STUDY PROTOCOL

Adherence to ASV Therapy in Heart Failure with Preserved Ejection Fraction Feasibility Study (CAT-PEF Feasibility)

Study Number: MA-16-12-01

NCT03195660

Version: 1.0
Date: 28Mar17

Sponsor:

ResMed Corp
9001 Spectrum Center Blvd
San Diego, CA 92123
(800) 424-0737

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 28Mar17	n/a	n/a	Original Release

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1. Responsibilities and addresses

Principal Investigator: Christopher M. O'Connor, M.D.
Inova Heart & Vascular Institute

Study Coordination: Amy Blase, CCRA
ResMed Corp
Medical Affairs Department

Statistician: Leslee Willes
Willes Consulting

Steering Committee: Chair:
Christopher M. O'Connor, MD, FACC, FESC, FHFSA
Inova Heart & Vascular Institute

Voting Members:
JoAnn Lindenfeld, MD
Vanderbilt University

David Whellan, MD
Thomas Jefferson University

Olaf Oldenburg, MD
Heart and Diabetes Center North Rhine-Westphalia

Mona Fiuzat, PharmD
Duke Clinical Research Institute

Naresh Punjabi, MD, PhD
Johns Hopkins Medical Institute

Dalane Kitzman, MD
Wake Forest Baptist Health

Sponsor's Representative (Non-Voting):
Adam Benjafield, PhD
ResMed Corp

Leader, Site PIs: Lauren Cooper, MD
Inova Heart & Vascular Institute

Adherence Core Lab: Johns Hopkins University (Naresh Punjabi, MD)

Thomas Jefferson University (David Whellan, MD)

2. ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
AFib	Atrial Fibrillation
AHI	Apnea-Hypopnea Index
ASV	Adaptive Servoventilation / Adaptive Servoventilator
BNP	B-type natriuretic peptide
CPAP	Continuous Positive Airway Pressure
CSA	Central Sleep Apnea
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e/hr	Events per hour
EF	Ejection Fraction
EPAP	Expiratory Positive Airway Pressure
FDA	Food and Drug Administration
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction; LVEF≥50%
HFrEF	Heart failure with reduced ejection fraction
IDE	Investigational Device Exemption
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left Ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NT pro-BNP	N-terminal prohormone of b-type natriuretic protein
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
SAE	Serious Adverse Event
SC	Steering Committee
SDB	Sleep-Disordered Breathing, also referred to as sleep apnea
SOP	Standard Operation Procedures
TIA	Transient ischemic attack

4. PROTOCOL SUMMARY

Objectives	Demonstrate feasibility of study conduct and that acceptable adherence to ASV therapy can be achieved in recently hospitalized HFpEF patients with moderate to severe SDB.
Study Design	This study is a prospective, single-arm, unblinded, multi-center study. All subjects meeting criteria will receive adaptive servo-ventilation (ASV).
Number of Subjects	The study will aim to enroll 160 evaluable subjects. For the purposes of this study, an evaluable subject is one with ASV usage of at least 4hrs per night for 70% of the study nights, excluding nights hospitalized at 30 days after study entry. In order to achieve 160 evaluable subjects it is estimated that up to 300 subjects will be initially enrolled in the study.
Selection criteria	**Inclusion criteria for the study are:** 1. Patients 18 years or older 2. Patients with heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%) 3. Hospital admission or equivalent (such as ER visit alone or clinic visit alone) and acute decompensated HF as determined by: a. Dyspnea at rest or with minimal exertion AND b. Treatment with at least one dose of IV diuretic or ultrafiltration AND c. At least two of the following signs and symptoms: i. Orthopnea ii. Pulmonary rales that do not clear with cough iii. Congestion on chest X-ray iv. Local BNP or NT pro-BNP level: A. No current atrial fibrillation (AFib): BNP≥100 pg/mL or NT pro-BNP≥300 pg/mL OR B. Current AFib: BNP≥150 pg/mL or NT pro-BNP≥450 pg/mL 4. Sleep disordered breathing (SDB) documented by screening polygraphy with an AHI≥15 events/hour (e/hr) 5. Patient is able to fully understand study information and sign informed consent **Exclusion criteria for the study are:** 1. Right-sided heart failure without left-sided failure 2. Current chronic use (within 4 weeks of study entry) of any PAP therapy (eg, CPAP, APAP, or bi-level) or contraindicated for PAP therapy

	3. Sustained systolic blood pressure <80 mmHg at baseline 4. Complex congenital heart disease 5. Constrictive pericarditis 6. Chronic hypoxemia as evidenced by sustained oxygen saturation ≤ 85% at rest during the day or at start of nocturnal oximetry recording or regular use of oxygen therapy (day or night) 7. Transient ischemic attack (TIA) or Stroke within 3 months prior to study entry 8. Definite clinically evident acute myocardial infarction within 3 months of study entry 9. Known amyloidosis, hypertrophic obstructive cardiomyopathy, or arteriovenous fistulas 10. Moderate or greater valvular heart disease as the primary reason for heart failure 11. Pregnant, or planning to become pregnant during the study period 12. In the opinion of the investigator, the index acute decompensated HF event was due primarily to uncontrolled AFib with fast ventricular response rate 13. Inability to comply with planned study procedures
Primary Endpoints	ASV Adherence rate (average hours used per day) at 3 months
Secondary Endpoints	• Feasibility of study conduct as measured by recruitment rate (subjects enrolled per month) by site, reasons for screen failures, and where in the hospital system patients are recruited (eg, HF clinic, general cardiology, etc) • Change in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) • Number of hospitalizations for any reason following study entry • Death for any reason during study participation
Scheduled follow up	For evaluation of the primary and secondary endpoints, subjects will be followed for a period of 3 months (12 weeks). • Visit 1 will occur at baseline for device set-up and KCCQ-12 • Visit 2 will occur at 12 weeks for disposition of device, KCCQ-12, and determination of hospitalizations and death

