Comparison of the ApneaLink Air Home Sleep Testing Device to Polysomnography

Investigational Plan

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Sponsor	ResMed Corp 9001 Spectrum Center Blvd. San Diego, CA 92123
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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 REVISION HISTORY

Version No. And Date	Section	Change	Rationale
Version 1.0 31Jan18	n/a	n/a	Original Release

Protocol Synopsis

Study Title	Comparison of the ApneaLink Air Home Sleep Testing Device to Polysomnography
PSG Central Scoring	University of Florida Health Sleep Disorders Center
Study Objectives	Primary: • Demonstrate the sensitivity in diagnosing Sleep Disordered Breathing (SDB) of the ResMed ApneaLink Air device (AL) compared to PSG is at least 0.825 when results are scored using the AASM 2012 Guidelines. Secondary: • Compare AL and PSG numbers of predominant obstructive and predominant central events using the effort band and flow sensor per AASM 2012 and 2007 Guidelines • Evaluate the AL capability to accurately calculate monitoring time per AASM 2012 and 2007 Guidelines • Evaluate the AL capability to accurately score hypopneas using the AASM 2012 arousal criterion (using monitoring time) vs PSG scoring of hypopneas • Estimate the positive likelihood ratio in diagnosing SDB of AL compared to PSG and evaluate it against a threshold of 5 per AASM 2012 and 2007 Guidelines
Study Design	This is a prospective, unblinded, open-label, single group study. All subjects will undergo concurrent ApneaLink Air testing and in-lab polysomnography.
Selection Criteria	*Inclusion Criteria* • Participant is 18 years of age or older • Participant is willing to provide informed consent • Participant is willing to participate in all study related procedures *Exclusion Criteria* • Unable to cease PAP therapy during PSG (if currently using) • Requires use of oxygen therapy during sleep • Diagnosis of untreated clinically relevant sleep disorder (other than SDB) • Pregnant • Participant is unsuitable to participate in the study in the opinion of the investigator
Number of Participants	75 participants total at 2 US sites
Study Duration	Each participant's participation will be 1 night. The entire study is expected to take approximately 6 months, depending on recruitment rates.
Study Endpoints	Primary endpoint: • Sensitivity in diagnosing SDB of the AL device using AASM 2012 guidelines. Secondary endpoints: • The number of predominant obstructive and predominant central events using the AL effort band and flow sensor vs. PSG per AASM 2012 and 2007 Guidelines • Monitoring times from AL vs total sleep time from PSG per AASM 2012 and 2007 Guidelines • Number of hypopneas using the AASM 2012 arousal criterion (using monitoring time) • Positive likelihood ratio in diagnosing SDB using AASM 2012 and 2007 guidelines

Contents

1 DEFINITIONS

ITEM	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
AHI	Apnea Hypopnea Index - Number of apnea and hypopnea events per hour when total sleep time is used
AL	ApneaLink Air – ResMed's FDA cleared HSAT type III device
BMI	Body Mass Index
CPAP	Continuous Positive Airway pressure
CSA	Central Sleep Apnea
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HSAT	Home Sleep Apnea Testing
IRB	Institutional Review Board
Monitoring Time	Estimation of total sleep time by an HSAT device, e.g., ApneaLink Air
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
REI	Respiratory Event Index – Number of apnea and hypopnea events per hour when calculated from an HSAT device
RERA	Respiratory Effort Related Arousal
SAE	Severe Adverse Event
SDB	Sleep Disordered Breathing
TST	Total Sleep Time - The amount of actual sleep time in a sleep episode; this time is equal to the total sleep episode less the awake time.

2 BACKGROUND AND RATIONALE

Sleep Disordered Breathing (SDB) is characterized by any abnormal breathing manifestation while asleep, including obstructive sleep apnea (OSA), central sleep apnea (CSA) and Cheyne-Stokes Respiration (CSR). Most recent data from the Wisconsin Sleep Cohort Study estimates sleep disordered breathing prevalence is 33.9% in males and 17.4% in females between the ages of 30 and 70[1]. The prevalence of symptomatic OSA in the adult population has been estimated to be 4% in males and 2% in females[2]. These patients demonstrate behavioral and neuropsychological consequences to varying degrees, including excessive daytime sleepiness, intellectual deterioration and depression[3]. More serious consequences include arterial systemic hypertension, arterial pulmonary hypertension and heart disease[4].

