

## Assessment of the effect of Positive Airway Pressure on energy and vitality in mild Obstructive Sleep Apnea patients. The Merge Study.

### Clinical Trial Protocol

Protocol Title:	Assessment of the effect of Positive Airway Pressure on energy and vitality in mild Obstructive Sleep Apnea patients. The Merge Study.
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## 1. Study Synopsis

<b>Protocol Title:</b>	Assessment of the effect of Positive Airway Pressure on energy and vitality in mild Obstructive Sleep Apnea patients. The Merge Study.
<b>Protocol Short Title:</b>	The Merge Study
<b>Patient Population:</b>	Apnea Hypopnoea Index (AHI) 5-15 events/hour as per American Academy of Sleep Medicine (AASM) 2007 scoring criteria (or AHI $\geq 5$ per AASM 2012 if AHI 0-4 per AASM 2007)
<b>Study Design</b>	A prospective randomised parallel trial with 3 months of active treatment versus a control arm
<b>Purpose of clinical trial:</b>	To determine the benefits of Continuous Positive Airway Pressure (CPAP) therapy in patients with mild Obstructive Sleep Apnea (OSA)
<b>Primary Objective:</b>	To determine the changes in quality of life (energy and vitality) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (as per <b>AASM 2012 criteria</b> ), compared to controls
<b>Secondary Objectives</b>	<ol style="list-style-type: none"> <li>1. To determine the changes in quality of life (on a range of measures) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (<b>as per AASM 2012 criteria</b>), compared to controls</li> <li>2. To determine changes in quality of life (on a range of measures) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (<b>as per AASM 2007 criteria</b>), compared to controls</li> <li>3. Comparison of automated scoring and manual review (as per AASM 2012 criteria)</li> </ol>
<b>Trial Design</b>	Prospective randomised open-label controlled trial
<b>Endpoints:</b>	<p><u>Primary Endpoint:</u> A Change in the Energy and Vitality Dimension of the SF-36 questionnaire from baseline (pre-treatment) to 3 months post CPAP initiation in mild OSA patients (<b>AASM 2012 criteria</b>), compared to controls</p> <p><u>Secondary endpoints</u></p> <ol style="list-style-type: none"> <li>1. Change in outcomes between baseline (pre-treatment) and 3 months post CPAP initiation in mild OSA patients (<b>AASM 2012 criteria</b>) compared to controls in a number of quality of life measures: <ul style="list-style-type: none"> <li>- Short Form 36 (SF 36)</li> <li>- Epworth Sleepiness Scale (ESS)</li> <li>- Fatigue Severity Scale (FSS)</li> <li>- Functional Outcomes of Sleep Questionnaire (FOSQ)</li> <li>- Hospital Anxiety and Depression Scale (HADS)</li> <li>- Insomnia Severity Index (ISI)</li> <li>- Health Questionnaire (EQ5D)</li> </ul> </li> <li>2. Change in outcomes between baseline (pre-treatment) and 3 months post CPAP initiation in mild OSA patients (<b>AASM 2007 criteria</b>) compared to controls in a number of quality of life measures: <ul style="list-style-type: none"> <li>- Short Form 36 (SF 36)</li> <li>- Epworth Sleepiness Scale (ESS)</li> <li>- Fatigue Severity Scale (FSS)</li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>- Functional Outcomes of Sleep Questionnaire (FOSQ)</li> <li>- Hospital Anxiety and Depression Scale (HADS)</li> <li>- Insomnia Severity Index (ISI)</li> <li>- Health Questionnaire (EQ5D)</li> </ul> <p>3. Comparison of automated scoring and manual review of scoring (as per AASM 2012 criteria)</p>
<b>Sample Size:</b>	224 (112 per group)
<b>Summary of eligibility Criteria:</b>	<p><b>Study Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Aged <math>\geq 18</math> and <math>\leq 80</math> years</li> <li>• Ability and willingness to provide written informed consent</li> <li>• AHI 5-15 events/hour as per AASM 2007 scoring criteria (or AHI <math>\geq 5</math> per AASM 2012 if AHI 0-4 per AASM 2007)</li> <li>• Ability to tolerate a one hour long CPAP run in test</li> </ul> <p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• The presence of unstable cardiac disease</li> <li>• Inability to give fully informed consent</li> <li>• Supplemental oxygen</li> <li>• Secondary sleep pathology e.g. Periodic Limb Movement Syndrome, Narcolepsy, Circadian Disorder, Obesity Hypoventilation Syndrome</li> <li>• ESS <math>\geq 15</math>, or concerns about sleepy driving from physician/ sleep lab staff</li> <li>• BMI <math>\geq 40</math> Kg/m<sup>2</sup></li> <li>• Previous CPAP usage</li> </ul>
<b>Intervention:</b>	Continuous Positive Airway Pressure (CPAP)
<b>Study Duration per subject:</b>	3 months

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### 3. Introduction

#### 3.1. Background

Obstructive sleep apnea (OSA) is classified into three groups based on the number of breathing events sufferers experience per hour (known as the apnea hypopnoea index (AHI)). The classifications are: mild (AHI 5-15), moderate (AHI 16-30) and severe (AHI >30).

The effects of moderate and severe OSA are well documented. In the short term, moderate to severe OSA is known to cause excessive daytime sleepiness, motor vehicle accidents, impaired cognitive function and reduced quality of life<sup>1</sup>. It has also been associated with serious health consequences such as hypertension, cardiovascular morbidity and mortality, stroke and diabetes<sup>1</sup>. Effective treatment with continuous positive airway pressure (CPAP) has been shown to improve symptoms and reduce health risks in these patients<sup>2</sup>.

Mild OSA has not been as extensively studied. Although there is a reasonable pool of evidence that suggests that even minor sleep related breathing disturbances are associated with negative consequences, there is no consensus on when treatment should be initiated or, indeed the best treatment for the patients<sup>3</sup>. The few randomised controlled trials (RCT) reviewing CPAP use in these patients have yielded mixed results, potentially due to methodology issues<sup>2</sup>. Two well-designed, adequately powered RCT's in mild OSA patients include the CATNAP and MOSAIC Clinical Trials.