5. INTRODUCTION

5.1. Background Information

Heart failure (HF) continues to present a social and economic burden, especially with regard to HF hospitalizations. The current HF treatment guidelines[1,2] include a number of treatments focused on HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] ≤45%), but no evidence-based therapies for HF with preserved ejection fraction (HFpEF; LVEF ≥50%).

Sleep-disordered breathing (SDB) is very common in HF populations that have reduced as well as preserved ejection fraction, with reported prevalence rates of 50-75%[3,4,5,]. There are very few studies that have evaluated the impact of treating SDB in HFpEF, and the studies that do exist generally include a small number of patients[6].

The Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure Study (SERVE-HF) showed that ASV in patients with stable HFrEF and SDB with predominant central sleep apnea increased cardiovascular mortality[7]. The results of secondary multistate modeling analysis showed that the risk of direct sudden cardiovascular death and hospitalization for worsening HF were associated with poor left ventricular function that attenuated as the LVEF approached normal[8].

Cardiovascular Improvements with Minute Ventilation-targeted ASV Therapy in Heart Failure Study (CAT-HF) was a randomized controlled clinical trial in the United States and Germany. It was designed to evaluate the effect of ASV in hospitalized heart failure (HFrEF and HFpEF) patients on a global rank endpoint of survival free from CV hospitalization and improvement in functional capacity measured by 6-minute walk distance. Analysis of the 126 subjects that were randomized showed a neutral result for the primary endpoint; however, in the pre-specified analysis of the primary endpoint by LVEF strata, there was a favorable statistically significant difference in the HFpEF subgroup (p=0.036) (O'Connor *in press*). There was no safety signal for increased mortality risk in patients randomized to ASV.

CAT-HF demonstrated that SDB can be effectively controlled by ASV in a HF population; however, adherence to ASV was very low, limiting the ability to determine the effect of ASV on HF outcomes. Despite this, analysis showed improved outcomes with ASV therapy in the HFpEF subgroup (O'Connor *in press*). Newer technologies include the web-based AirView system, which allows the patient's care team to monitor adherence, and the myAir application, which provides patients with immediate feedback on their actual therapy use. These have been shown to improve adherence by addressing issues with therapy as they arise, thus increasing patient engagement and adherence to therapy[9].

Although the CAT-HF study showed a positive signal in the HFpEF subgroup, these patients represented a small percentage of the randomized subjects in the study. The current study aims to show that by applying newer technologies to support adherence, as well as focusing on the lessons learned in CAT-HF to identify and recruit HFpEF patients, acceptable adherence to ASV therapy can be achieved in HFpEF patients. Demonstrating feasibility of study conduct in this way will help support a future phase III randomized controlled trial with morbidity and mortality endpoints.

5.2. Intended Use

The AirCurve 10 ASV device is indicated for the treatment of patients weighing more than 66 lb (30 kg) with obstructive sleep apnea (OSA), central and/or mixed apneas, or periodic breathing. It is intended for home and hospital use. The humidifier is intended for single patient use in the home environment and re-use in a hospital/institutional environment.

Contraindications

ASV therapy is contraindicated in patients with chronic, symptomatic heart failure (NYHA II-IV) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea.

Positive airway pressure therapy may be contraindicated in some patients with the following pre-existing conditions:

- severe bullous lung disease
- pneumothorax or pneumomediastinum
- pathologically low blood pressure, particularly if associated with intravascular volume depletion
- dehydration
- cerebrospinal fluid leak, recent cranial surgery, or trauma.

6. STUDY OBJECTIVES

The objective of the study is to demonstrate feasibility of study conduct, and to evaluate adherence to ASV therapy at 3 months in HFpEF patients diagnosed with moderate to severe sleep apnea. Adherence will be monitored using cloud-based technology in which data from each ASV machine is automatically transmitted to a secure, HIPAA-compliant system (AirView). The system is accessible through the internet with a secure interface. This technology can be customized to “flag” patients who do not meet criteria for minimal use. Data will be reviewed by each site’s respiratory/sleep team, and in patients where the use of ASV is less than 3 hours per night, the respiratory/sleep team will contact the patient to troubleshoot the reasons for low usage, and provide appropriate solutions. In addition, a central Adherence Core Lab will oversee the ASV usage at all sites, providing guidance and support where necessary.

7. STUDY DESIGN

The CAT-PEF Feasibility Study is a prospective, single-arm, unblinded, multi-center, study of HFpEF subjects diagnosed with SDB using ASV therapy.

This study will be conducted in up to 10 centers in the US and Germany.

7.1. Enrollment

Subjects will be recruited from in-patient clinical services or in the outpatient setting if within 14 days of discharge. If a subject is willing to participate in the CAT-PEF Feasibility Study, a written

informed consent for the study must be obtained prior to any study related procedure. Before dispensing a device, all eligibility criteria must be confirmed.