The current gold standard for SDB diagnosis is in-laboratory polysomnography (PSG). The high demand for this labor intensive and time-consuming test results in patients waiting 2-10 months[5] for an appointment. Over 80% of patients with OSA remain undiagnosed[6] leaving the majority of the affected population with co-morbid consequences. The need for a diagnostic test that is more widely available and less expensive is necessary, not only to lessen the burden on sleep labs but also to provide patients with a diagnosis and treatment as soon as possible.

A barrier of acceptance of Home Sleep Apnea Testing (HSAT) devices as a diagnostic test is their inability to accurately measure total sleep time (TST)[7]. Currently most HSAT devices use monitoring time to calculate the respiratory event index (REI) as a surrogate for apnea hypopnea index (AHI). The need for TST determination from a HSAT device has been suggested to further validate and expand the use of HSAT devices. A novel algorithm developed by ResMed, Ltd. allows the AL device to accurately calculate TST, however, this algorithm has not yet been validated.

The ApneaLink Air (AL) device is a type III HSAT device. The device is capable of recording up to four channels of data including: flow and snore via a nasal cannula attached to a pressure transducer, a respiratory effort belt, a pulse oximeter to measure pulse and oxygen saturation, and an actigraphy monitor to measure TST along with flow. The AL device has been validated against PSG for AHI[8,9] and Cheyne-Stoke respiration detection[10]. Further validation of the effort belt is necessary to determine the accuracy of the AL ability to differentiate between obstructive and central apneic events.

In 2012, the American Academy of Sleep Medicine (AASM) changed the criteria needed to score a hypopnea during a sleep study. Previous 2007 criteria had required a hypopnea to include a decrease in oronasal airflow by ≥30% from baseline for at least 10 seconds and ≥4% SpO_2 desaturation[11]. These criteria have been widely accepted by healthcare providers to form the basis of reimbursement for patient equipment. In 2012, a change was made to this these criteria which permitted hypopneas to be scored with an arousal only, or an oxygen desaturation of ≥3%. This change in rules significantly increases the percentage of patients who may now be diagnosed with OSA, potentially by up to 40%. The need for HSAT devices to detect sleep arousal is now evident with the 2012 AASM update. The AL contains software to detect respiratory effort related arousals (RERA) and score hypopneas using the new 2012 AASM arousal criterion, however, the algorithm has not been validated.

3 OBJECTIVES

The aim of this study is to evaluate the accuracy of the ResMed ApneaLink Air device (AL) as it compares to PSG. The AASM criteria for out-of-center testing devices are used to evaluate the accuracy of AL[12]. Specifically, the sensitivity in diagnosing SDB of the ResMed ApneaLink Air device will be estimated per AASM 2012 guidelines and compared to the threshold of 0.825. Participants will use an AL device while undergoing concurrent PSG, which will be considered the gold standard for the estimate of sensitivity.

3.1 Primary Objectives

The primary objective is to show that the sensitivity in diagnosing SDB of the ResMed ApneaLink Air device is at least 0.825 when results are scored using the AASM 2012 Guidelines.

3.2 Secondary Objectives

The secondary objectives of the study are:

- Compare AL and PSG numbers of obstructive and central events using the effort band and flow sensor per AASM 2012 and 2007 Guidelines
- Evaluate the AL capability to accurately calculate monitoring time per AASM 2012 and 2007 Guidelines
- Evaluate the AL capability to accurately score hypopneas using the AASM 2012 arousal criterion (using monitoring time) vs PSG
- Estimate the positive likelihood ratio in diagnosing SDB of AL compared to PSG and evaluate it per AASM 2012 and 2007 Guidelines against the threshold of 5

4 METHODS AND MATERIALS

4.1 Population/Participant Selection

Eligible participants will be adults who are referred to a sleep lab for investigation of SDB. Only participants who meet the inclusion and exclusion criteria and sign the informed consent form (ICF) will be considered for enrollment.

4.2 Study Design

This is a prospective, non-blinded, open label, single arm study to evaluate the AL ability to correctly score SDB compared to the gold standard diagnostic tool, in-lab PSG. All participants will meet the inclusion and exclusion criteria and will sign the informed consent form before any study related procedures are performed. All participants will wear the AL device and undergo concurrent PSG testing. The AL and PSG tests will only be considered evaluable if the evaluation time is ≥4 hours. Participants with <4 hours evaluable time will asked if they would like to repeat the test.