The rationale for the CATNAP study was to understand the effect of CPAP on daily functioning in patients with daytime sleepiness (ESS >10) and mild to moderate OSA (AHI 5-30)<sup>4</sup>. Patients were randomised to receive either CPAP treatment or placebo (Sham CPAP) for a period of 8 weeks. The primary outcome was the FOSQ questionnaire, and 223 patients completed the trial. The investigators found a significant improvement in daily functioning in the active CPAP group compared with the placebo group<sup>4</sup>.

What remained unclear following the CATNAP study was whether mild OSA patients without excessive daytime sleepiness would also benefit from CPAP treatment<sup>4</sup>. The MOSAIC trial aimed to answer this question in an RCT of 391 mild patients who were diagnosed with OSA (Oximetry Disturbance Index (ODI) >7.5/h), but with symptoms at a level not severe enough to warrant treatment by conventional guidelines<sup>5</sup>. Patients were randomised to receive either CPAP therapy or standard care for 6 months. The investigators found that CPAP improved daytime sleepiness (based on ESS scores); objective sleepiness; and self-assessed health status (SF36), but not vascular health risk<sup>5</sup>.

The CATNAP and MOSAIC clinical trials suggest that treating mild OSA is beneficial for patients, however despite this evidence treatment for mild OSA is not consistently offered.

**In 2012, the American Academy of Sleep Medicine (AASM) changed the criteria needed to score a hypopnoea during a sleep study.** Previous 2007 criteria had required a hypopnoea to include a decrease in oronasal airflow by  $\geq 30\%$  from baseline, an event of at least 10 seconds, and  $\geq 4\%$  SpO<sub>2</sub> desaturation<sup>6</sup>. These criteria had been widely accepted by healthcare providers to form the basis of reimbursement for patient equipment<sup>6</sup>. In 2012, a change was made to these criteria which permitted hypopnoeas to be scored with an arousal only, or an oxygen desaturation of  $\geq 3\%$ <sup>6</sup>.

Recommended Hypopnoea Definition:	
AASM 2007	<ul style="list-style-type: none"> <li>• A decrease in oronasal airflow by <math>\geq 30\%</math> from baseline AND</li> <li>• The event is <math>\geq 10</math> sec long AND</li> <li>• Associated with <math>\geq 4\%</math> SpO<sub>2</sub> desat</li> </ul>
AASM 2012	<ul style="list-style-type: none"> <li>• A decrease in oronasal airflow by <math>\geq 30\%</math> from baseline AND</li> <li>• The event is <math>\geq 10</math> sec long AND</li> <li>• Associated with <math>\geq 3\%</math> SpO<sub>2</sub> desat OR arousal</li> </ul>

The AASM updated their criteria as they felt that patients who suffer from frequent respiratory events and arousals from sleep, but insufficient to cause hypoxia, and therefore not meeting the older AASM 2007 criteria, may benefit from treatment<sup>6</sup>. This change in rules significantly increases the percentage of patients who may now be diagnosed with OSA, potentially by up to 40%<sup>7,8</sup>.

However, the new scoring rules remain controversial as there is no compelling evidence that patients with mild OSA according to this new criteria benefit from treatment. As a result, health insurance reimbursement rules in some countries have not adopted the 2012 criteria. **No adequately powered RCTs have shown the benefits of CPAP treatment in this expanded group of mild OSA patients.**

In summary, there are two current issues regarding the treatment of mild sleep apnea:

- 1) There is not universal agreement on whether treatment of mild OSA, as scored by the commonly used AASM 2007 criteria is necessary. Indeed, some countries have limited reimbursement for OSA to only moderate and severe patients
- 2) The newer criteria of OSA defined by the AASM in 2012 are broader, and increase the potential OSA population by up to 40%. The criteria were expanded due to growing clinical evidence that this newly defined mild OSA has detrimental effects on quality of life and cognitive performance. However, there is no objective evidence that treating these patients with CPAP is beneficial. Therefore, this new criteria has not been widely adopted.

### 3.2. Rationale for this study

The primary focus of this study is mild OSA as per the AASM 2012 criteria. We wish to prospectively determine the response to CPAP in patients presenting with mild OSA (AHI 5-15) when scored using the AASM 2012 criteria. As there is no clear evidence regarding the benefits of treatment in this group of patients, this study will provide future guidance for physicians, and policy makers on how to best manage these patients. Our primary objective for this study is to analyse the changes in quality of life from baseline to 3 months post CPAP initiation in mild OSA patients (AASM 2012) compared with a control group.

A secondary focus of this study is mild OSA as per the AASM 2007 criteria. Because an AASM 2012 criterion has not been universally adopted into clinical practice, many healthcare systems are still using AASM 2007 criteria. Although some evidence exists of the benefits of treating mild OSA when scoring as per AASM 2007 criteria, more evidence is required. As part of this proposed study, we wish to add to this pool of knowledge by analysing the quality of life improvements of CPAP in patients diagnosed using the AASM 2007 criteria as a secondary endpoint.

In addition, previous studies have focused on the use of daytime sleepiness as a measure of CPAP success. It is our clinical experience that many mild patients complain of symptoms other than sleepiness (e.g. fatigue, depression, lack of energy, restless sleep etc.). Therefore, we have designed this study to measure the CPAP response in a way which may be more applicable to these patients. The study primary endpoint is the Energy and Vitality dimension of the SF 36, as this has consistently shown to be the most sensitive dimension of the SF 36 for measuring quality of life improvements in mild OSA patients<sup>4,5,9</sup>.

## 4. Objectives

### 4.1. Study Objectives

#### Primary Objective:

1. To determine the changes in quality of life (energy and vitality) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (**as per AASM 2012 criteria**), compared to untreated controls.

