ESS			X
FOSQ			X
AE/SAE Monitoring			X
Return study equipment		X	
Receive future home therapy equipment and training		X	

Abbreviations: AE = adverse event; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event

2 Introduction

2.1 Study Rationale

A device able to provide inspiratory positive airway pressure (PAP) < expiratory PAP, designated TPAP, is being developed by SleepRes for the treatment of obstructive sleep apnea (OSA). In prior studies, the administration of higher inspiratory than expiratory PAP did not substantially increase treatment efficacy or adherence to continuous PAP (CPAP), which remains low. In our recent investigation, we demonstrated that the addition of a resistor to the CPAP circuit to reduce inspiratory PAP increased subjective comfort. The present study, TheraPAP Adherence, is a Crossover study designed to examine whether TPAP can improve adherence over CPAP as an at home treatment for OSA.

2.2 Background

2.2.1 Obstructive Sleep Apnea

The National Commission on Sleep Disorders Research identified sleep disorders as a major public health burden. OSA is the most common of the more serious sleep disorders and affects approximately 20 million people in the United States (US), with approximately 13% of men and 6% of women affected (1). OSA is characterized by repetitive collapse or ‘obstruction’ of the pharyngeal airway during sleep, manifesting as repetitive episodes of hypopnea (i.e., shallow breathing) or apnea (i.e., paused breathing). These episodes of hypopnea or apnea may lead to hypoxemia, arousal from sleep, sleep fragmentation, excessive daytime sleepiness, and/or neuropsychological impairment.

Long-term, OSA is associated with increased mortality and a number of adverse cardiovascular, neurocognitive, metabolic, and daytime functioning consequences (2-11).

2.2.2 Unmet Medical Need

The large majority of OSA patients are treated with positive airway pressure, the most common of which is CPAP, provided by a machine that mechanically maintains an open airway. However, long-term adherence to therapy remains a challenge for many patients (12, 13). Common complaints include inconvenience, lack of perceived benefit, discomfort related to improper fitting of the interface, and difficulty expiring against positive pressure (14, 15).

As many patients cannot use CPAP because they find it intolerable, this represents a significant health concern, as OSA is associated with numerous adverse health outcomes and increased mortality. Strategies to improve tolerance of CPAP, and subsequently adherence, are needed.

2.2.3 Biological Rationale

TPAP is an innovative device/algorithm designed to deliver a lower inspiratory than expiratory PAP. The drop in inspiratory pressure can be modulated during the inspiratory phase. Previous research has shown that reducing inspiratory PAP by placing a resistor in the inspiratory line can enhance subjective comfort and decrease leaks when compared to CPAP, despite maintaining a similar residual apnea-hypopnea index (AHI). However, the resistor could only provide a fixed inspiratory PAP reduction based on existing PAP settings. TPAP addresses this limitation by allowing for adjustable drops in inspiratory PAP throughout the inspiration phase, offering a potentially more personalized and adaptive therapeutic approach.

3 Endpoints

	Endpoints
Primary	• Nightly adherence (usage) with device (TPAP versus APAP)

Secondary	• Evaluation of P95, Leak and AHI over each 6-week period
	• 6-week Subjective Questionnaires (TheraPAP versus APAP) following each arm
	  o ESS
	  o FOSQ
	• Adverse Event rate

Safety Endpoints[2]	• Spontaneous adverse events

[2] Although there will not be any direct treatment vs. control comparison here, we will assume that CPAP is safe and that any abnormal value recorded in the next morning compared to the evening before the polysomnography is due to treatment with TPAP.

4 Study Design

4.1 Overall Design

Safety issues regarding this study are detailed in Appendix 1: Regulatory, Ethical, and Study Oversight Considerations.

The TheraPAP Adherence 1 Study is a randomized, controlled, crossover study in PAP-naïve participants with OSA. Pre-screening is conducted to establish potential eligibility based on an in-lab polysomnogram (PSG), a PSG split-night PSG/titration or a home sleep study (HST) that has been conducted within the previous 3 months. Participants would then be recruited as described below. For those who consent, they will be given the equipment and instructions to complete both arms of the study but will have their therapy device set to the parameters necessary to start the first arm, which will be randomly assigned. They will use the device nightly for 6 weeks, after which they will use no therapy for 1 full week (washout period). During this washout period, their therapy device will be remotely set to their second arm. When they restart therapy, they will use the device nightly for a further 6 weeks. During each arm, various data will be remotely collected from their therapy device, and after completion of each arm, they will fill out 3 questionnaires and average data during the 6 weeks of that arm will be downloaded. Once all activities are completed, they will be eligible to receive the incentive pay and their involvement will be completed.