The AL device will be scored automatically using both AASM 2012 and 2007 guidelines. The AL automatic results will be compared with the PSG using all variables identified by the study objectives. These variables are defined in Section 4.7. Results collected in this study may be used for further algorithm and product development that are outside the scope of this protocol.

4.3 Measures Taken to Minimize Bias

A qualified sleep scientist who is approved to score sleep studies will score all PSGs. This individual will not have information about the participant's AL results.

4.4 Environment of Clinical Study

Recruitment, screening, and testing will occur in an accredited Sleep Lab.

4.5 Number of Study Sites and Participants

Up to 75 participants meeting the inclusion and exclusion criteria will take part in this study.

4.6 Inclusion/Exclusion Criteria

Inclusion Criteria

- Participant is 18 years of age or older
- Participant is willing to provide informed consent
- Participant is willing to participate in all study related procedures

Exclusion Criteria

- Unable to cease PAP therapy during PSG (if currently using)
- Requires use of oxygen therapy during sleep
- Diagnosis of uncontrolled clinically relevant sleep disorder (e.g., untreated insomnia or restless leg syndrome)
- Pregnant
- Participant is unsuitable to participate in the study in the opinion of the investigator

4.7 Clinical Definitions

AHI/REI

Following AASM guidelines, an apnea will be scored when there is a drop in the peak signal excursion by ≥90% of pre-event baseline and the duration of the ≥90% drop in sensor signal is ≥10 seconds.

Both 2007 and 2012 AASM definitions for hypopnea will be used:

AASM 2007 - A hypopnea will be scored when the peak signal excursions drop by ≥30% of pre-event baseline, the duration of the ≥30% drop in signal excursion is ≥10 seconds and there is a ≥4% oxygen desaturation from pre-event baseline.

AASM 2012 - A hypopnea will be scored when the peak signal excursions drop by ≥30% of pre-event baseline, the duration of the ≥30% drop in signal excursion is ≥10 seconds and there is a ≥3% oxygen desaturation from pre-event baseline or the event is associated with an arousal.

AHI

Apnea-hypopnea Index is derived from apneas plus hypopneas per hour of total sleep time from a PSG.

REI

Respiratory Event Index is derived from apneas plus hypopneas per hour of monitoring time from an HSAT.

OAI
Following AASM guidelines, an apnea will be scored as obstructive if it meets apnea criteria and is associated with continued or increased inspiratory effort throughout the entire period of absent airflow. The use of both the monitoring time and total sleep time will be used for OAI calculation and comparison.

CAI
Following AASM guidelines, an apnea will be scored as central if it meets apnea criteria and is associated with absent inspiratory effort throughout the entire period of absent airflow. The use of both the monitoring time and total sleep time will be used for CAI calculation and comparison.

Mixed apneas
Following AASM guidelines, an apnea will be scored as mixed if it meets apnea criteria and is associated with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.

TST
Total Sleep Time as defined as sum of all sleep epochs from PSG between lights off and lights on.

Monitoring Time
Estimation of total sleep time by an HSAT device.

RERA
Following AASM guidelines, an event will be scored as a respiratory event related arousal (RERA) if during the diagnostic study there is a sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort or by flattening of the inspiratory portion of the nasal pressure leading to an arousal from sleep when the event does not qualify as an apnea or hypopnea.

4.8 Sample Size Justification

The sample size for this clinical study will be up to 75 eligible participants undergoing PSG.

Recruitment goals are as follows:

- At least 30 men and at least 30 women
- At least 5 participants in each of the following SDB categories (per PSG):
  - No SDB (AHI <5)
  - Mild SDB (AHI 5-14)
  - Moderate SDB (AHI 15-29)
  - Severe SDB (AHI ≥ 30)
- At least 5 participants with CSA
- At least 5 participants in each of the following BMI categories (applies to both men and women):
  - Normal BMI: < 25.0
  - Overweight BMI: 25.0 – 29.9
  - Obese: ≥ 30
- At least 5 participants in each of the following race categories:
  - White
  - Black
  - Asian

The primary objective of this study is to demonstrate the sensitivity in diagnosing SDB per the AASM 2012 guidelines. Sensitivity will be assessed according to the AASM criteria for out-of-center testing devices. The hypotheses tested are:

$$H_0: \pi \leq 0.825 \text{ versus } H_A: \pi > 0.825$$

where π is the sensitivity of AL in diagnosing SDB (using a cut-off of 5 events per hour as the threshold for SDB and AHI from PSG and REI from HSAT). The hypothesis will be tested with an exact binomial test using a one-sided significance level of 0.025.