7.2. Selection of subjects

7.2.1. 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)/Ethics Committee (EC).

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/EC prior to use.

A signed, IRB/EC-approved consent form must be obtained from the patient prior to the performance of any protocol-related testing or procedures unless obtained as part of standard care. The consent process must be performed by a designated clinical study team member authorized by the IRB/EC 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.

7.2.2. Number of Subjects

Up to 300 subjects will be initially enrolled in this study. For endpoint evaluation, 160 evaluable subjects are required. For the purposes of this study, an evaluable subject is one with ASV usage of at least 4hrs per night for 70% of the study nights, excluding nights hospitalized after 30 days (1 month) of ASV usage.

7.2.3. Subject Inclusion Criteria

1. Patients 18 years or older
2. Patients with heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%)
3. Hospital admission or equivalent (such as ER visit alone or clinic visit alone) and acute decompensated HF as determined by:
    a. Dyspnea at rest or with minimal exertion
    AND
    b. Treatment with at least one dose of IV diuretic or ultrafiltration
    AND
    c. At least two of the following signs and symptoms:
        i. Orthopnea
        ii. Pulmonary rales that do not clear with cough
        iii. Congestion on chest X-ray

iv. Local BNP or NT pro-BNP level:
   A. No current atrial fibrillation (AFib): BNP≥100 pg/mL or NT pro-BNP≥300 pg/mL
   OR
   B. Current AFib: BNP≥150 pg/mL or NT pro-BNP≥450 pg/mL

4. Sleep disordered breathing (SDB) documented by screening polygraphy with an AHI≥15 events/hour (e/hr)
5. Patient is able to fully understand study information and sign informed consent

7.2.4. Subject Exclusion Criteria

1. Right-sided heart failure without left-sided failure
2. Current chronic use (within 4 weeks of study entry) of any PAP therapy (eg, CPAP, APAP, or bi-level) or contraindicated for PAP therapy
3. Sustained systolic blood pressure <80 mmHg at baseline
4. Complex congenital heart disease
5. Constrictive pericarditis
6. Chronic hypoxemia as evidenced by sustained oxygen saturation ≤ 85% at rest during the day or at start of nocturnal oximetry recording or regular use of oxygen therapy (day or night)
7. Transient ischemic attack (TIA) or Stroke within 3 months prior to study entry
8. Definite clinically evident acute myocardial infarction within 3 months of study entry
9. Known amyloidosis, hypertrophic obstructive cardiomyopathy, or arteriovenous fistulas
10. Moderate or greater valvular heart disease as the primary reason for heart failure
11. Pregnant, or planning to become pregnant during the study period
12. In the opinion of the investigator, the index acute decompensated HF event was due primarily to uncontrolled AFib with fast ventricular response rate
13. Inability to comply with planned study procedures

8. STUDY DEVICES

8.1. AirCurve™ 10 ASV

The AirCurve 10 ASV (“AirCurve”) is a market-released device that has been FDA-cleared in the US (K160822) and CE-marked in Germany to provide non-invasive ventilatory support to treat patients weighing more than 66 lbs (30 kg) with OSA, central and/or mixed apnea or periodic breathing. The device is intended for home and hospital use.

AirCurve is a non-invasive device, providing minute ventilation-targeted ASV algorithms to deliver ventilatory support for OSA, CSA and/or mixed apnea, and periodic breathing by automatically adjusting the pressure support (PS) in a defined pressure range to maintain a target minute ventilation. The AirCurve 10 ASV device offers three different therapy modes, CPAP mode, ASV

mode and ASVAuto mode. The CAT-PEF Feasibility Study will only use the ASVAuto mode. Ancillary equipment includes the humidifier, air delivery hose, mask, and headgear.

In ASVAuto mode, the device automatically adjusts the expiratory pressure in order to provide only the amount of pressure (EPAP) required to maintain upper airway patency. The device analyzes the state of the patient's upper airway on a breath-by-breath basis and delivers expiratory pressure within the allowed range (Min EPAP and Max EPAP) according to the degree of obstruction. EPAP is automatically adjusted depending on three parameters: inspiratory flow limitation, snore, and obstructive apnea.

Pressure Support (PS) is defined as the difference between the peak pressure at the end of inspiration, and the minimum pressure at the end of expiration (ie, the amplitude of the pressure waveform delivered). The AirCurve pressure support (Inspiration:Expiration and Expiration:Inspiration) trigger points are set automatically based on measurement of the patient respiratory flow. The AirCurve algorithm will automatically adjust pressure delivery to keep the patient's respiratory flow even.

See AirCurve Clinician's Manual for details.

8.2. ApneaLink Air

The ApneaLink Air ("ApneaLink") is a market-released polygraphy ("home sleep testing [HST]") device that has been FDA-cleared (K143272) for use by Health Care Professionals, where it may aid in the diagnosis of sleep disordered breathing for adult patients. ApneaLink records the following data: patient respiratory nasal airflow, snoring, blood oxygen saturation, pulse, and respiratory effort during sleep. ApneaLink uses these recordings to produce a report that may aid in the diagnosis of sleep disordered breathing or for further clinical investigation. The ApneaLink may be used with an optional dual-lumen cannula in cases where the patient cannot be taken off low flow oxygen therapy for the duration of the test.

