Study Protocol

The Evaluation of the Astral VAPS AutoEPAP Treatment Algorithm

Short Title: Astral VAPS AutoEPAP Clinical Trial

Study Number: MA-15-12-15

Revision: 4.0

Date: 06.June.2016

Sponsor*:*

ResMed Corp
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This protocol has been written in accordance with current applicable guidelines (IDE for USA) as well as all other relevant additional references, medical and legal.

PROTOCOL SIGNATURE PAGE

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable FDA good clinical practice and ICH GCP guidelines (ICH GCP E6 8.2.2).

Deviations from the protocol may not proceed without prior approval of the Sponsor and the IRB, unless under emergency circumstances where deviations are performed to protect the rights, safety and the well-being of human subjects. Such deviations shall be documented and reported to the Sponsor and to the IRB as soon as possible.

The study may not begin until IRB approval is obtained and regulatory bodies have been notified and all additional requirements imposed by the IRB or regulatory body shall be followed.

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Name of Principal Investigator

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Signature of Principal Investigator Date

Rev	Date	Section	Change Details	Rationale
1.0	17 Dec 2015	N/A	N/A	Original Release
2.0	01.Feb.2016	6.2.4	Update power calculation definitions and removed extraneous reference.	To be more clear with calculations and reference only 1 applicable source.
		6.2.4	Removed non-inferiority calculation.	Moved to more appropriate section.
		12.	Added explanation for non-inferiority margin. This was previously in section 6.4.2.	To make protocol more clear.
3.0	02.Feb.2016	4.1	Clarified patient population and aim of study	Clarification
		6.2.2	Clarified patient population for the study	Clarification
		6.2.4	Reference non-inferiority margin in section 12 and rationale for differences in events per hour	Clarification between power and non-inferiority margin calculations
		12.	Further explanation on non-inferiority margin and clinical justification for the margin	To make statistical analysis more clear
4.0	06.June.2016	Various	iVAPS to VAPS	To better define the objective of comparing AutoEPAP to manual EPAP; these modes will be utilized *within the iVAPS mode* on the Astral study device
		4.1	Updated study device with current FDA clearance status and K number Updated language referencing previous clinical data	To reflect current FDA clearance status on study device Provide clarity to the details of this research
		4.2	Update to intended use language	Ensure protocol is consistent with currently cleared IFU language

		5.2	Update patient description to be “respiratory failure”	Update language of patient population to be more clinically accurate
		6.2.5	Update to I#6 wording	Clarify purpose of this criteria
		6.2.6	Removal of “dependent” from Exclusion criteria	Current cleared IFU for study device does not exclude this type of patient
		7.4	Update to training process	Reflect current protocol training procedures
		9.1	Update to appropriate data transfer method	Previous version was inaccurate with old SD card method
		9.3	Summary of Visit 3 added	Clarification of visit 3 procedures
		10.	Update to study timeline and total enrollment	Change in IEC of protocol dictates an increase of total sample size, and consequently, increase in study timeline
		14.3.1	Update to NSR justification	Provide current FDA clearance for study device

Table of Contents

1. RESPONSIBILITIES AND ADDRESSES

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2. ABBREVIATIONS AND DEFINITIONS

ITEM	DEFINITION
AASM 2007	American Academy of Sleep Medicine 2007 guidelines
ABGs	Arterial blood gases
AHI	Apnea Hypopnea Index
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
CRF	Case report form
DSBM	Data & Safety Monitoring Board
EEG	Electroencephalography
EFL	Expiratory flow limitation
EPAP	Expiratory positive airway pressure
EPR	Expiratory Pressure Relief (ResMed comfort setting)
HREC	Human Research Ethics Committee
iBR	Intelligent Back-Up Rate
ICF	Informed Consent Form
IRB	Institutional Review Board
iVAPS	Intelligent Volume Assured Pressure Support
Astral	The name given to the clinical trial device
LSLV	Last subject, last visit
NIPPV	Non-invasive positive pressure ventilation
NMD	Neuromuscular Disease
NSR	Non-Significant Risk
ODI	Oxygen desaturation index (≥ 3% desaturation)
OHS	Obesity Hypoventilation Syndrome
OSA	Obstructive Sleep Apnea
PAP	Positive airway pressure

PS	Pressure Support
PSG	Polysomnography
PtCO2	Transcutaneous carbon dioxide
SIV	Site initiation visit
Standard ST mode	Commercially available ST modes utilizing a fixed EPAP
UAO	Upper airway obstruction
VAPS	Volume Assured Pressure Support