4.2 Detailed Design

4.2.1 Pre-Screening

The first phase of recruiting for the TheraPAP Adherence 1 study will be done during the phone follow up during which the patients will be scheduled to come to the office of Sleep Centers of Middle Tennessee (SCMT) to collect their CPAP equipment. The following regarding the study will be conveyed to them: goals, a summary protocol, risks/benefits, other activities required by them, financial compensation and timing. They will also be asked for verbal permission to review their records so that office personnel can conduct a preliminary screening for eligibility. If they agree and show interest based on the first phase, they will be added to the eligibility roster.

The second phase of recruiting will be conducted when they come into the office to pick up the equipment. The coordinator will review the material related to the study, as well as the details within the informed consent. If the patient agrees to continue, they will sign the informed

consent in ink and be enrolled in the study. The coordinator will conduct a final check that the patient satisfies all enrollment criteria. After this, they will be enrolled in the study.

They will then be randomly assigned to start in either the APAP or TPAP arms of the study, and their equipment will be set up by the coordinating staff to operate according to the randomly chosen arm. During this setup, the pressure range will also be set to 5-20 cmH_2O irrespective of study arm. They will receive this equipment for the study, then be given instructions for use on both arms both verbally and through material that they can take home.

4.2.2 First 6-Week Arm

Patients will start using their equipment the first night. The study coordinator will monitor usage nightly and after the third night with a minimum of 5 hours of use, they will remotely adjust the device pressure range to P95 ± 2 cmH_2O, using the P95 from the third night. This range will be used for the remainder of both arms of the study. During the study, daily remote collection of usage will be conducted both for later primary endpoint analysis and to guide further contact with the patient if they need help.

During usage in the first arm, P95 and AHI will be monitored to assure that the patient is receiving proper therapy. If P95 is near the upper limit and the AHI is above 5 events per hour, the range will be bumped up by 2 cmH_2O.

A contact schedule will also be set up with each patient to follow up on any needs for help. Similar interaction is customary with new CPAP patients. The schedule is as follows and will be conducted on both arms of the study:

- 1 Day Phone Call (+2 days)
- 7 Day Phone Call (+/- 3 days)
- 14 Day Phone Call (+/- 3 days) IF deemed necessary per 7 Day compliance
- 28 Day Phone Call (+/- 3 days)

Participants using the device less than an average of 5 hours per night during the first week will be contacted on a more regular basis (weekly until 5 hour per night use is achieved) to address any problems and encourage use. If patients discontinue use of the device during the home use period, they will still be encouraged to complete surveys per protocol. If a patient refuses to complete such surveys, they will be considered lost to follow up and excluded from efficacy analysis.

At the end of the 6-week period, patients will stop using any sleep therapy for 1 week as a washout between arms. The study coordinator will remotely switch the mode of operation of the

therapy device to that for the second arm employing the same pressure range as was used in the bulk of the first arm. Patients will be asked to fill out the questionnaires during this period (ESS and FOSQ). Additionally, the following data averaged over the 6-week period of the trial will be downloaded from the device:

- Usage
- Leak
- P95
- AHI

4.2.3 Second 6-Week Arm

Following the one-week washout period, patients will start the second arm therapy for the next six weeks of nightly use. The procedure will be exactly the same as for the first arm, described above except that the device pressure range will be retained at the same settings that were present during the bulk of the first arm.

4.2.4 TPAP Arm Specifics

The TPAP arm involves other pressure settings because the therapy involves reducing pressure in two steps starting at inhalation and following through the peak of exhalation. An auto-adjusting algorithm will continuously choose the pressure within the active pressure range, and the settings for the two pressure drops will also instantly and continuously adjust to those specified in Table 1 above.

4.2.5 Risk-Benefit Analysis

All patients will be using a Sefam S.Box as their therapy device. Although the S.Box does not have 510K approval, it is CE-marked and approved for use in Europe. All TheraPAP algorithms will be thoroughly verified and validated for safety and efficacy in each device according to the SleepRes QMS before being provided to a patient. When not in use and when returned, these devices will be sequestered in a locked location. TheraPAP is a new OSA therapy designed to improve CPAP comfort. Testing in awake PAP-naïve patients thus far has shown a preference of it over CPAP. Thus, we expect there are no risks associated with it.

Regarding benefits to the participants:

- It is anticipated that patients on the TheraPAP arm of the study will find it more comfortable than regular CPAP and hopefully sleep better.

- The results of the study could yield future benefit to the participants in terms of wider treatment alternatives for their OSA.

4.3 End of Study Definition

Once the second 6-week arm is over and questionnaires have been completed, the patients will return their equipment to the office. Once the equipment is returned, the participants' involvement in the study will be complete and they will be able to receive their study incentive. They will also then be given their regular take-home equipment with usage instructions.