#### Secondary Objectives:

1. To determine the changes in quality of life (on a range of measures) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (**as per AASM 2012 criteria**), compared to untreated controls
2. To determine changes in quality of life (on a range of measures) from baseline (pre-treatment) to 3 months post CPAP initiation in patients with mild OSA (**as per AASM 2007 criteria**), compared to untreated controls
3. Comparison of automated scoring and manual review (as per AASM 2012 criteria)

### 4.2. Study Endpoints

#### 4.2.1. Primary Endpoint

A Change in the Energy and Vitality Component of the SF 36 questionnaire from baseline (pre-treatment) to 3 months post CPAP initiation in mild OSA patients (**scored with AASM 2012 criteria**) compared to control subjects.

#### 4.2.2. Secondary Endpoints

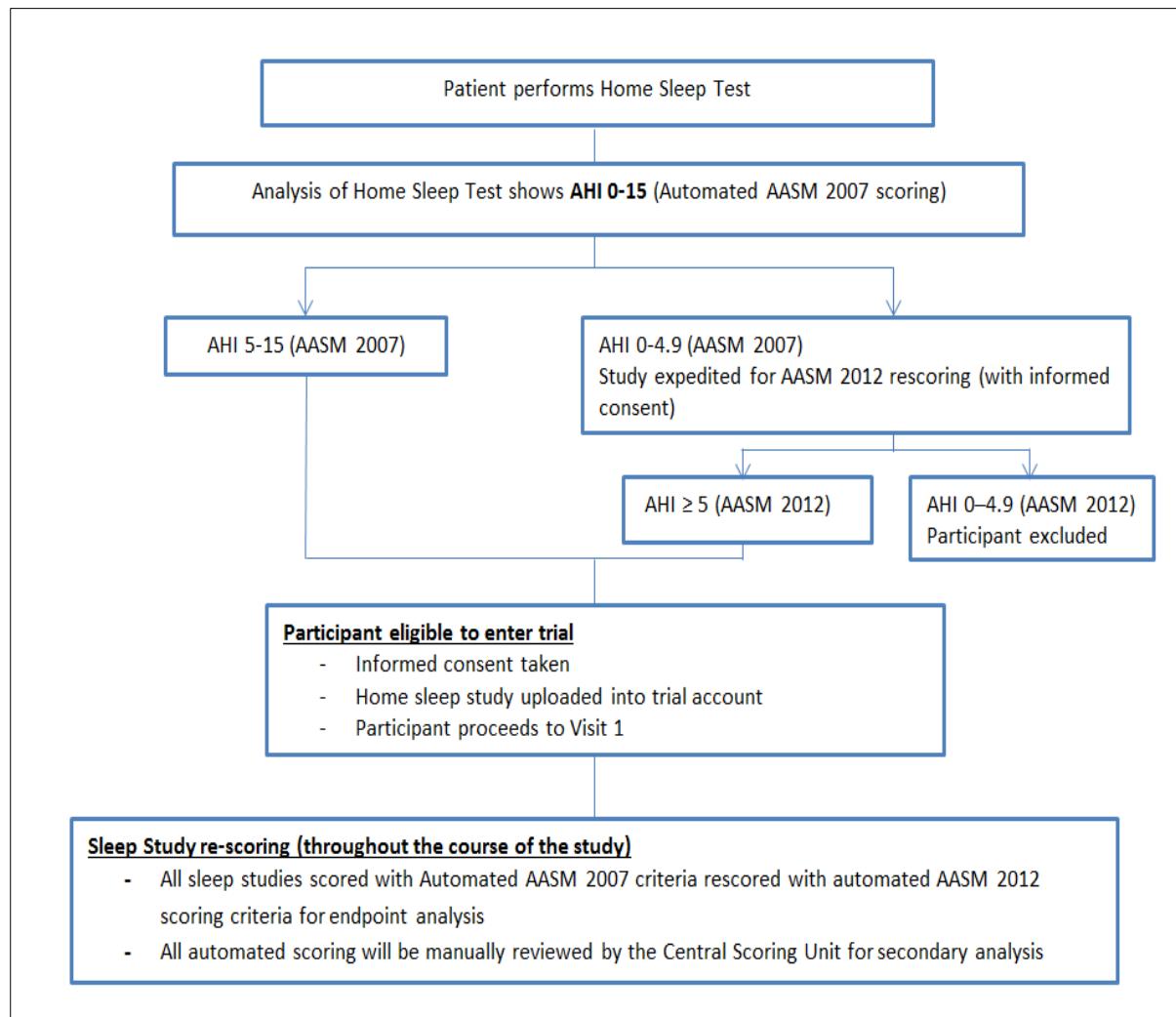
1. Change in outcomes between baseline (pre-treatment) and 3 months post CPAP initiation in mild OSA patients (**scored with AASM 2012 criteria**) compared to controls in a number of quality of life measures:
  - Short Form 36 (SF 36)
  - Epworth Sleepiness Scale (ESS) (8 scales, and 2 [physical and mental composite] domains)
  - Fatigue Severity Scale (FSS)
  - Functional Outcomes of Sleep Questionnaire (FOSQ)
  - Hospital Anxiety and Depression Scale (HADS)
  - Insomnia Severity Index (ISI)
  - Health Questionnaire (EQ5D)
2. Change in outcomes between baseline (pre-treatment) and 3 months post CPAP initiation in mild OSA patients (**scored with AASM 2007 criteria**) compared to controls in a number of quality of life measures:
  - Short Form 36 (SF 36) (8 scales, and 2 [physical and mental composite] domains)
  - Epworth Sleepiness Scale (ESS)
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  - Functional Outcomes of Sleep Questionnaire (FOSQ)
  - Hospital Anxiety and Depression Scale (HADS)
  - Insomnia Severity Index (ISI)
  - Health Questionnaire (EQ5D)
  - 
  - 3. Comparison of automated scoring and manual review of scoring (as per AASM 2012 criteria)
  -

### 4.3. Study Design Overview

A prospective randomised parallel trial with 3 months of active treatment versus a control arm

## 5. Study Methods

### 5.1. Pre Study Screening



[Figure 1]

Patients who visit a participating local sleep service for an overnight sleep test will be screened for the study. Screening will involve the use of the Apnealink home sleep test. The home sleep test can be done instead of, or as well as, routine patient screening. The Apnealink is a 5 channel recording device which is undertaken in the patients home (see section 0). The Apnealink contains automatic scoring software which provides the clinician with an AHI (scored as per AASM 2007) of the screening night.