3. PROTOCOL SUMMARY

Objectives	The objective of this study is to evaluate AutoEPAP versus manual EPAP in iVAPS mode on the Astral device.
Study Design	This will be a prospective, multi-center, single-blind, randomized, cross-over design. The study will occur in a lab/hospital setting. Eligible subjects that represent patients with respiratory failure will complete two PSG study nights.
Number of Subjects	Up to 40 subjects overall will be randomized to obtain endpoint data on at least 36 evaluable subjects. This accounts for the expected dropout rate (10%).
Selection criteria	**Inclusion criteria for the study are:** 1. Participant has ability to provide written informed consent 2. Participants aged ≥18 years old 3. Participant has documented respiratory failure (e.g. sleep hypoventilation with historical PtCO2 increase ≥ 10mmHg) and/or daytime hypercapnia (>45 mmHg) 4. Participant is currently using non-invasive positive pressure ventilation in ST or VAPS mode for ≥ 3 months 5. Participants with a previously documented AHI ≥ 5/hr 6. Participants with a recently (≤ 12 months ago) reviewed EPAP setting **Exclusion criteria for the study are:** 1. Participants are not compliant on NIPPV (e.g. < 4 hr/night) 2. Participants who are pregnant 3. Participants on oxygen therapy ≥5 L/min 4. Participants with an invasive interface (e.g. tracheostomy) 5. Participants who have had an acute exacerbation within the last 3 months that resulted in a hospitalisation 6. Participants who are acutely ill, medically complicated or who are medically unstable 7. Participants in whom NIPPV therapy is otherwise medically contraindicated 8. Participants who have had surgery of the upper airway, nose, sinus, or middle ear within the previous 90 days 9. Participants with untreated, non-OSA sleep disorders, including but not limited to; insomnia, periodic limb movement syndrome, or restless legs syndrome. 10. Participants who have the following pre-existing conditions: severe bullous lung disease, recurrent pneumothorax or pneumomediastinum, cerebrospinal fluid leak, recent cranial surgery or trauma. 11. Participant does not comprehend English 12. Participant is unable or unwilling to provide written informed consent 13. Participant is physically and/or mentally unable to comply with the protocol 14. Participant is not suitable to participate in the trial for any other reason in the opinion of the investigator

Primary Endpoints	The primary outcome is the Oxygen Desaturation Index (ODI4%) as a measure of upper airway obstruction. The primary aim of this protocol is to compare ODI values following the use of the AutoEPAP algorithm in comparison to manual EPAP in VAPS mode.
Secondary Endpoints	The secondary objectives will be used to determine if the AutoEPAP algorithm remains effective in treating respiratory failure patients. 1. To assess the apnea hypopnea index (AHI) as measured by the Astral device. 2. To assess sleep-breathing parameters (e.g. nadir SpO_2 and PtCO2) with AutoEPAP algorithm compared to manual EPAP on an Astral device. 3. To assess sleep parameters (e.g. sleep efficacy and arousal index) with AutoEPAP algorithm compared to manual EPAP on an Astral device.
Scheduled Visits	<u>Visit 1</u> • Informed Consent • IEC requirements • Baseline Characteristics • Medical History <u>Visit 2 (Night 1) and 3 (Night 2)</u> • Mask fitting • Overnight PSG, including oximetry and PtCO2

4. INTRODUCTION

4.1. Background Information

Patients with chronic respiratory insufficiency or failure such as those associated with Chronic Obstructive Pulmonary Disease (COPD) [1], Obesity Hypoventilation Syndrome (OHS) [2], Obstructive Sleep Apnea (OSA) [3] or Neuromuscular Disease (NMD) [4, 5] are increasingly managed with domiciliary non-invasive positive pressure ventilation (NIPPV) [1, 6-8].

Optimal settings of non-invasive ventilation are usually titrated manually and require time and expertise [9]. One such setting is expiratory positive airway pressure (EPAP) which is used to manage the lower airway and, if needed, prevent upper airway obstruction (UAO). In order to optimally adjust a fixed EPAP setting in a NIPPV device, a sleep study is usually required where respiratory flow waveforms may be monitored and recorded [10]. The waiting time for NIPPV titration sleep studies can be lengthy and/or be poorly performed due to resource limitations, and once they are, respiratory flow waveforms are often not recorded. In the instances where respiratory flow waveforms are recorded and analyzed, optimization of fixed EPAP settings are only based on the patient's condition for that single night. As a result, single night titrations may not capture significant alterations in factors which may affect the level of EPAP required, such as posture [11] and sleep state (e.g. supine in REM) [12].

Additionally, patient requirements may change over time due to progression of their chronic illness, weight fluctuations and prescribed medications, and, in some patients, changes in tissue edema location and severity with posture changes [13]. As such, the EPAP pressures, which are all under clinician control, are set during a titration study and must be high enough to deal with the worst conditions which may occur during the night. Clinicians must also regularly monitor patients, and possible perform re-titrations to make sure the manually set EPAP is optimal.

For all these reasons, an automatic adjustable EPAP (i.e. "AutoEPAP") with clinician controlled minimum and maximum EPAP levels, may offer advantages over a fixed EPAP for managing UAO.

While an AutoEPAP algorithm could be used in the context of conventional fixed pressure support bilevel therapy (e.g. Spontaneous/Time (ST) mode), it would be useful to be used with a therapy mode which aims to automate all other aspects of ventilation as much as possible. Similar automated techniques have been successfully developed and established in current practice for OSA and periodic breathing [14, 15].

The Astral ventilator includes the Intelligent Volume Assured Pressure Support (iVAPS) (ResMed, Sydney, Australia, K152068) mode - a pressure support servoventilator which automatically adjusts pressure support to achieve a target alveolar ventilation (minute ventilation minus the anatomical deadspace) for patients who require mechanical continuous or intermittent ventilation. The amount of anatomical deadspace is calculated from an algorithm based on patient height. iVAPS also has a variable respiratory backup rate (i.e. Intelligent breathing rate; iBR), in which the set backup rate is delivered during periods of hypoventilation or central apnea only. When the user is breathing spontaneously and is triggering the device, the iBR algorithm will decrease the backup rate down to 2/3 of the 'target breath rate'. When necessary, iBR will rapidly increase the backup breath rate to the set 'target breath rate' to achieve target alveolar ventilation. The 'Target breath rate' is set according to the user's spontaneous breath rate during quiet wakefulness or in accordance with clinical needs (i.e. optimal PaO_2 and $PaCO_2$). The 'Target breath rate' can be measured and set by the ventilator itself, or manually adjusted by the clinician. Clinical trials evaluating a VAPS mode have been performed and have demonstrated VAPS is equivalent in treating respiratory insufficiency or failure as per manually titrated pressure support ventilation [16, 17, 19, 20, 21, 22, 23].