The ApneaLink Air recorder is a 4-channel battery-powered respiratory pressure sensor and oximetry system. The ApneaLink Air 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 and respiratory effort sensor. The disposable plastic nasal cannula is connected to the ApneaLink Air 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 ApneaLink recorder and held in place by the belt. The physician can generate a report with the recorded and analyzed data through the web-based AirView. The default settings for the ApneaLink Air includes a flow reduction of 80% for at least 10 seconds to automatically score an apnea, a flow reduction of 30% combined with a desaturation of 3% to automatically score a hypopnea, and a respiratory effort sensor to differentiate between central, obstructive and mixed apneas.

See ApneaLink Air Clinician's Manual for details.

8.3. Device Accountability

An accurate and current accounting of the dispensing of ResMed devices (AirCurve, ApneaLink) will be maintained on an on-going basis by a qualified member of the study site using the Sponsor-provided "Device Disposition 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.

8.4. 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

8.5. Packaging

The AirCurve 10 ASV and ApneaLink Air study devices are FDA 510(k) cleared and will be used with the standard packaging. The devices are CE marked according to the European Declaration of Conformity.

8.6. Instruction for Use

The devices will be used as specified in the relevant Instructions for Use.

8.7. Required Training

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

9. THERAPY

9.1. Treatment with Adaptive Servo-ventilation (AirCurve)

The AirCurve device will be used at home; however the therapy can be initiated in the hospital or as an outpatient within 14 days of hospital discharge. Although the AirCurve has three therapy modes, CPAP, ASV, and ASVAuto, only the ASVAuto mode will be used for this study. Subjects are advised to use the AirCurve device during any significant sleeping period, including naps. Ideally, AHI should be at or below 5 e/hr. However, if the AHI cannot be maintained below 10 e/hr, the subject's therapy should be adjusted (mask and/or pressure settings).

9.2. Set up of AirCurve in ASVAuto Mode

For initiation of therapy, AirCurve will be set to a minimum expiratory PAP (EPAP) of 4 cmH_20, a maximum EPAP of 15 cmH_2O, a minimum pressure support of 3 cmH_2O, and a maximum pressure support of 15 cmH_2O. All subjects will be provided humidifiers and ClimateLine tubing to address

any instance of upper airway dryness or other forms of discomfort with the airflow of the device during the initiation or during therapy with the device. For the initiation of therapy, a ResMed full face mask is recommended, but if this mask is unsuitable for the subject another type of mask such as a nasal mask or nasal pillows mask will be tried. Adherence to therapy will be evaluated centrally through AirView. The recommended target for AHI within 7 days of therapy initiation is lower than 10 e/hr, and major mask leaks should be avoided. If these targets are not able to be achieved, the subject will be contacted to implement corrective actions.

The subject's AirCurve device will be added to the Trial AirView account for ongoing monitoring during the study.

9.3. AirView

AirView is the HIPAA compliant web based system that is routinely used for telemonitoring. The AirCurve device contains built in wireless connectivity which transmits data via a mobile network to a secure data center. Data is transmitted at the completion of each period of use (e.g. after each night of use). Data can then be accessed, via a login code, by the respiratory/sleep team to assess items such as device efficacy (AHI), mask leak, and usage hours.

The Adherence Core Lab will review data at least once per week for each site. Enrolling sites consistently not achieving an average of 3 hours of use per night with their subjects will be identified and contacted. The Adherence Core Lab will provide an analysis of adherence to better target potential interventions. For example, if the participant did not initiate use, the recommended intervention may be focused on remembering to put the mask on at night and promoting adherence. If the data shows that ASV was initiated but was discontinued within 1 hour, the intervention by the site may be focused on mask comfort. The study team will intervene if the subject is having issues with therapy or is struggling with compliance. See Appendix I.

AirView is compliant with HIPAA, EU 95/46/EC, and national privacy laws. Data are encrypted and all database accesses are logged and can be re-traced.