The required sample size to achieve 80% power was estimated using PASS 14, Tests for One Proportion Procedure, assuming a true sensitivity of 0.95 (13 out of 13 true positives were correctly classified in a previous study). To achieve an 80% probability of rejecting the null hypothesis, a minimum of 56 SDB participants are required. Seventy-five participants will be enrolled in order to meet recruitment goals.

4.9 Endpoints

Primary endpoint:

- Sensitivity in diagnosing SDB of the AL device using AASM 2012 guidelines.

Secondary endpoints:

- The number of predominant obstructive and predominant central events using the AL effort band and flow sensor vs. PSG per AASM 2012 and 2007 Guidelines
- Monitoring times from AL vs total sleep time from PSG per AASM 2012 and 2007 Guidelines
- Number of hypopneas using the AASM 2012 arousal criterion (using monitoring time)
- Positive likelihood ratio in diagnosing SDB using AASM 2012 and 2007 guidelines

4.10 Investigational Devices

ApneaLink Air

The ApneaLink Air is a market-released device that has been FDA-cleared (K143272) for use by Health Care Professionals for screening and diagnosis of SDB for adult patients. The device records the following data: patient respiratory nasal airflow, snoring, blood oxygen saturation, pulse, respiratory effort and actigraphy. The AL uses these recordings to produce a report that may aid in the diagnosis of sleep disordered breathing or for further clinical investigation.

The AL recorder is a 4-channel battery-powered HSAT device. Patients may perform the recording independently at home. The AL recorder and the respiratory effort sensor must be fastened with the re-usable belt on the patient's chest. All relevant respiratory information during sleep will be collected via nasal cannula, pulse oximetry adapter, actigraphy sensor and respiratory effort sensor. The disposable plastic nasal cannula is connected to the AL recorder and fixed at the patient's nose. The oximetry sensor is connected to the patient's finger. The respiratory effort sensor is connected to the AL recorder and held in place by the belt. The physician can generate a report containing automated sleep data from the device.

See ApneaLink Air Clinician's Manual for more details.

Labeling

Devices will be labeled to contain 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 (Appendix)

4.11 Data Collection Method and Storage

4.11.1 Data Collection

All data from the study will be documented via:

- CRFs (Appendix)
- Sleep study reports (AL and PSG reports and EDF files)

Participant identification will be coded to maintain confidentiality

ApneaLink Air

The ApneaLink Air will be set up by sleep lab staff. Participants and site staff will have access to the AL clinical guide and AL user guide to help with set up.

After testing is complete, reports will be generated with automatic scoring using both AASM 2007 and AASM 2012 Scoring rules. The raw data will be exported and saved in mmrx format. These three reports will be uploaded to the electronic data capture (EDC) system.

PSG

The PSG will be conducted on the participant following the normal procedures of the Sleep Lab. After testing is complete, the unscored EDF and associated technotes file for the PSG will uploaded to the EDC system. PSGs will be centrally scored by the University of Florida Sleep Lab.

The recording montage should include EEG channels F4-M1, C4-M1, O2-M1, E1-M2, E2-M2, chin EMG (3 electrodes), ECG, nasal pressure, oronasal thermal airflow, snore, thoracic and abdominal effort (uncalibrated RIP), pulse rate, and pulse oximetry. It is preferred to also include channels F3-M2, C3-M2, and O1-M2 as backup electrodes. Body position must be included in the tech notes, or body position sensor included, with video to confirm.

4.11.2 Study Documentation

Throughout the conduct of the study, all required data will be entered into the eCRF for each participant. 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 participant-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.

4.11.3 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.

4.11.4 Data Storage

All electronic systems used by the site and Sponsor will have adequate security to protect participant 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.

4.11.5 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.

4.11.6 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) participant 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.

4.11.7 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.