Patients with respiratory failure may also have upper airway obstruction. These patients therefore may benefit from NIPPV therapy which incorporates the management of volume assurance pressure support (i.e. VAPS) and UAO (i.e. AutoEPAP).

One such algorithm which has been developed is the iVAPS AutoEPAP algorithm (ResMed, Sydney, Australia). The iVAPS AutoEPAP algorithm has been previously trialed in patients with respiratory insufficiency or failure such as Obesity Hypoventilation Syndrome (OHS), Chronic Obstructive Pulmonary Disease (COPD) or neuromuscular disease (NMD) [24]. The patients completed two sleep studies (PSG) with iVAPS: one a manually titrated EPAP, and a second sleep study to observe and record the EPAP pressure generated from the AutoEPAP algorithm. Results showed that the algorithm was able to automatically titrate the EPAP level to effectively treat UAO in conjunction with respiratory insufficiency or failure compared to iVAPS mode with a fixed EPAP pressure. Treatment of UAO was shown to be comparable between the manually titrated EPAP with iVAPS, versus iVAPS AutoEPAP (mean AHI 1.7 (2.8) hr^{-1} and 1.3 (2.3) hr^{-1}, respectively; p = 0.52) [24].

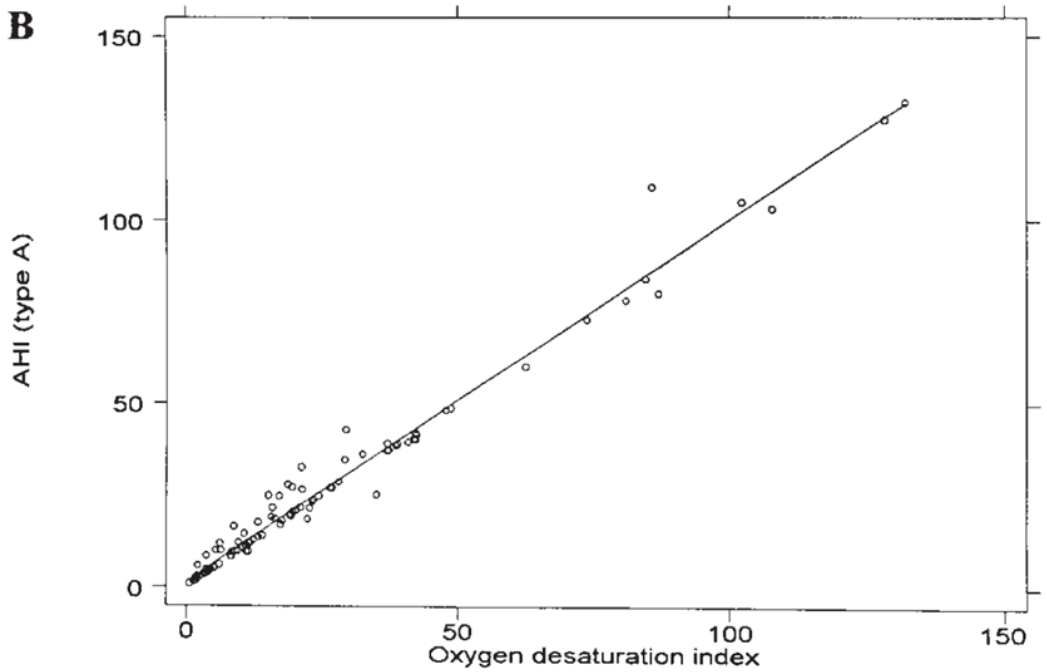
The aim of this study is to now compare the AutoEPAP algorithm with manual EPAP in iVAPS mode on an Astral ventilator. It is proposed that the automatic settings of AutoEPAP will be as effective at managing respiratory failure and UAO as manual EPAP on the Astral device. Specifically demonstrating that the AutoEPAP function is as effective at treating UAO as manual EPAP.

Astral is a homecare and hospital ventilator and not compatible with PSG systems for the measurement of respiratory flow estimate for the scoring of AHI. While total flow might be measured at the outlet of the Astral ventilator, this flow would include uncompensated components of flow from the mask vent and unintentional mask leak that will vary both within the breath due to varying pressure and over a longer time course due to changing mask leak. Based on the offset and variation of these components, accurate measurement of apneas and hypopneas would not be possible.

Since it is not technically feasible to calculate AHI, a surrogate for AHI is the ODI4% based on pulse oximetry that can be accurately obtained with PSG systems whilst a patient is using the Astral ventilator.

Clinically, ODI4% correlates exceptionally well with the AASM 2007 scoring rules for AHI (r = 0.98) [25]. See figure 1.

Figure 1. Correlation of ODI and AHI



Secondary aims include assessing the other potential physiological (i.e. sleep and sleep-breathing variables and gas exchange) that the algorithm may have on the patient.

4.2. Intended Use

The Astral device provides continuous or intermittent ventilatory support for patients who require mechanical continuous or intermittent ventilation (ResMed, Sydney, Australia, K152068). Intelligent Volume Assured Pressure Support (iVAPS) is a mode of therapy for patients who require mechanical ventilation. The Astral device with the AutoEPAP algorithm and manual EPAP in iVAPS mode will be used in this protocol.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary outcome is the Oxygen Desaturation Index (ODI4%). The primary aim of this protocol is to compare ODI values following the use of the AutoEPAP algorithm in comparison to manual EPAP on the Astral ventilator.