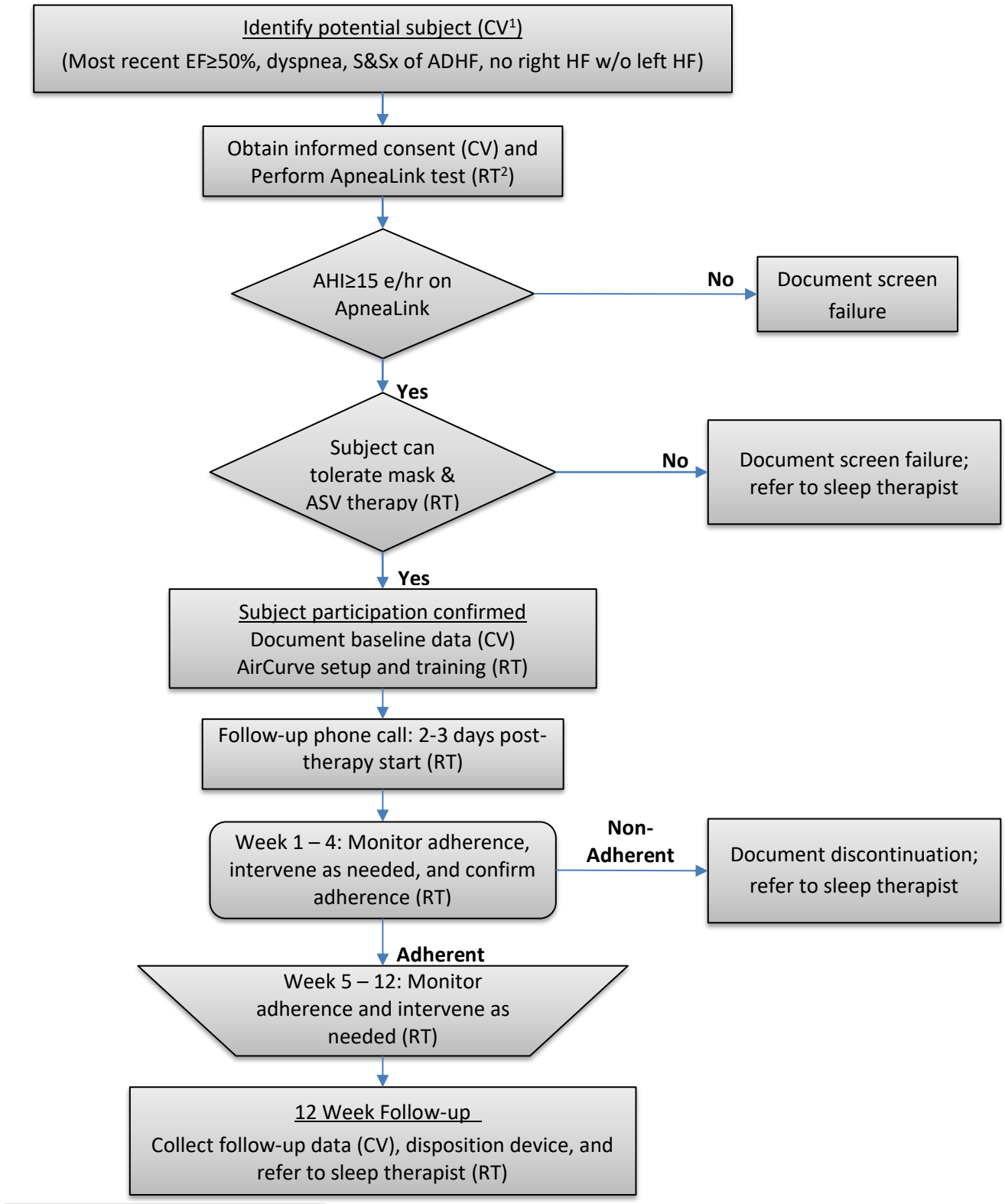
In addition to AirView, a patient-focused version of the data is available through the myAir application. The myAir application can be accessed via the subject's smartphone and allows the subject to monitor their own treatment data. The myAir application also provides tips to the subject on things like coping with therapy, managing mask leaks, and adjusting comfort settings. These tips are personalized based on each individual's data. Although the myAir App is not mandatory in this trial, subjects will be strongly recommended to use it to assist their usage of ASV. If subjects are unable to use the App they will be shown how to access equivalent information (myAir website).

10. STUDY SCHEDULE

10.1. Study Entry

A patient meets eligibility criteria of the study if all of the inclusion criteria and none of the exclusion criteria are met. Subjects will stay enrolled for the duration of the study even if they are re-hospitalized during their enrollment.

10.2. Study Flow



[1]CV = Cardiology Study Coordinator
[2]RT = Respiratory/Sleep Team

10.3. Follow-Up

The clinical study plan for the CAT-PEF Feasibility Study includes 1 follow up visit, which may be conducted by phone, at 3 months.

See **Section** 11 for description of specific study procedures.

10.4. Screening Procedures

Patients who have been admitted to the hospital, or in the outpatient setting, if within 14 days of discharge, and have symptoms of acute decompensated heart failure will first be evaluated for eligibility for the study based on chart review.

Review the patient's records to ensure the following:

1. Evidence of HFpEF (EF≥50%) that is not solely right-sided. HFpEF is based on most recent echocardiogram results, but must be within last 12 months.
2. This (or the most recent) hospitalization includes acute decompensated HF as determined by dyspnea and other signs and symptoms as listed in inclusion criteria.
3. The first healthcare encounter related to this hospitalization (e.g., ER, cath lab) was at least 24 hours and no more than 14 days prior to consent.

If the patient appears to be eligible based on the cardiology-related entry criteria, they may be approached about study participation. A brief interview may be conducted to further address potential eligibility criteria.

If the patient continues to appear to be eligible for participation in the study then consent will be obtained. A log of patients screened but not eligible for the study will be maintained.

NOTE: All subjects who sign a consent form must be entered in the data management system, whether or not they are entered into the study.

1. Document demographics and eligibility criteria data
2. Arrange for AHI measurement using the ApneaLink overnight. Subject is <u>not</u> eligible for study entry if AHI<15 e/hr from ApneaLink.
3. If AHI≥15 e/hr with ApneaLink Air and other entry criteria are met, confirm tolerability of the mask and ASV therapy by having the subject use the system for a short time (awake or asleep).
4. If they are not eligible for study entry, document the reason for screen failure in the data management system.

10.5. Detailed Visit Schedule

The following visit schedule applies to subjects who met all eligibility criteria, and are enrolled in the CAT-PEF Feasibility Study.