A successful study is one where at least 4 hours have been recorded and all signals are working correctly (see Section 0.) If a study is not successful, the participant will be contacted by the local sleep service and asked if they would like to re-do the screening Apnealink home sleep test.

Participants are entered into the study based on automatic AASM 2007 scoring. Those who meet either of the following criteria are eligible to continue:

- Mild OSA (AHI 5–15) shown on an ApneaLink Air home sleep test (scored as per AASM 2007);
- No OSA (AHI 0–4.9) shown on the ApneaLink Air home sleep test (scored as per AASM 2007), however rescoreing with AASM 2012 shows an AHI  $\geq 5$  (see section 5.1.2)

### 5.1.2. Participants with no OSA (AHI 0-5) scored with AASM 2007

Participants whose home sleep test shows no OSA (AHI 0-4.9; AASM 2007) may still be eligible to enter the study if, when the study is rescored using AASM 2012 scoring criteria, they have an AHI  $\geq 5$ . In this case, these participants' sleep studies will be expedited for rescored with AASM 2012 scoring criteria before commencing study activities. If rescored with AASM 2012 criteria shows no OSA (AHI  $< 5$ ), the participant will be excluded from the study

### 5.2. Apnealink AirView account

Participants who may wish to take part in the study will have their home sleep test uploaded to the ApneaLink AirView account. Before the participant's ApneaLink Air data is uploaded, the study will be discussed with participants, they will be provided the *Participant Information Sheet* and participants will give written *Informed Consent*.

Data from the ApneaLink Air can be uploaded and stored on a cloud based system known as AirView (see section 0). For the purpose of this study, a dedicated AirView account will be set up for study participants only. Access to this account will be restricted to only those in the study team.

### 5.3. Home Sleep Test Scoring Review

Following on from participant enrolment in the study, all ApneaLink Air home sleep tests will be rescored using automated software, based on AASM 2012, criteria by ResMed Ltd (Sydney). The AHI provided by this automated AASM 2012 scoring will be the AHI used in the primary study objective. The AHI provided by automated AASM 2007 scoring will be the AHI used for secondary study objectives.

The algorithm for AASM 2007 automated scoring has been commercially available for many years and has been validated in many studies. The automated AASM 2012 algorithm is newly developed at ResMed, and is being concurrently validated. All automated scoring by AASM 2012 criteria will be reviewed by an expert Central Scorer. The AHI provided by the Central Scorer will be reported as a secondary study outcome.

As the primary outcome of the study relates to mild OSA as per AASM 2012, it may seem more intuitive to screen and enrol using this criterion. This has not been done for two reasons:

- 1) Treatment for Mild OSA as per AASM 2007 scoring is not routinely reimbursed due to a lack of evidence. We wish to add to this pool of knowledge by including AASM 2007 mild OSA as a secondary endpoint.
- 2) A home sleep test which scores using AASM 2012 (including arousals) is not commercially available at the time of writing this protocol. However, during the course of the study this technology is being validated and expected to be available at the time of study completion.