5.2. Secondary Objectives

The secondary objectives will be used to determine if the AutoEPAP algorithm remains effective in treating respiratory failure.

1. To assess the apnea hypopnea index (AHI) as measured by the Astral device.
2. To assess sleep-breathing parameters (e.g. nadir SpO_2 and PtCO2) with AutoEPAP algorithm compared to manual EPAP on an Astral device.
3. To assess sleep parameters (e.g. sleep efficacy and arousal index) with AutoEPAP algorithm compared to manual EPAP on an Astral device.

6. STUDY DESIGN

This will be a prospective, multi-center, single-blind, randomized, cross-over design. The study will occur in a lab/hospital setting. This study will be conducted at several centers in the United States.

6.1. Enrollment

Subjects will be recruited from pulmonary clinics at each site.

6.2. Selection of Subjects

6.2.1. Informed Consent

The consent form is written in accordance with applicable data privacy acts and FDA Regulations and approved by the responsible Institutional Review board (IRB).

The investigator or responsible staff will explain the nature, purpose and risks associated with the study. The patient will be given sufficient time to consider the study's implications before deciding whether to participate. Information materials created by the investigators and Sponsor must be approved by the responsible IRB prior to use.

A signed, IRB-approved consent form must be obtained from the patient prior to the performance of any protocol-related testing or treatment procedures. The consent process must be performed by a designated clinical study team member authorized by the IRB to consent patients and listed on the Delegation of Authority Log as having privileges to consent patients. A signed copy of the consent form must be maintained in the study files and a copy provided to the patient. The patient's permanent medical records should indicate study participation.

6.2.2. Study Population and Randomization

Enrolled subjects will be representative of patients with respiratory failure who fulfill the inclusion criteria and none of the exclusion criteria for this study and who sign the consent form(s) are considered as potential candidates for randomization into the study.

After verification of the subject's eligibility for the study, the study coordinator will assign the subject to 1 of 2 arms of the study, using the computer-generated randomization schedule provided by the Sponsor.

This is a single-blind study. This means that the subjects will be blinded to the randomization group that they are assigned to; the site Investigator and site study staff will know which randomization group the subject has been assigned to. The scorer(s) of the PSG will be blinded to which therapy is being used for objective determination of the primary and secondary endpoints.

6.2.3. Number of Subjects

Up to a total of 40 subjects will be enrolled across all centers.

6.2.4. Sample Size Justification

This study is powered for demonstrating ODI4% non-inferiority between the AutoEPAP algorithm and manual EPAP algorithm on the Astral device.

This protocol has been powered with the following inputs based on a previous study [26].

Expected mean difference in ODI: 0
Expected standard deviation in ODI: 1.55
Power = 80%
Alpha = 0.05

Power to detect a difference of 1 per hour using a paired two-tailed t-test:

$n = (Z\alpha + Z\beta)^2 \times (SD/difference)^2 = 22.84 = 23$

Therefore, based on a crossover non-inferiority hypothesis test (one in which the outcome is dependent) we can be 95% sure that a sample size of 23 is sufficient to detect inferiority of AutoEPAP compared to with manual EPAP with respect to difference of ODI.

The update to this protocol (v3.0 to v4.0) was completed to be consistent with the recent FDA clearance of Astral with iVAPS. The increase in enrollment goal will provide additional power (95%) to detect a difference between AutoEPAP and manual EPAP.

We pre-specify a non-inferiority margin for ODI4% of 2 per hour (refer to Section 12). Basing the sample size on being able to detect the smallest difference in ODI (1 per hour) will provide greater power, through a larger sample size, in testing the non-inferiority margin (2 per hour).

6.2.5. Subject Inclusion Criteria

1. Participant has ability to provide written informed consent
2. Participants aged ≥18 years old
3. Participant has documented respiratory failure (e.g. sleep hypoventilation with historical PtCO2 increase ≥ 10mmHg) and/or daytime hypercapnia (>45 mmHg)
4. Participant is currently using non-invasive positive pressure ventilation in ST or VAPS mode for ≥ 3 months
5. Participants with a previously documented AHI ≥ 5/hr
6. Participants with a recently (≤ 12 months ago) reviewed EPAP setting

6.2.6. Subject Exclusion Criteria

1. Participants are not compliant on NIPPV (e.g. < 4 hr/night)
2. Participants who are pregnant
3. Participants on oxygen therapy ≥5 L/min
4. Participants with an invasive interface (e.g. tracheostomy)
5. Participants who have had an acute exacerbation within the last 3 months that resulted in a hospitalisation
6. Participants who are acutely ill, medically complicated or who are medically unstable
7. Participants in whom NIPPV therapy is otherwise medically contraindicated
8. Participants who have had surgery of the upper airway, nose, sinus, or middle ear within the previous 90 days
9. Participants with untreated, non-OSA sleep disorders, including but not limited to; insomnia, periodic limb movement syndrome, or restless legs syndrome.
10. Participants who have the following pre-existing conditions: severe bullous lung disease, recurrent pneumothorax or pneumomediastinum, cerebrospinal fluid leak, recent cranial surgery or trauma.
11. Participant does not comprehend English
12. Participant is unable or unwilling to provide written informed consent

13. Participant is physically and/or mentally unable to comply with the protocol
14. Participant is not suitable to participate in the trial for any other reason in the opinion of the investigator

7. STUDY DEVICES

ResMed (ResMed, Sydney, Australia, K152068) is a developer, manufacturer and distributor of medical device equipment, including the Astral device which is designed for treating patients with respiratory disorders. ResMed is also the manufacturer responsible for the iVAPS and AutoEPAP algorithms.