4.11.8 Distribution of Results

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

4.12 Clinical Study Procedures

Visit 1 – Screening and PSG/HSAT

1. Eligible participants will be identified at the research site via referral, electronic medical record search, database searches or other methods determined by the research site.
2. Participants will be provided verbal and written information on the study, have the opportunity to ask any questions and will provide written informed consent if they elect to participate.
3. The inclusion/exclusion criteria checklist is to be completed by the researcher to assess whether the participant is eligible to participate in the study.
4. If eligible, the participant will be enrolled in the trial through the EDC, which will assign a coded identifier for the participant.
5. Demographics form will be completed in the EDC
6. Participants will be fitted with the AL and PSG equipment
7. Participants will undergo an overnight PSG. Full PSG set-up, data acquisition, monitoring and reporting will be performed using both the AASM 2007 and 2012 criteria. At least 4 hours of recording will be required. Participants with <4 hours of recording time will be asked to repeat the exam.
8. Upload de-identified (subject ID only) PSG files to the EDC system:
    a. Technotes file
    b. Scored PSG (optional)
    c. Unscored PSG
9. Upload de-identified AL files to the EDC system:
    a. Raw AL data as an mmrx file
    b. Auto-scored report using AASM 2007 rules
    c. Auto-scored report using AASM 2012 rules
10. Participant will be provided with a gift card for their participation.

4.13 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. This will include information regarding testing for sleep disordered breathing. The possible side effects will be explained to the patient. 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 medical records should indicate study participation.

4.13.1 Participant Remuneration

Participants will be compensated $150 for their time and reimbursed at the standard rate for travel required to attend study-required visits and procedures.

Any published and presented data will not include individually identifiable participant information.

5 STATISTICAL ANALYSIS METHODS

Analysis Populations:

All subjects who meet the inclusion and exclusion criteria and who complete at least 4 evaluable hours will be included in the Intention-to-Treat population (ITT). All primary and secondary analyses will be generated for the ITT population.

Primary Analysis:

The diagnostic sensitivity of AL will be estimated as the number of participants with REI ≥ 5 events per hour according to AL per AASM 2012 Guidelines divided by the number of participants with AHI ≥ 5 events per hour according to PSG. The diagnostic sensitivity of AL will be compared to the threshold of 0.825 (AASM criteria for out-of-center testing devices) with an exact binomial test, using a significance level of 0.025. Further a one-sided 97.5% confidence interval for the diagnostic sensitivity will be calculated using the Wilson score method.

Secondary Analyses:

To compare the numbers of predominant obstructive and predominant central events measured by AL and PSG, each patient will be classified as having (1) fewer than 5 events per hour, (2) 5 to 10 events per hour, (3) 10 to 30 events per hour or (4) more than 30 events per hour. The categories obtained by AL and PSG will be compared with the weighted kappa statistic. Events will be assessed per both the AASM 2012 and 2007 guidelines.

To compare the AL monitoring times to the PSG total sleep times, Bland-Altman plots will be constructed and the 95% limits of agreement will be calculated. Times will be assessed per both the AASM 2012 and 2007 guidelines.

To compare the number of hypopneas measured by AL and PSG, the number of hypopneas per hour will be categorized as follows: (1) fewer than 5 events per hour, (2) 5 to 10 events per hour, (3) 10 to 30 events per hour or (4) more than 30 events per hour. The categories obtained by AL and PSG will be compared with the weighted kappa statistic. Events will be assessed per both the AASM 2012 and 2007 guidelines.

The positive likelihood ratio (the estimated sensitivity divided by 1 minus the estimated specificity) will also be calculated along with the associated one-sided 97.5% confidence interval. The positive likelihood ratio will be compared with the threshold of 5 (AASM criteria for out-of-center testing devices[12]) using a Wald test. The positive likelihood ratio will be calculated per the AASM 2012 and 2007 guidelines.

AEs

A listing of all adverse events reported for each participant enrolled in the study will be presented, including event description, time of occurrence, severity, outcome, action taken and relationship to the study.

6 MONITORING

The study and devices to be used have been evaluated by the sponsor under 21 CFR Part 812. The sponsor has determined this to be a non-significant risk study, which is further discussed in Section 8. Accordingly, initial training of the clinical study team will be provided by ResMed personnel. This training will involve protocol review, proper use of the ResMed devices, and review of clinical study regulations. Review of clinical data will be performed per federal regulations for non-significant risk (abbreviated IDE) studies.