## 5.4 Study Visits

### 5.4.1. Study Visit 1

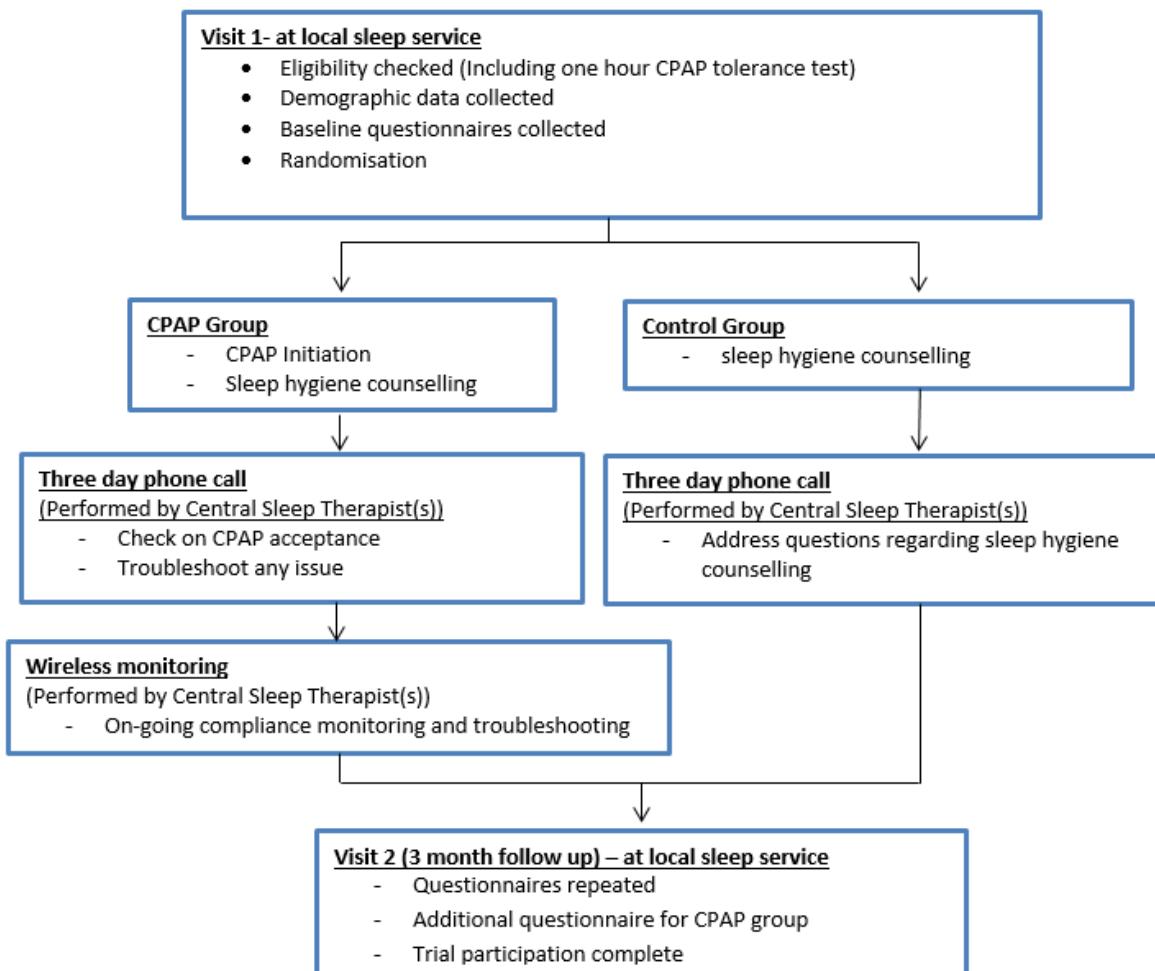


Figure 2: Study Flowchart

Participants will attend their local sleep service for Study Visit 1. The inclusion criteria will be checked (*Inclusion Checklist CRF*). As part of the inclusion criteria participants will complete a one hour CPAP run in test. During this test participants will be informed about the standard treatments for mild OSA, and what they can expect if they are randomised to treatment or the control arm of the study.

**Participants who are unable to tolerate CPAP at least an hour will be excluded from participation in the study.**

Following the one hour CPAP trial, baseline demographics such as gender, age, height, and weight, will be collected, along with basic medical history (*Baseline Demographics Form*). During this visit participants will be asked to complete a series of standardised questionnaires (as per Section 10). These questionnaires will be self-administered, although the staff at the site will be available to assist participants with any queries.

At this point participants will be randomised by use of a computer generated randomisation schedule into one of two arms; the CPAP arm or the control arm. Randomisation with minimisation will be used, based on age, BMI and gender (See *Randomisation Schedule*).

## 5.5 CPAP Arm

### 5.5.1 CPAP Initiation

Participants randomised into the CPAP group will be set up on the Auto-adjusting CPAP device (ResMed AirSense S10; response setting for male patients, and AutoSet for Her mode for female patients). The participants will be shown the device and given further instructions on how to use it. They will have the opportunity to try on multiple masks in order to find a mask which is well fitting, comfortable, and unobtrusive. All participants will be provided with humidification to alleviate any discomfort from dry air.

Participants will then take home the device and instructions for use, and will be asked to use the device nightly. As part of the CPAP education participants will be provided with CPAP information and internet links, such as the CPAP user guide, the ResMed youtube channel, and NHS CPAP websites, in order to assist them adapting to CPAP use. Participants will also be shown how to view their nightly usage and mask leak data on their device. Participants with a smart phone will also be introduced to the MyAir App (ResMed). The MyAir app wirelessly downloads data from the device and provides feedback, coaching and tips to patients to assist them with using therapy (see Section 0.) **The MyAir App will not be mandatory in this study, but it will be highly recommended to patients.** If participants are unable to use the MyAir App, they will be shown where to find the equivalent information (CPAP device screen + ResMed websites). This information will also be discussed with them by the Trial Sleep Therapist.

It will be explained that participants device data will be wirelessly monitored on an ongoing basis using the ResMed AirView System (see Section 0) and that the Trial Sleep Therapist may contact them if their data shows that their treatment is not optimal (e.g. their compliance is low, mask leak is high, or AHI is not well controlled).

At this point the participants CPAP details will be entered into the wireless monitoring system (AirView).

### 5.5.2 Phone calls after 3 nights (performed by Trial Sleep Therapist or the local centre)

All participants will be contacted after 3 nights of CPAP use by the Trial Sleep Therapist to discuss their experiences with the PAP treatment and troubleshoot any difficulties that the participant is having. If the participant is having issues which cannot be resolved over the phone they will be invited for an additional clinic visit where the Trial Sleep Therapist may take additional steps such as changing the mask (*Three day phone call CRF*).

These phone calls will be performed by the Trial Sleep Therapist. This person is experienced with the use of CPAP and setting up patients. In order for the advice and care during the study to be consistent, the Trial Sleep Therapist will be responsible for managing the participants during the three- month study. However if the site wish to actively manage the patients themselves, they will be trained to do so by the Trial Sleep Therapist.

If the Trial Sleep Therapist is unable to contact the patient following 3 nights, they may try again after 4 nights and 5 nights. If the Trial Sleep Therapist is still unable to contact the patient during this time they may contact the patient's local sleep service and ask for assistance in contacting the patient.

### 5.5.3 Ongoing monitoring

Participants randomised to the CPAP arm will have their CPAP compliance monitored using the ResMed AirView Remote Monitoring system which accompanies the CPAP devices used in the study (see Section 0.) The Trial Sleep Therapist will be responsible for monitoring all the CPAP data regularly. In order to ensure consistent monitoring and patient follow-up, responsibility of the patient care during the three month study fall to the Trial Sleep Therapist.

The Trial Sleep Therapist will review the data on a regular basis (at least twice per week) and will intervene when compliance is low or other issues are identified. For example, the Trial Sleep Therapist will intervene if they see that for a period of  $\geq 3$  consecutive nights either of the following takes place:

- Compliance is low (<4 hours per night);
- leak is high (>24L/min);
- treatment is not optimal (AHI $\geq 5$ )

In this instance the Trial Sleep Therapist will contact the patient to discuss the issue and potential solutions. Participants will be invited for further clinic visits if required (*CPAP Therapist CRF*). Visits will take place at the participants local sleep service, and will be conducted by the Trial Sleep Therapist. The patient's local sleep service will be informed of any contact and what follow up was taken.

If the participant is unable to be contacted after multiple attempts, the Trial Sleep Therapist will contact the patient's local sleep service and ask for assistance contacting the patient. If contact is still unsuccessful the participant will be withdrawn from the trial and deemed 'lost to follow-up'.