7.1. Astral device

The ResMed "Astral" device is a mixed mode ventilator and for this protocol will provide mechanical ventilation. The Astral device will have iVAPS with manual EPAP and AutoEPAP algorithms, and the clinician will have the ability to manually change between the two modes.

The Astral device will deliver positive airflow to the patient via approved tubing and a vented mask. The device will therefore only come into direct contact with the surface of the skin, primarily the hands, during movement, setup, or adjustment of the device.

For the purpose of this clinical trial, user and clinical guides (Appendix A) will be provided with the devices to the clinicians and participants which will include iVAPS AutoEPAP specifications.

The iVAPS AutoEPAP algorithm is currently not approved by the FDA, and is therefore considered an Unapproved Medical Device.

7.2. Device Accountability

An accurate and current accounting of the dispensing of ResMed devices (Astral) will be maintained on an on-going basis by a qualified member of the study site using the Sponsor-provided "Device Disposition Log". The serial number unique to each Astral device will be documented on this Log. Devices will be made available to the investigator by ResMed. If a replacement device is dispensed, it will be documented per device accountability procedure. All non-disposable ResMed devices must be returned to ResMed at the end of the study.

7.3. Labeling

The label contains the information as required by relevant regulatory requirements:

a) Sponsor name and address

b) Serial number to identify the individual device

c) Instruction For Use

7.4. Packaging

The Astral device is FDA 510(k) cleared (K152068) and will be used with the standard packaging. "Investigational Use Only" stickers will be placed on all study devices prior to sending to study sites.

7.5. Instruction for Use

The devices will be used as specified in the relevant Instructions for Use provided by ResMed Corp.

For the purpose of this clinical trial, the Astral device is intended to treat stable patients with respiratory failure and who weigh at least 30 kg..

7.6. Required Training

Subjects will be instructed on usage of the devices by the local Investigators or designee. ResMed will provide the investigators' training.

All staff involved in the clinical trial will be experienced in the operation and set-up of NIPPV devices and PSG. The site will be provided with User and Clinical Guides to assist with device setup and operation.

It is expected that the trial site will use their usual equipment for conducting overnight pressure determination PSGs for the purpose of the investigational sleep studies. Therefore, it is not anticipated that any additional training on using the study equipment is required for the trial site.

Prior to the commencement of the study, the Sponsor will educate the investigators and site coordinators on the protocol, including data collection and data management. The Sponsor will educate the investigators and site coordinators on any protocol amendments and updates.

8. THERAPY

8.1. Treatment with Astral device

During this study, the Astral device will be used in a clinic setting during monitored PSG testing. AutoEPAP and manual EPAP will be used in iVAPS mode for this study.

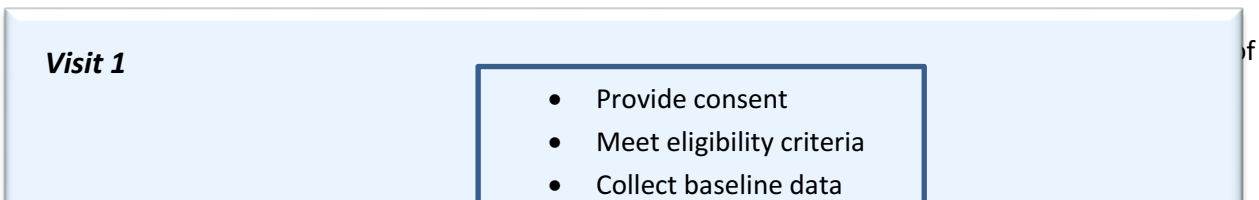
8.2. Set up of Astral device

For initiation of therapy, for subjects in either arm of the study, the Astral device will be set with clinically appropriate settings, as determined by the treating physician and investigator. These settings include: target volume and minimum and maximum pressure support (PS). For subjects randomized to the manual EPAP group on Visit 2, the EPAP settings will be based on the subject's previous titrated settings. For subjects randomized to the AutoEPAP group on Visit 2, the minimum and maximum AutoEPAP settings will be set to default, or as clinically appropriate. Additional details and instructions will be included in the study Manual of Procedures.

9. STUDY SCHEDULE

A summary of the procedure is summarized in Figure 2.

Figure 2. Summary of trial procedure



9.1. Visit 1

Participants will be recruited from existing hospital patient databases. Participants will be pre-screened and those meeting the required criteria will be contacted by the investigators via follow up phone call or during an office visit, and asked if they wish to take part in the study.

Participants wishing to participate will attend the sleep clinic/hospital where written informed consent will be obtained (Appendix B). All participants will be checked for study eligibility using the Inclusion/Exclusion criteria of this protocol. Participants who do not meet the eligibility criteria will not be included in the study. Participants meeting the eligibility criteria will have baseline information collected, including participant demographics, medical history, and information about the participants' current therapy. If available, the following information will also be collected into the subject chart: diagnostic sleep study report, their most recent spirometry report, and at the physicians' discretion, a capillary blood gas test.

9.2. Visit 2

Participants will attend an office visit where they will be randomized (1:1) to receive iVAPS with AutoEPAP or iVAPS with manual EPAP first. Participants will be randomized according to a computer-generated randomized list.

Participants will undergo an overnight PSG at the site per their randomized group assignment. Full PSG set-up, data acquisition, monitoring and reporting will be performed using the AASM 2007 criteria. Therapy will be delivered using the clinical trial device, Astral. At least 4 hours of recording will be required.