10.5.1. Visit 1: Screening/Baseline	Primary Responsibility	
	Cardiology	Sleep
Determination of eligibility	X	
ApneaLink Test		X
Mask fitting, ASV set-up and training, myAir set-up		X
Document demographics and baseline data	X	
KCCQ-12	X	

10.5.2. ASV Adherence Monitoring	Primary Responsibility	
	Cardiology	Sleep
Follow-up with subject 2-3 days after start of therapy		X
Review AirView for adherence flags weekly		X
Contact subjects with sub-optimal adherence as needed		X
Review overall adherence at 30 days post-therapy start. Subjects not meeting adherence criteria will be discontinued from the study		X
Document contact in EDC		X

10.5.3. Visit 2: End of study Follow-up	Primary Responsibility	
	Cardiology	Sleep
Collect follow up data on death and hospitalizations	X	
Disposition AirCurve device and refer to sleep therapist		X
KCCQ-12	X	

10.6. Overview of visits

	Screening	**Baseline "Day 0"** (≤3 days from AL report)	**2-3 days Post-device start**	**30 days** (±2 days) **"1 mo"**	**Weekly during study**	**12 weeks** (±2 weeks) **"3 mo"**
Visit Location:	Hospital or Clinic	Hospital or Clinic	Phone call			Clinic or Phone Call
Review of HF history, signs & symptoms	X					
ApneaLink Air test	X					
ASV therapy and mask tolerance	X					
KCCQ-12	X					X
Initiation of ASV Therapy		X				
ASV Device use monitoring			X	X*	X	X

*Check to confirm adequate device use

10.7. Duration of the study

An individual subject's participation is expected to be 3 months.

With an expected enrollment period of up to 24 months for 160 evaluable subjects, and a follow-up period of 3 months, the overall study duration is calculated to be approximately 27 to 30 months.

11. VISIT PROCEDURES

11.1. Polygraphy

Every subject in the study will undergo polygraphy (including pulse oximetry) using ApneaLink at screening. Data acquisition and analysis is described in the ApneaLink Systems Clinical Guide and data collection and the settings required for automatic scoring will be described in the Manual of Procedures. Completion of the test is defined as the time the report is generated.

11.2. KCCQ-12

The short form of the Kansas City Cardiomyopathy Questionnaire is a 12-item instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.

11.3. Mask and ASV Therapy Tolerance

All subjects meeting eligibility criteria (AHI≥15 e/hr per ApneaLink) will be fitted with a mask and set up on the AirCurve. Subjects will also be entered into the AirView system, and be encouraged to use the myAir application. Preferably, subjects will use the AirCurve device and mask overnight to determine tolerance; however, if that is not possible (due to planned discharge, outpatient clinic, eg), the device and mask should be used long enough to demonstrate tolerance (awake or

asleep). Subjects who are unable to tolerate the mask or the delivered pressure will not continue with the study.

If the subject can tolerate the mask and delivered pressure, they will complete the baseline assessments and be issued an AirCurve device.

11.4. Treatment Adherence

Adherence to therapy with ASV is determined by evaluating the usage data from the AirCurve device in AirView. Additionally, discussion with the subject will indicate issues with the mask or other barriers to use. See Appendix I.

11.5. Subject Discontinuation Criteria

If, after 30 days after initiation of therapy, a subject has not met the adherence criteria of at least 4hrs ASV usage per day (24hr period) for 70% of the days enrolled (excluding days spent in the hospital), they will be discontinued from the study. Follow procedures for Device and Subject Disposition in Section 11.6. Record the number of hospitalizations and date of discontinuation on the end of study eCRF.

11.6. Device and Subject Disposition

When the subject completes their participation in the CAT-PEF Feasibility Study, the AirCurve device must be dispositioned and the subject must be referred for further management.

- If the subject wishes to keep their device and continue ASV therapy, they may do so and should be referred to the appropriate sleep care team for continued management
- If the subject does not wish to continue therapy, they should be referred to the appropriate sleep care team for discussion of options for treating their SDB

Document the device disposition in the eCRF. If the subject does not continue therapy (or has left the study for other reasons, such as death), the device must be returned to the clinical site either at a clinic visit or by mail. Return labels will be provided by the sponsor.

12. 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 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 AirCurve devices in accordance with their local IRB/EC requirements. Investigators should follow usual clinical practice at their institutions for reporting serious events to the regulatory authorities.

12.1. Hospitalization

For this protocol, the definition of hospitalization is in-patient care of more than one calendar day (overnight admission). The number of hospitalizations the occurred during a subject's participation in the study will be recorded at the final visit.

12.2. Labeled Adverse Device Effects

Expected adverse device events are determined to be mild and are related to the interface (mask) between the device (AirCurve) and the subject. In this study any skin or eye irritation that is transient (ie, resolves within 24 hours following device use and requires no medical intervention), will not be classified as an adverse device effect.

Mask

- Mild skin irritation around the nose and forehead from the mask
- Mild facial abrasions from ill-fitting mask interface
- Eye irritation, caused by leakage of air from the sides of the mask

Flow Generator

- Drying of the nose, mouth, or throat
- Nosebleed
- Bloating
- Ear or sinus discomfort
- Eye irritation
- Skin rashes

13. STATISTICAL ANALYSIS

This study aims to evaluate the adherence to ASV therapy in HFpEF patients with moderate to severe SDB. Descriptive summaries, including means, standard deviations, medians, 25^{th}, and 75^{th} percentiles will be presented for continuous variables; the number and frequency of subjects in each category will be presented for nominal variables. Analyses will be performed using SAS Version 9.3 or later.