## 5.6 Control Arm

All participants (including the CPAP group) will be counseled regarding healthy lifestyle behaviors including sleep hygiene habits based on national guidelines and recommendations. Sleep hygiene counseling is considered standard care in this patient group, and many mild patients see an improvement in daytime symptoms when following basic sleep hygiene measures such as spending adequate amounts of time in bed<sup>10</sup>.

### 5.6.1 Three day phone call

The control arm will also receive a phone call three days after visit one, to discuss the sleep hygiene behaviors and answer any questions the participant may have. This phone call will be conducted by the Trial Sleep therapist to ensure that all information given to participants is consistent.

## 5.7 Three month follow up visit

At the end of the 3 month study, participants in both arms will be asked to attend their local sleep service for a three month follow up visit. Participants will be asked to complete the same standardised questionnaires as they completed at the baseline visit (as per Section 10), including the participants weight.

Participants in the CPAP arm will be asked to complete an additional questionnaire regarding their experiences with CPAP and their wish to continue using it (*CPAP Questionnaire CRF*).

At this stage the subject's participation in the trial is complete, and participants will revert to routine clinical practice. **Participants using a CPAP as part of the clinical trial who wish to continue with it will be permitted to keep the CPAP.**

**Participating centres will be provided with sufficient number of CPAPs that patients in the control arm will also have the opportunity to use CPAP at the end of the trial if the patient and their care team feel it is the best option for them.**

In order to select an appropriate study length, similar studies were reviewed. CATNAP found a positive treatment effect from a 2 month trial participation period; however we felt that some patients may need slightly longer to adjust to CPAP therapy. Participants were enrolled in the MOSAIC study for six months; however a study endpoint also included vascular risk. A similar RCT reviewing the effects of treatment on mild OSA had follow up appointments at both three months and six months. The data showed no significant differences in quality of life between the three and six month visits<sup>3</sup>. Therefore, 3 months was considered an appropriate trial length for this study.

## 5.8 Pilot Phase

In order to test the trial methodology, the trial will start with a pilot phase of 20 randomised participants. At this stage the steering committee will meet to review the following:

- Average CPAP compliance
- Trial methodology and flow

**Compliance to treatment is crucial for study to be able to demonstrate whether CPAP treatment yields improvements in mild patients.** In order for patients to experience quality of life benefits, it has been shown that at least 4 hours usage per night is required<sup>11</sup>, with greater use associated with increased benefits<sup>12,13</sup>. If, during the pilot phase, average compliance is lower than 4 hours per night, the protocol will be amended to include the use of a CPAP 3 day run in phase, in order to include only patients who are able to use the device for greater than four hours per night. Additional changes to the protocol may also be made based on findings from the pilot phase.

# 6 Study Responsibilities

## 6.1 Terms

**Local Sleep Service** refers to UK based sites which currently screen, diagnose and treat sleep disorders, such as hospital respiratory departments. These sites are those experienced with diagnosing and treating obstructive sleep apnea, as well as initiating CPAP treatment, and will be involved in the screening and set-up of trial participants

**Central Scorer** refers to an expert Central scorer who will review all studies scored using AASM 2012 criteria.

**Trial Sleep Therapist** refers to a specialist with extensive experience initiating CPAP in patients, managing OSA patients, and troubleshooting equipment problems. The Trial Sleep Therapist is part of the trial team (independent from the trial sites), and is centrally located.

## 6.2 Trial Tasks

Task	Timeline	Responsibility
Home Sleep Screening Test	Screening	Local Sleep Service
AASM 2007 scoring (Automatic software scoring)	Screening	Local Sleep Service
Data uploaded to Trial account	Screening	Local Sleep Service
AASM 2012 scoring (Automatic software scoring)	*Occurs at the point of screening if patient has an AHI 0-4 using AASM 2007, otherwise occurs throughout course of study	ResMed

AASM 2012 scoring reviewed by Central Scorer	Throughout course of study	Central Scorer
<u>Visit 1</u> <ul style="list-style-type: none"> <li>- Check inclusion (including CPAP tolerance 1 hour test)</li> <li>- Demographics</li> <li>- Questionaries</li> <li>- Randomisation</li> <li>- Sleep hygiene counselling</li> <li>- CPAP initiation (CPAP group only)</li> <li>- Add CPAP details to Trial AirView Account</li> </ul>	Visit 1	Local Sleep Service
<u>3 day phone call</u> <ul style="list-style-type: none"> <li>- Address questions regarding sleep hygiene counselling</li> <li>- Check on CPAP acceptance (CPAP group only)</li> </ul>	3 day phone call	Trial Sleep Therapist
<u>Ongoing wireless monitoring</u> <ul style="list-style-type: none"> <li>- Intervene if Compliance is low or other issues are seen</li> <li>- Organise additional visits if required</li> </ul>	Continuously throughout 3 month study	Trial Sleep Therapist
<u>Visit 2 (3 month follow up)</u> <ul style="list-style-type: none"> <li>- Repeat baseline questionnaires</li> <li>- Additional questionnaire for CPAP group</li> <li>- Trial participation complete, patient continues with routine clinical care</li> </ul>	3 month follow up visit	Local Sleep Service

## 7 Selection and Withdrawal of Participants

### 7.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all the following criteria:

Inclusion Criteria
<p>Study Screening:</p> <ul style="list-style-type: none"> <li>• AHI 5-15 events/hr as per AASM 2007 scoring criteria or AHI <math>\geq 5</math> per AASM 2012 if AHI 0-4 per AASM 2007</li> <li>• Aged <math>\geq 18</math> and <math>\leq 80</math> years</li> <li>• Ability and willingness to provide written informed consent</li> <li>• Ability to tolerate a CPAP one hour long run in test</li> </ul>

### 7.2 Exclusion Criteria

Exclusion Criteria
<ul style="list-style-type: none"> <li>• The presence of unstable cardiac disease</li> <li>• Inability to give fully informed consent</li> <li>• Supplemental oxygen</li> <li>• Secondary sleep pathology e.g. Periodic Limb Movement Syndrome, Narcolepsy, Circadian Disorder, obesity hypoventilation syndrome suspected or diagnosed at local sleep service</li> <li>• BMI <math>\geq 40</math> Kg/m<sup>2</sup></li> <li>• ESS score at baseline <math>\geq 15</math>, or concerns about sleepy driving from physician/ sleep lab staff</li> <li>• Previous CPAP usage</li> </ul>

### 7.3 Selection of sites

Study sites (“local sleep services”) are defined as sites which currently screen, diagnose and treat sleep disorders, such as hospital respiratory departments. Eligible sites are those experienced with diagnosing and treating obstructive sleep apnea, as well as initiating CPAP treatment. These factors, as well as the ability of the site to conduct research, will be assessed at the site selection/ site initiation visits. Appropriate Health Research Authority (HRA) and National Health Service (NHS) approval will be obtained for each participating site.