Participants' trial devices will be setup according to the therapy settings detailed in the Therapy section of this protocol. The set-up of manual EPAP or AutoEPAP settings shall occur before lights out. Study staff will also set up the subject to test PtCO2. This may be done with a device clipped to the outside of the subject's ear, and does not introduce risk to the subject.

Ensure a new USB flash drive is labelled and inserted into the Astral device prior to the commencement of the study. The device's ID number is to be recorded in the CRF before the end of the visit. Ensure there is an SD card in the machine, and the SD card is labelled with the participant ID number, therapy type, Night 1.

Visit 1 and 2 may be conducted on the same day.

9.2.1. Visit 3

Participants will undergo an overnight PSG at the site per their randomized group assignment. Full PSG set-up, data acquisition, monitoring and reporting will be performed using the AASM 2007 criteria. Therapy will be delivered using the clinical trial device, Astral. At least 4 hours of recording will be required.

Participants' trial devices will be setup according to the therapy settings detailed in the Therapy section of this protocol. The set-up of manual EPAP or AutoEPAP settings shall occur before lights out. Study staff will also set up the subject to test PtCO2. This may be done with a device clipped to the outside of the subject's ear, and does not introduce risk to the subject.

Ensure a new USB flash drive is labelled and inserted into the Astral device prior to the commencement of the study. The device's ID number is to be recorded in the CRF before the end of the visit. Ensure there is an SD card in the machine, and the SD card is labelled with the participant ID number, therapy type, Night 2.

The completion of Visit 3 marks the completion of study participation. Participants will return to their usual NIPPV therapy and have the option of keeping the mask and chinstrap that was used during the study.

9.3. Study Completion

PSG scoring will be centralized to ensure scoring consistency across sites. De-identified scored PSGs, Astral devices and flash cards will be returned to the Sponsor following study completion.

Data analysis will be performed by an independent statistician.

A final study report will be prepared by ResMed's Medical Affairs department.

10. STUDY TIMELINE

The investigators estimate it will take up to 16 weeks to recruit a total of 40 participants from all US sites.

Each participant is to attend 2-3 visits to the site (Visit 1 and 2 may be combined). Visits 2 and 3 will be overnight visits at the site's sleep unit. Ideally, sleep studies will occur on 2 consecutive nights. However, it is permitted that Night 2 can occur within 1 week from Night 1.

Therefore, the duration of the study is expected to take approximately 5 months to complete. This time frame also accounts for data monitoring, analysis and the development of the clinical study report.

10.1. Suspension or Early Termination of Study

The study or a site may be suspended or terminated early by the Sponsor, IRB or regulatory body, including but not limited to issues with safety, disease management, and unethical conduct. Should this occur, all participants currently participating in the trial will be notified, will be withdrawn safely from the study, and will resume their usual NIPPV therapy.

11. SAFETY

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding adverse events on the appropriate eCRF within the EDC system. Investigators are responsible for following all serious adverse events (SAEs) until resolution, stabilization, or the event is otherwise explained, and to report serious adverse events as well as serious injury or death that were related to (caused by or contributed to) the Astral study device in accordance with their local IRB requirements. Investigators should follow usual clinical practice at their institutions for reporting serious events to the regulatory authorities.

11.1. Definition of Adverse Events

11.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medical product and which not necessarily have to have a causal relationship with this treatment.

11.1.2. Unanticipated Adverse Device Effect

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

11.1.3. Serious Adverse Effect (event or reaction) (SAE)

Any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization (voluntary hospitalizations for elective surgeries are not considered as serious adverse events)
- results in persistent (symptomatic or moderate) or significant disability /incapacity
- an important medical event; or
- is a congenital anomaly/birth defect

All known details of the SAE will be sent to the Principal Investigator and Sponsor within 24 hours. Together the PI and Sponsor will determine whether the SAE may be device related and whether it is safe for the trial to continue. The PI and Sponsor will determine if the SAE requires reporting to the IRB, and will follow the SAE to completion.

12. STATISTICAL ANALYSIS

Data recorded during 'Ramp' time (i.e. the time taken for the pressures to increase to the prescribed settings when the device is first turned on) will be excluded. Data will be checked for normality. If the data is normally distributed, descriptive data will be presented as mean and standard deviation (SD), and marginal differences. Comparisons between the two modes will be done using paired T-test.

If the data is not normally distributed, descriptive data will be presented as median and interquartile range (IQR). Comparative analysis between AutoEPAP and manual EPAP will be performed using the Mann-Whitney U test.

A $p < 0.05$ will be considered significantly different between AutoEPAP and manual EPAP if: 1. there is no significant difference between AutoEPAP and manual EPAP or 2. AutoEPAP is significantly better than manual EPAP, than the null hypothesis will be rejected and the AutoEPAP algorithm will be considered as 'passed'.

We pre-specify a non-inferiority margin for ODI4% of 2 per hour and specify a statistical test for non-inferiority as:

Non-inferiority margin for ODI: d=2
H0: $\mu_A - \mu_B \leq -d$ (new algorithm is inferior)
H1: $\mu_A - \mu_B > -d$ (new algorithm is non-inferior)

To show non-inferiority the lower bound of the 95th confidence interval of the difference between the groups must not cross the margin boundary (ODI4% of 2 per hour).

Which will be tested with a single-sided t-test with an alpha of 0.05 and a power of 80%. This pre-specified non-inferiority margin for ODI4% of 2 per hour is considered clinically unimportant, is the same margin as used in a previous study [26], and 2 per hour represents approximately 7% of severe UAO (30 per hour).