13.1. Justification of the Sample Size

The sample size has been determined to estimate the primary objective (the mean usage in hours per night) with sufficient precision. A sample size of 160 evaluable subjects yields a margin of error equal to 0.25 hours per night or less, when the confidence level is 95% and the standard deviation of usage is 1.6 hours per night or less (as observed in a similar study of myAir[9]). Subjects not meeting the evaluability criteria of at least 4hrs ASV usage per day (24hr period) for 70% of the days enrolled (excluding days spent in the hospital) within the first 30 days of therapy initiation, will be discontinued from the study. Assuming that 60% of the study subjects will be evaluable, 266 (which can be rounded up to 300) subjects are expected to be initially enrolled in the study.

13.2. Primary endpoint analysis

The mean usage and its 95% confidence interval will be estimated.

13.3. Secondary endpoint analyses

The mean change in KCCQ-12 scores and its 95% confidence interval will be estimated. The morbidity rate (the average number of hospitalizations per subject) and its 95% confidence interval will be estimated.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Collection

The investigator, sub-investigator(s), or study coordinator participating in the study will record progress notes to document all data required by the protocol.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in the progress notes as described above.

Any changes to information in the study progress notes, or other source documents, must be initialed and dated on the date the change is made by a clinician authorized to make the change.

14.2. 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. 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 information entered into the eCRF will be accessible to the appropriate ResMed Medical Affairs personnel.

14.3. Query Generation and Resolution

Queries will be generated based upon anomalous or missing data and will be tracked via the EDC System.

Once all queries are resolved, the database will be verified by ensuring all electronic files were completely and correctly loaded.

14.4. Data Storage

Access to data maintained in the EDC System and AirView is strictly limited to authorized personnel.

14.5. Inspection of Records

Periodically the Sponsor or representative may 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.

14.6. 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.

14.7. 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/EC 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/EC, 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/EC approving the protocol
- IRB/EC approved informed consent (copy) and any other adjunctive materials to be used in the study as required.

15. ETHICAL CONSIDERATIONS

15.1. Institutional Review Board (IRB)/Ethics Committee (EC)

The investigator must have written and dated approval from the IRB/EC 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/EC with a copy of the product labeling information and any updates. The investigator will provide the IRB/EC with

reports, updates, and other information (e.g., safety updates and protocol amendments) as required by regulations.

15.2. 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/EC and FDA. According to FDA regulation 21 CFR § 812.150(a)(4), an investigator shall notify the sponsor and the reviewing IRB/EC 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/EC approval may also be required in accordance with 21 CFR § 812.35(a).

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments. Prior to data base lock, an evaluation of subjects with significant protocol deviations will be performed to assess the appropriateness of their inclusion in the analysis.

15.3. Risk Analysis and Confidentiality

15.3.1. Risk Determination of the Study

The AirCurve device has been cleared by FDA to provide non-invasive ventilatory support to treat patients weighing more than 66 lbs (30 kg) with OSA, central and/or mixed apnea or periodic breathing. The device is intended for home and hospital use. The purpose of this study is to evaluate the effect of an adjunctive therapy for adult patients with acute decompensated heart failure and moderate to severe sleep apnea.

Clinical personnel will observe the subject on the fitting and use of all AirCurve devices. They will monitor the subject’s clinical parameters, which include hemodynamics and will intervene, if required.

This study is considered to be of moderate risk to the patients receiving ASV therapy. PAP therapy is the most widely accepted and effective form of treatment for SDB, and the risks associated with its use in this study are reasonable in terms of knowledge gained and potential benefits to patients. By its nature, use of PAP therapy may be associated with minor side effects. Side effects may cause minor discomfort, especially in a patient who has not previously used PAP therapy. In this study, these side effects will not be classified as adverse events unless they do not resolve within a reasonable period of time when PAP therapy is discontinued.

Subjects should be encouraged to discuss any issues they are having with PAP 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 has your health been since the last visit?"). 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.

15.3.2. Subject Data Confidentiality

All information and data collected for the CAT-PEF Feasibility Study 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.

16. QUALITY CONTROL AND QUALITY ASSURANCE

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.

16.1. 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. In addition, sites must include both cardiology and sleep expertise involvement. Sites must permit clinical trial related monitoring, audits, IRB/EC review, and regulatory inspections, providing direct access to source data/documents, as appropriate.

16.2. Polygraphy Data

Each participating site will be trained and follow the clinical guide for use of the ApneaLink device and interpretation of data produced in the report.

16.3. Adherence to ASV Therapy

Leak, residual AHI, and therapy adherence will be monitored by a trial sleep therapist using data from AirView. Suggestions provided to the subjects and personnel at each clinical site on ways to optimize AirCurve/mask use and subject adherence. See Appendix I.

16.4. Training

The Sponsor will conduct an initiation visit at each site to review relevant documentation such as the clinical protocol, ApneaLink and AirCurve Instructions for Use, 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 Sponsor for instructions on how to document the training).

16.5. Audits and Inspections

The Sponsor (or designee), FDA, NIH and any other regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with Federal regulations. The investigator must immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection. Audits may also be conducted by representatives of the study Sponsor.

17. RESPONSIBILITIES

17.1. Clinical Investigator Responsibilities

With the approval of their institution's IRB/EC, qualified investigators will conduct the CAT-PEF Feasibility Study 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.