### 7.4 Selection of participants

Potential participants who meet the screening criteria will be identified through U.K. based local sleep services. These patients will be told about the study by their treating clinician at the local sleep service. Those who would like more information will be given the Patient Information Statement. Participation in the trial is voluntary and Informed Consent will be obtained for each participant before their home sleep test is sent for independent review.

### 7.5 Handling of Subject withdrawals

Enrolment is completely voluntary and participants are free to withdraw from the study at any time. Subjects who withdraw will continue to visit their local sleep service for routine clinical care. Reason for withdrawal will be documented on the participants CRF.

### 7.6 Premature Termination or suspension of study

In the unlikely event that the study is terminated or suspended, participants will continue to visit their local sleep service for routine clinical care.

## 8 Expected Duration of the Trial

### 8.1 Duration per participant

The duration for each trial participant is expected to be 13 weeks. 1 week for Apnealink testing and baseline visit, and 12 weeks of CPAP use for the active arm.

### 8.2 Duration of the study

Between 5 and 15 UK centres are expected to take part in the trial. Enrolment is expected to occur at a rate of approximately 2 patients per centre per month. Recruitment and follow up is estimated to take 1.5 years. **The entire study, including analysis and reporting, is anticipated to take approximately 2 years.**

## 9 Trial Devices and Procedures

### 9.1 Apnealink Air Home Sleep Test

Portable Home Sleep Testing devices are widely used in the screening and diagnosis of sleep apnea, and have been validated in many studies. In the screening phase of this trial, the ResMed Apnealink Air device will be used to diagnose sleep disordered breathing in the patient’s home. The Apnealink Air is a commercially available PG device which is small and simple to use. Many sleep services in the UK already use the Apnealink Air for routine screening. It contains software which allows for the

scoring of apneas, hypopnoea and arousals. It is a portable device which consists of a nasal cannula to measure nasal flow and snoring, oximeter to measure pulse and blood oxygen levels, and a chest band to measure respiratory effort.



Participants will be provided with an Apnealink Air from their local sleep service. They will be shown how to use it and instructed to take it home for use. The Apnealink Air contains user feedback which shows if a successful night has been recorded. The device can be re-used up to three nights. Participants will return their Apnealink Air to the sleep clinic either in person or in a replied paid envelope. The device will be downloaded and automatically scored using the electronic software.

If the sleep report shows an AHI  $\leq 15$ , the participants will be asked if they are happy to proceed to the next stage. If the patient provides consent, the Home Sleep Test data will be uploaded to the Trial AirView account for review to assess the participants eligibility to enter the study.

## 9.2 ResMed AirSense 10 AutoSet CPAP



The ResMed AirSense 10 AutoSet CPAP is a non-invasive PAP device indicated for the treatment of obstructive sleep apnea in patients weighing more than 30 kg. The device is intended for home and hospital use. It provides a pressure range of 4-20 cm H<sub>2</sub>O as required to maintain an "air splint" for effective treatment of flow limitation.

The ResMed AirSense CPAP comes in two models, a standard model and an AutoSet for Her model. The devices contain unique algorithms, with the standard model designed to overcome OSA in all patients, Response Setting for mild patients who may have difficulty tolerating high pressures, and the AutoSet for Her designed to treat specific female breathing patterns. All modes are commercially available with CE mark. In this trial, male patients will be given the AutoSet using Response Setting and female patients will be given the AutoSet for Her.

The devices come with in-built humidification and heated tubing which heats and humidifies the air prior to delivery to the patient. A comfortable well-fitting mask will be provided to patients.

**Patients will be requested to use the CPAP (with mask and tubing) every night while sleeping to treat their OSA.**

The participants CPAP will be added to the Trial AirView account for ongoing monitoring during the study.

### 9.3 AirView Wireless Monitoring and MyAir App



Each ResMed AirSense device contains built in wireless connectivity which transmits data via a mobile network tower to a secure data centre. When enabled, 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 patients local sleep service and study team to assess items such as device efficacy (AHI), mask leak, usage hours and CPAP pressure. This data will be viewed by the Trial Sleep therapist, who will intervene if the patient is having issues with therapy or is struggling with compliance (as per section 0).

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

In addition to the AirView computer program, a patient friendly version of the data is available through the ResMed MyAir application. The MyAir application can be accessed via the patient's smartphone and allows the patient to monitor their own treatment data. The MyAir application also provides tips to the patient on things like coping with therapy, managing mask leaks, and adjusting comfort settings. Although the MyAir App is not mandatory in this trial, participants will be strongly recommended to use it to assist their usage of CPAP. However, if patients are unable to use the App they will be shown how to access equivalent information (CPAP device screen + ResMed websites).

#### 9.3.1 Manufacturer Details

The Apnealink Air, AirSense 10 CPAPs, and AirView and MyAir data applications are manufactured by ResMed Ltd, Sydney, Australia

ResMed is a developer, manufacturer and distributor of medical equipment designed for treating, diagnosing, and managing sleep-disordered breathing.