We also pre-specify that we will reject subjects where the ODI4% cannot be controlled during the control arm phase (manual EPAP). This is defined as an ODI ≥ 10 per hour. This process will be documented in the study Manual of Procedures and training provided for all participating sites.

12.1. Withdrawal of Subjects

Due to factors not able to be predicted prior to the commencement of clinical studies, participants may at times either "drop-out" or withdraw from the study by their own volition, or be withdrawn from the study by the investigator or Sponsor. Data from participants who are excluded, drop-out or withdraw from the study prior to study completion will be collected until the point of study discontinuation, unless the participant explicitly withdraws his/her data. Where participants formally revoke their consent, which includes the revocation of consent for any data collection, all data collected from these participants will not be used in any data analyses.

All efforts will be made to follow-up on the collection of missing data. If collection of missing data is not possible, all enrolled participants' remaining collected data will still be included in the final data set for analysis on the condition that the participant has completed all required study-related procedures. Enrolment is considered as taking place at the point of randomization.

13. DATA MANAGEMENT AND STORAGE

13.1. Data Collection

All raw data from the study will be non-identified format and documented on:

- CRF's (Appendix C)
- Sleep study reports (which details sleep and respiratory variables and therapy settings)
- Flash drives from the devices.

13.2. Study Documentation

Throughout the conduct of the study, all required data will be entered into the eCRF for each subject. The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports and will be asked to sign and date the appropriate eCRF page(s) to verify the data collected. Data entered into the eCRF must be consistent with source documents. Any change or correction to an eCRF will be captured in the EDC system audit trail.

The clinical site will provide study data to the Sponsor by recording data in the EDC System (21 CFR Part 11 compliant).

In cases of subject-reported data, the eCRF will be the source record.

The site PI or designee and the clinical monitor will review completed eCRFs for accuracy, discrepancies, and missing information. The information entered into the eCRF will be accessible to the appropriate ResMed Medical Affairs personnel.

13.3. Query Generation

Any data queries will be sent to site for reconciliation via the eCRF system and final close-out will be from the study monitor.

13.4. Data Storage

All electronic systems used by the site and Sponsor will have adequate security to protect patient privacy and data integrity. All paper documentation will be locked in a secured cupboard. All trial data and documentation will be retained for a minimum of 15 years before it is destroyed. Access to data maintained in the EDC System is strictly limited to authorized personnel.

13.5. Inspection of Records

Periodically the Sponsor or representative will review the Investigator study file and the study data to verify compliance with applicable regulations and the protocol, and to verify accuracy of the data.

13.6. Study Files and Record Retention

The investigator must maintain adequate and accurate records as specified in Essential Documents for the Conduct of a Clinical Trial (E6, Section 8 of the ICH Guideline for GCP) to enable the conduct of the study to be fully documented and the study data to subsequently be verified. These documents should be classified into two separate categories: (1) investigator's study file and (2) subject clinical source documents.

Essential documents must be retained until at least 2 years after notification by the Sponsor that the investigations have been discontinued OR 2 years after the last approval of a marketing application. The investigator must notify the Sponsor prior to destroying any clinical study records.

13.7. Regulatory Documentation

Documents that must be provided to the Sponsor prior to study initiation are:

- Signed, dated current (within 2 years) curriculum vitae of Investigator and Sub-Investigator(s)
- Financial disclosure for physicians and nurses
- Signed (original), dated Investigator Agreement
- Assurance that the IRB complies with requirements set forth in Title 21 Part 56 of the Code of Federal Regulations. The required documentation consists of name and address of the IRB, a current list of members including title, gender, occupation and any institutional affiliation of each member. A general assurance number from the Department of Health and Human Services may be substituted for this list.
- Written notification (copy) to the Investigator from the IRB approving the protocol
- IRB approved informed consent (copy) and any other adjunctive materials to be used in the study as required.

13.8. Distribution of Results

Data analyses will be completed by an independent statistician and the clinical study report will be completed by the Sponsor.

Any published and presented data will be non-identifiable.

14. ETHICAL CONSIDERATIONS

14.1. Institutional Review Board (IRB)

The investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the product labeling information and any updates. The investigator will provide the IRB with reports, updates, and other information (e.g., safety updates and protocol amendments) as required by regulations.

14.2. Protocol Deviations

An investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this Investigational Plan, applicable laws and FDA regulations, and any conditions of approval imposed by the reviewing IRB and FDA. According to FDA regulation 21 CFR § 812.150(a)(4), an investigator shall notify the sponsor and the reviewing IRB of any deviation from

the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for a change in or deviations from a plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, FDA and IRB approval may also be required in accordance with 21 CFR § 812.35(a).

14.3. Risk Analysis

14.3.1. Non-Significant Risk Determination

The Astral device with the iVAPS algorithm has been cleared (K152068) by the FDA to provide therapy to patients who require mechanical continuous or intermittent ventilation. The device is intended for home and hospital use. The purpose of this study is to evaluate the effect of a new algorithm that auto titrates EPAP to treat patients with UAO and respiratory failure.

Clinical personnel will observe the subject on the fitting and use of all Astral devices. They will monitor the subject's clinical parameters and will intervene, if required.

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

Subjects should be encouraged to discuss any issues they are having with therapy during the study. The investigator should assess for changes in the health or well-being of the subject in response to general, non-directed questioning (e.g., "How are you feeling while using the therapy?"). Side effects should be documented on the site's source documents. Any transient side effects, at a minimum, should be documented in the clinic record.