5 Study Population

Eligible participants will be recruited from the pool of PAP-naïve patients who have undergone some form of sleep study and will be receiving CPAP therapy equipment.

5.1 Inclusion Criteria

5.1.1 Age and Sex

1. Between 20 and 70 years of age, inclusive.

5.1.2 OSA Measures

2. Diagnosis of OSA meeting all the following criteria:
    a. AHI > 10 on a previous PSG or HST (hypopneas requiring 4% desaturation).
    b. Central apneas < 25% of events
    c. PLM arousal index < 15

5.1.3 Informed Consent

3. Subject is fluent in English and subject understands the study protocol and is willing and able to comply with study requirements and sign informed consent.
4. Participant voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB)-approved informed consent prior to performing any of the study-related procedures.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1 Medical Conditions

1. A female of child-bearing potential that is pregnant or intends to become pregnant.
2. Any unstable or severe medical condition of any organ system including congestive heart failure, COPD, renal failure, neuromuscular disease, etc., or at the discretion of the site Principal Investigator (PI).
3. Taking medication that may affect sleep, sleepiness, or alertness including hypnotics, sedatives, alerting agents, stimulants, anticonvulsants, etc.
4. The presence of any other sleep disorder (insomnia, periodic limb movement disorder, etc).

5.2.2 Prior/Concomitant Therapy

5. Prior therapy or treatment for OSA.
6. Chronic oxygen therapy.

5.2.3 Other Exclusions

7. Excessive alcohol consumption (>14 drinks/week).
8. The use of any illegal drug(s).
9. Any condition that in the investigator's opinion would present an unreasonable risk to the participant, or which would interfere with their participation in the study or confound study interpretation.

5.3 Screen Failures

Patients that do not meet the inclusion/exclusion criteria at the outpatient screening visit will not be invited to, or further contacted to, participate in the study.

5.4 Preparation/Handling/Storage/Accountability

Devices will be provided by the sponsor and will be kept in a locked designated area within the DME (Durable Medical Equipment) office. It will only be accessible by office personnel. They will be used only for approved study purposes as designated by the study coordinator who will oversee their use in this study.

5.5 Measures to Minimize Bias

Each participant will begin the study in one of the treatment arms, (either APAP or TPAP). The starting treatment arm is determined by a random number generator, as described in Section 7.2.

5.6 Concomitant Therapy

Usual therapy is allowed as indicated by the patient's general practitioner, except for oxygen therapy, which is an exclusion criterion.

5.7 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an adverse event (AE).

5.8 Stopping Criteria

5.8.1 Individual Participant Stopping Criteria

Participants reporting any SAE considered possibly related or related to study device will be withdrawn from the study.

Any other AE that in the judgment of the Investigator necessitates the participant stopping to protect participant safety, will result in early withdrawal from the study.

5.9 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.

If the participant withdraws consent, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.
Participation may be terminated before completing the study and the reason recorded as follows:

- Withdrawal due to AE
- Participant withdrew consent at their own request, (e.g., intolerance to study procedures)
- At the discretion of the Investigator for safety, behavioral, or administrative reasons
- Other reasons, as they occur

5.10 Participant compensation

Participants will be compensated for their time and participation with an office credit of $200.

6 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 At Home Study

- **Methods**: Equipment taken home for the study (Sefam S.Box and associated patient interface materials) has been given European approval via a CE mark. Additions of TheraPAP algorithms, which have been tested extensively for safety and efficacy in our lab, will be evaluated on the S.Box machines via a testing procedure that is part of our quality system.
- Regular contact with patients according to the call schedule will be conducted and any problems will be discussed and reported.
- Study data reported by the S.Box (usage, P95, leak and AHI) will be averaged over a night and recorded daily through the S.Box remote access system, and will be stored according to HIPAA requirements at the sponsor's office.

6.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Safety assessments will include measurement of vital signs, monitoring and recording of AEs, SAEs, and recording of study or treatment discontinuations. Effects on OSA and sleep parameters (e.g., sleep time and sleep stages) will also be monitored by PSG.

6.3 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Adverse events will be reported by the participant.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study device or the study, or that caused the participant to discontinue the study.

6.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from randomization until the end of the study at the timepoints specified in the SoA.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

6.3.2 Follow-up of AEs and SAEs

Ongoing AEs and SAEs will be followed until resolution or stability as determined by the Investigator.