7 ADVERSE EVENT MANAGEMENT

All adverse effects/events (including SAEs) will be documented and reported in the trial report.

Serious Adverse Events (SAE)

A **serious adverse event** is defined as 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

In the event of a serious adverse effect (event or reaction) the following notifications will be made:

- The site will inform ResMed within 24 hours of becoming aware of the event
- ResMed will alert the FDA according to regulations

The decision will be made by the Chief Medical Officer, and/or the Principal Investigator as to whether the participant shall remain in the study and whether the study should continue.

Non-serious adverse events (AE)

Non-serious adverse events are defined as any untoward event that do not meet the criteria for serious adverse events.

If a non-serious adverse event occurs during the trial, it will be documented, stored with that participant's source documents and documented in the eCRF.

Unanticipated Adverse Device Effects (UADE)

Unanticipated adverse device effects (UADEs) are defined as any serious adverse effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other

unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Under the requirements of the FDA's IDE Regulations, an investigator must submit to the sponsor (or its designee) and to the reviewing Institutional Review Board any unanticipated adverse device effect occurring during the study as soon as possible, but in no event later than ten (10) working days after the investigator first learns of the effect.

Serious adverse device effect (SADE)

In the event of a serious adverse device effect, as defined by ISO14155:2011, the following notifications will be made:

- The site will notify ResMed within 24 hours of becoming aware of the event
- ResMed will alert the FDA according to local regulations

The decision will be made by the Chief Medical Officer, and/or the Principal Investigator as to whether the participant shall remain in the study and whether the study should continue.

Expected Adverse Device Effects

8 NON-SIGNIFICANT RISK DETERMINATION

The sponsor has determined that both the study and device are non-significant risk, based on the risk profile of this non-invasive device, and a review of the Code of Federal Regulations for significant risk devices. The following rationale is cited as determination of non-significant risk:

The device does not meet the four elements of the definition for a significant risk device per 21 CFR 812.3, (m) in that the device does not pose significant risk to the participant and is not an implant, does not support or sustain human life, and is not of substantial importance for diagnosis, curing, mitigating, preventing impairment to human health or treatment of sleep disordered breathing.

This study involves FDA cleared SDB screening and diagnostic devices. The participant will be encouraged to contact a member of the investigator's team for any questions or concerns.

9 RISK MITIGATION/ASSESSMENT

This study is considered to be of low risk to the participant due to the fact that the participant will not be receiving any therapy. The sites will have access to the ResMed Medical Affairs department if any issues arise concerning the safety or welfare of the study participants. The site investigative staff will determine if any AEs have occurred at each evaluation and if the event is device or disease related; these events will be directly reported to the study manager at ResMed.

Technical Observations and Protocol Deviations will also be assessed as they are reported by the sites to determine if an event affects the safety and welfare of the participant(s) or data integrity.

Every effort will be made to maintain confidentiality of all participants' records. For this study, ResMed may share health data with authorized users. Authorized users may include: internal employees at

ResMed, representatives of the IRB, the Food and Drug Administration (FDA) and other US governmental agencies.

10 STUDY CLOSE OUT

The sponsor requires the investigational site collects and returns all devices dispensed to the research site. All data should be entered into the EDC system and all queries answered at study closure. A final study report will be sent to Investigators and IRB after study completion or termination.

11 CLINICAL SUPPLIES AND ACCOUNTABILITY

ResMed will provide the ApneaLink Air and ancillary supplies for the duration of the trial. Investigational sites will meet all requirements for controlled access to the devices. An accurate and current accounting of the receipt and dispensing of the device will be maintained on an ongoing basis by the investigator or investigator's designee in a device accountability log. All supplies given to the site must be returned to ResMed upon completion of the study.

12 SPONSOR RESPONSIBILITIES

The Sponsor will train study personnel on the clinical study protocol, procedures and study devices. Throughout the study period, the ResMed Medical Affairs representative will be available to address any issues that may arise. This availability includes access by phone, and/or e-mail. Additional site visits or conference calls may be scheduled to help the sites with the study procedures or materials. A close out visit may be scheduled at the end of the study to formally close the clinical study.

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