Furthermore, if during the evaluation the subject believes the mask or therapy is intolerable, the study staff will be instructed to discontinue use of the protocol device on the patient and ensure the patient returns to using their current mask and therapy. Potential expected adverse events are believed to be mild and similar to other commercially available mask systems.

Participants will be asked to use the study device only during the two study visits that are fully attended PSG nights in a sleep lab. The attending technicians have experience setting up the eligible patient population in this study. All subjects return to their current NIPPV therapy after completing the study visits.

As the trial involves a minimally tested algorithm for the treatment of respiratory failure, there is a small chance that treatment will be ineffective and will result in a maximum of one night with suboptimal therapy. This may result in a temporary increase in the participant's CO_2 levels causing dyspnea, tachypnea, flushing, and/or sweating. This is being mitigated in two ways:

1. Trained study staff are able to stop the study and resume normal treatment at any time if they feel the patient requires more effective treatment.
2. Participants' oxygen and carbon dioxide levels will be monitored overnight using oximetry and transcutaneous CO_2 monitoring equipment (as per routine practice), to ensure further medical treatment is not required for hypoxia or hypercapnia.

Potential expected adverse events are believed to be mild and similar to other commercially available NIPPV systems. The anticipated adverse effects during this trial are minimal and limited to those recognized with standard use of NIPPV treatment. These include:

- drying of the nose, mouth, or throat
- nosebleed
- bloating
- ear or sinus discomfort
- eye irritation
- skin rashes on the face from the mask

Eligible patients will already be established on NIPPV treatment (ST or VAPS mode). It is expected that any anticipated adverse events linked to AutoEPAP in iVAPS mode will be similar to ST or VAPS modes.

14.3.2. Subject Data Confidentiality

All information and data collected for this study protocol concerning subjects or their participation in this investigation will be considered confidential. Only authorized Sponsor personnel or a Sponsor representative will have access to these confidential files. All data will be handled in accordance with applicable local laws. Authorized FDA personnel or Regulatory Authorities have the right to inspect and copy all records pertinent to this investigation. All data used in the analysis and reporting of this investigation will be without identifiable reference to specific subject name.

15. QUALITY

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

15.1. Site Selection

The sites should have previously participated in clinical studies and must have adequate experience, time, staff, and facilities to perform all required duties. Sites must permit clinical trial related monitoring, audits, IRB review, and regulatory inspections, providing direct access to source data/documents, as appropriate

15.2. PSG Data

This study will utilize a sleep core lab to ensure consistency in scoring across all participants and all sites. The sleep core lab member responsible for scoring the participant PSGs will be blinded to the subject's randomization group as well as to the therapy settings of the participant. It is the responsibility of the site investigator to collect and send this data to the sleep core lab.

15.3. Training

The clinical monitor will conduct an initiation visit at each site to review relevant documentation such as the clinical protocol, study manual, Astral Instructions for Use, GCP, applicable regulations, and investigator's obligations with site study personnel. In addition, training on the Data Management System will be conducted. If new study staff members are employed at the site after the initiation meeting, experienced site personnel must train new employees as noted above and document the training (contact the clinical monitor for instructions on how to document the training).

15.4. Site Monitoring

The study will be initiated by the study monitor, or designee, during an on-site visit after all required documents have been processed. Qualified clinical monitors will perform on-site monitoring visits as frequently as is deemed necessary.

During the site visits, the monitor will compare the data entered into the eCRF with the source documents. In addition, the monitor will verify that standards of Good Clinical Practice (GCP) are being followed. Findings from the review of eCRFs, source documents and study conduct will be discussed with the investigator. The Sponsor expects that, during monitoring visits, the study coordinator and investigator will be available, the source documentation will be available and a suitable environment will be provided for review of study related documents

16. RESPONSIBILITIES

16.1. Clinical Investigator Responsibilities

With the approval of their institution's IRB/EC, qualified investigators will conduct the CAT-HF clinical investigation in accordance with the Declaration of Helsinki: "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects". Each site principal investigator and their co-investigators are responsible for the following:

- Completion of all required agreements
- Screening and evaluation of subjects
- Strict adherence to the Clinical Protocol, Study Manual of Procedures and all Federal Regulations
- Supervising investigational device use and return
- Obtaining informed consent prior to study related procedures and the collection of data during study and follow-up examinations in a timely manner
- Timely reporting of all SAEs and UADEs
- Providing death notes, when applicable

It is acceptable for the site principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the site principal investigator remains responsible for proper conduct of the clinical investigation and signing an investigator agreement. The investigation is non-transferable to other centers attended by the investigator unless prior approval is obtained from the appropriate IRB/EC and the Sponsor.

16.2. Sponsor Responsibilities

The Sponsor will provide each site with a study Manual of Procedures and study materials. The Sponsor will train study personnel on the clinical study protocol and procedures. Clinical monitors will conduct site visits in order to ensure the site procedures are being carried out in accordance with the clinical study protocol and GCP. Clinical monitors will ensure that the study is progressing as expected, study data are accurate and up to date, data recording is complete, and protocol deviations are recorded and reviewed with the PI. Throughout the study period, the clinical monitor will be available to address any issues that may arise. This availability includes access by phone, fax, and/or e-mail. An additional site visit or conference call may be scheduled at the end of the study period to formally close the clinical study.

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18. APPENDIX A – ASTRAL CLINICAL GUIDE

19. APPENDIX B – INFORMED CONSENT FORM

20. APPENDIX C - CRFs