17.2. Sponsor Responsibilities

The Sponsor will provide each site with study materials. The Sponsor will train study personnel on the clinical study protocol and procedures. Sponsor representatives 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 sponsor representative will be available to address any issues that may arise. This availability includes access by phone and/or e-mail.

18. STUDY ORGANIZATION

18.1. Steering Committee

The steering committee for the study will include at least three cardiologists, a sleep expert, and a representative (non-voting) from ResMed Medical Affairs.

Any required modifications to the protocol will be reviewed and approved by the committee prior to implementation.

18.2. Adherence Core Lab

An Adherence Core Lab comprised of at least one sleep expert and one cardiologist will periodically review ASV adherence data in AirView for all sites over the course of the study. The Adherence Core Lab may contact sites when adherence is low to help troubleshoot issues (See Appendix II), and will provide reports to the Steering Committee as needed.

19. STUDY REPORTS AND PUBLICATIONS

Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements. Publication policy is discussed in the Investigator's Clinical Trial Agreement.

20. REFERENCES

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[4] Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. Arch Intern Med. 2006 Sep 18;166(16):1716-22.

[5] Levy P, Pepin J-L, Arnaud C, et al. Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. Eur Respir J 2008; 32: 1082–1095.

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[7] Cowie MR, Woehrle H, Wegscheider K. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med 2015; 373:1095-1105

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Appendix I. Site Sleep Therapist Guidance

This guidance is to inform the Site Sleep Therapist of steps to be taken when contacting the study subjects for the post-therapy initiation phone call, and for on-going monitoring of ASV adherence. The purpose of this guidance is to keep the contact and information given to the subjects consistent among all subjects and sites.

Post-Therapy Initiation Follow-up Call (2-3 days following start of therapy)

STEP	ACTIVITY	COMMENTS
1	When a new subject has been enrolled in the study, ensure the subject and their device have been entered into the Study AirView Account	Remember to keep the subject details in your restricted, password protected file
2	Phone the subject after they have been enrolled in the study for 3 nights. Introduce yourself to the subject.	If the 3 day phone call falls on a weekend, the Site Sleep Therapist may delay the call until the following Monday. If you are unable to contact the subject, you may try again after 4 nights and 5 nights. If you are still unable to contact the subject you should contact the cardio study coordinator and ask for assistance. Document any activities in the Adherence Follow Up Call CRF
3	Remind the subject of the basics of good sleep hygiene	▪ Refrain from drinking alcoholic beverages within 2 hours of bedtime ▪ Refrain from drinking caffeinated beverages within 6 hours of bedtime ▪ Exercise regularly, but try not to do strenuous exercise within 4 hours of bedtime ▪ Avoid smoking as bedtime approaches, or quit altogether! ▪ Use your bedroom only for sleep and intimate activities; for example, do not watch TV in bed ▪ Go to bed and wake up at approximately the same time each day ▪ Try to avoid taking a nap past 3pm. ▪ Manage stress by relieving your worries through relaxation techniques such as Yoga or Meditation, or talking to a trusted companion ▪ Select a relaxing bedtime ritual, like a hot bath, listening to calming music or 10 minutes of reading
4	Review the subject's usage so far. - Ask the subject how they have found using ASV - Provide reassurance and troubleshoot any issues	[refer to On-going Monitoring below for ASV hints and tips] If the subject is having extreme difficulties with their ASV you may suggest a clinic visit.
5	Remind subjects of your contact details and let them know they can contact you if any additional queries come up. Remind the subjects that you will be monitoring their data on an on-going basis.	
6	Complete the **Adherence Follow Up Call CRF**	

On-going Adherence Monitoring

STEP	ACTIVITY	COMMENTS
1	Monitor the Study AirView database regularly (at least once a week) If, for ≥3 nights you see any issues such as the following: - Compliance is low (<3 hours per night); - leak is high (>24L/min); - treatment is not optimal (AHI≥10) Contact the subject. Troubleshoot the issue. If the issue doesn't improve over the next few nights, consider arranging a clinic visit with the subject.	Contact is at your discretion. If the leak is high but compliance is excellent and the SDB is well controlled, you may choose not to intervene.
2	Complete the **Adherence Follow Up Call CRF** to document any contact which was made and any additional steps taken	

Non-Compliant Patients

STEP	ACTIVITY	COMMENTS
1	There is no maximum number of interventions that may be made by the Site Sleep Therapist. However if despite repeated attempts (≥5 discussions with the subject or attempted contacts with the subject) the subject doesn't appear to be making any efforts to improve ASV compliance, the subject may be considered non-compliant.	The Site Sleep therapist cannot exclude subjects from the trial.

Appendix II. Adherence Core Lab Guidance

This guidance is to inform the Adherence Core Lab of steps to be taken for on-going monitoring of ASV adherence for all sites in the study. The purpose of this guidance is to keep the contact and information given to the sites consistent.

On-going Adherence Monitoring

STEP	ACTIVITY	COMMENTS
1	Monitor the Study AirView database regularly (at least once a week) for adherence triggers. If a site has multiple subjects with adherence issues such as the following: - Compliance is low (<3 hours per night); - leak is high (>24L/min); - treatment is not optimal (AHI≥10) Contact the Site Sleep Therapist to help troubleshoot the issue.	Contact is at your discretion. If a site's subjects generally have good adherence, you may choose not to intervene.
2	Overall adherence status for the study should be compiled for each site on a monthly basis for review with the CAT-PEF Study Steering Committee.	