6.3.3 Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours, see Appendix 2) by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority and IRB.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

7 Statistical Considerations

7.1 Sample Size Determination

Sample sizes are estimated to achieve 80% power based on a 1-sided 5% significance level. As this is an exploratory proof of concept trial, a 1-sided 5% significance level was selected. The within subject standard deviation is assumed to be 1 hour and the minimum treatment difference is assumed to be 0.5 hours.
When there are 2 treatments and a sample size of 14 in each of the 2 sequences, a 2x2 Williams Crossover Design will have approximately 82% power to detect a minimum pairwise difference of 0.5 or greater, assuming that the standard deviation of the paired differences is 1 at a one-sided 5% significance level.

Assuming ~20% dropout and total of 36 patients (18/sequence) is planned.

7.2 Randomization

The treatment arm is determined by random selection using an MS Excel spreadsheet on the night of the study. The spreadsheet generates a number between 1 and 10,000. The TPAP therapy will be the starting therapy when an even number is generated by the spreadsheet; the CPAP therapy will be the starting therapy when an odd number is generated.

7.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Set	Description
Randomized	All participants who were randomized.
Modified Intent to Treat (mITT) Set	The mITT set comprises all participants who are randomized, undergo at least 1 night in either study arm, and have at least 1 measurement on the primary endpoint. Participants will be analyzed for equivalence.
Safety Set	The Safety Set consists of all participants who are randomized and undergo at least 1 night in either study arm.
Per Protocol (PP) Set	The PP Population consists of all participants without any major protocol violations and have considered to be evaluable for study analysis.

7.4 Interim Analyses

No interim analysis is planned.

8 Supporting Documentation and Operational Considerations

- Appendix 1: Regulatory, Ethical, and Study Oversight Considerations
- Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting
- Appendix 3: List of Abbreviations

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
- Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB guidelines, and all other applicable local regulations.

2 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must consent to the most current version of the ICF(s) during their participation in the study.

A copy of the signed ICF(s) must be provided to the participant.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and signed by all participants subsequently enrolled in the study.

4 Data Protection

Participants will be assigned a unique identifier by the study site. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

5 Data Quality Assurance

All participant data relating to the study will be recorded on electronic reports and spreadsheets. Any study data will be de-identified. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the study records.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the study records.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the site personnel will be captured and stored in an internal password-protected system.

6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site.

7 Publication Policy

The Sponsor will generally support publication, reserving the right to review prior to submission.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements.

A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinTrials.gov).

8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/Competent Authority approval prior to implementation (if appropriate). Any deviations from the protocol will be reported to the Sponsor as Protocol Deviations.

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by medical steps taken during the study.

10 Access to Source Data

Regulatory authorities of certain countries, IRBs, and/or the Sponsor's Clinical Quality Assurance Group (or designee) may wish to carry out source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor and affiliates or designees (such as a CRO) of the necessary for support at all times.

Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of a study treatment, whether considered related to the device product. • NOTE: An AE can therefore be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal safety assessments (e.g., vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition includes either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Recording and Follow-up of AE and SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities. Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The Investigator will also consult the Instruction for Use, in his/her assessment. For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.** The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a participant dies during participation in the study, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed CRF. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAE

SAE Reporting
The Investigator must report any SAEs to the Sponsor within 24 hours of becoming aware of the event. The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference documents. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE, report to the Sponsor within 24 h. Contacts for SAE reporting can be found in the Study Operation Manual.

All SAEs will be recorded from randomization until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to study treatment.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
Any AE that is serious, associated with the use of the study treatment, and unexpected (SUSAR) has additional reporting requirements, as described below. If the SUSAR is fatal or life-threatening, associated with study treatment, and unexpected, regulatory authorities and IRB will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total). If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study treatment, and unexpected, regulatory authorities and IRBs will be notified within 15 calendar days after the Sponsor learns of the event.

Appendix 3: List of Abbreviations

AE	adverse event
AHI	Apnea-hypopnea index
BMI	body mass index
CFR	Code of Federal Regulations
CPAP	continuous positive air pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EOS	end of study
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
OSA	obstructive sleep apnea
NREM	non-rapid eye movement
P90 / P95	pressure levels that eliminate breathing obstructions for at least 90 / 95% of the sleep period
PAP	positive airway pressure
PSG	polysomnography
REM	rapid eye movement
SAE	serious adverse event
SCMT	Sleep Centers of Middle Tennessee
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TPAP	TheraPAP algorithm
US	United States

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Declaration of the Investigator

Title: Randomized Crossover Study to Compare Effectiveness of a Device Providing Pressure Drops During Inspiration (TPAP) to Continuous Positive Airway Pressure in Obstructive Sleep Apnea

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, study guide, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the participants.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator of the local study center

_____ _____

Signature Date

Abinash Joshi, MD_____

Name (block letters)

_____

Title (block letters)

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Institution (block letters)

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Phone number