### 9.3.2 Required Training/Experience for Device Use

The PG, APAP and computer software for use in this trial are commercially available and already used in multiple UK locations. Their mode of operation is similar to other commercially available devices, and as such minimal training is required. **Staff at participating centres will undergo standard training on the device equipment, along with training on study procedures.**

## 10 Questionnaires

### 10.1 Short Form 36 (SF-36)

The SF-36 questionnaire is a well validated widely used generic health questionnaire<sup>14</sup>. It was developed as a set of standard, easily administered, quality of life questions for use in routine monitoring and assessment of treatment outcomes in adult patients<sup>15</sup>. The SF-36 measures the limitations of a person's quality of life due to poor health on eight scales: physical activity; social activity; physical health problems; bodily pain; mental health; emotional health; vitality (energy and fatigue); and health perceptions. It takes about 5 minutes to complete<sup>16</sup>.

In this study the Energy and Vitality Component of the SF-36 will be used as the primary outcome, and the entire SF-36 will be used as a secondary outcome.

We have chosen to use a study endpoint of the Energy and Vitality dimension of the SF36, as this has consistently shown to be the most sensitive dimension of the SF-36 for measuring quality of life improvements in mild OSA patients<sup>4,5,9</sup>.

### 10.2 Epworth Sleepiness Scale (ESS)

The ESS is a questionnaire used to assess average levels of daytime sleepiness. Patients rate their likelihood to fall asleep in 8 scenarios. The ESS is commonly used in clinic practice to assess for dangerous levels of sleepiness (score of >15) in patients with sleep disorders. It has shown to be a reliable measure of sleepiness with correlation to OSA severity, and sensitivity to post-treatment changes<sup>17</sup>.

### 10.3 Fatigue Severity Scale (FSS)

The FSS is designed to measure the severity of fatigue and how it impacts an individual's daily life in terms of motivation, exercise, daily activity, work, family and social life. It takes 2-3 minutes to complete the 9 scales. The FSS has been used in a number of health conditions, including sleep apnea<sup>18</sup>.

### 10.4 Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a questionnaire designed to assess the impact of excessive sleepiness on multiple activities of everyday living. The FOSQ contains 30 items and takes approximately 15 minutes to complete<sup>19</sup>. The FOSQ includes five subscales: activity level; vigilance; intimacy and sexual relationships; general productivity; and social outcomes<sup>19</sup>.

The FOSQ has been shown to be a good instrument for assessing the daily impact of the symptoms of sleep apnea<sup>20</sup>. Studies have found consistent improvements in CPAP groups when using the FOSQ, and it has been recommended for future use when validating the OSA treatments<sup>9</sup>.

## 10.5 Hospital Anxiety and Depression Scale (HADS)

The HADS questionnaire contains 14 items in which patients must choose from a number of four choices to describe their current state of being. It has been found to be a useful tool for validated severity of symptoms of anxiety and depression in both primary care patients and the general population<sup>21</sup>. As anxiety and depression are common in OSA, a specific measure of these conditions is considered important in this study<sup>22</sup>.

## 10.6 Insomnia Severity Index (ISI)

The ISI seven-item questionnaire asks the individual to rate the level of insomnia and perceptions of sleep problems in the last two weeks. Answers must be provided using a scale from 0-4, with 0 reflecting no problem or being very satisfied to 4 indicating a very severe or very dissatisfied experience. Scores are divided into four tiers: 0-7 equates to no clinically significant insomnia, 8-14 equates to sub-threshold insomnia, 15-21 indicates moderate severity insomnia, and 22-28 reflects severe insomnia. Insomnia is frequently reported as a symptom of OSA in female patients<sup>23</sup>, and may also be common in mild OSA patients<sup>22,24</sup>, therefore, a measure of insomnia has been included as a secondary endpoint in this study.

## 10.7 EQ5D Health Questionnaire

The EQ5D health questionnaire contains several questions relating to health and mobility, the second part of the questionnaire asks the participants how they feel their health is on the day of the visit.

## 10.8 Data Entry

This trial will utilise a web-based, trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trial database designed for data capture. The Chief Investigator will act as Data Custodian for the trial. Relevant ORTU staff will have overview of all entered data.

The trial database is bespoke and hosted on the University of Oxford server with services provided through Oxford University Medical Sciences Division IT Services (MSD IT). The server and database are protected by a number of measures including anti-virus and anti-spyware applications, firewalls, encryption technology and permissions. The database will be backed up on a daily basis.

The database and access to computers are password protected. Paper-based identifiable data at each site will be kept in a locked cabinet, in a locked or ID-access controlled area. The Data Manager will maintain a list of personnel to grant and revoke access

# 11 Sample Size

## 11.1 Sample Size

The required sample size is 224 (112 per group) in the primary outcome group (Mild OSA 2012 classification).

## 11.2 Sample Size calculation

### 11.2.1 Primary Endpoint Calculation

The primary outcome for this evaluation is the Energy and Vitality subscale of the SF-36 questionnaire. Previous clinical trials considering CPAP outcomes in mild OSA patients were reviewed. The MOSAIC study<sup>5</sup>, which has the most similar patient selection criteria, reported an increase in vitality score of 10.8 (SE 1.3) points between baseline and 6 months in the CPAP group, compared with an increase of 4.2 (SE 1.4) in the standard care group. This difference between the treatment groups of 6.6 is considered a significant clinical improvement.

The sample size was calculated using a difference in treatment effect of 6.6 comparing CPAP change between 3 months and baseline (mean change 10.8, SD 17.00) to standard care change between 3 months and baseline (mean change 4.2, SD 18.1) with a 5% significance level and 80% power.

### 11.2.2. Clinical significance of the primary endpoint

A mean change of 6.6 was considered clinically significant by the MOSAIC authors<sup>5</sup>; however a universally agreed clinically significant score change does not currently exist. Minimal Clinically Important Difference (MCID) is a way of calculating the sample size based on the smallest change in a treatment outcome that a patient would identify as important. While a MCID has not been established for treatment of OSA, an expert panel has attempted to define consensus on a change in SF-36 which would be meaningful to a patient with chronic lung disease or asthma. The smallest MCID accepted by the panel was 10 for both COPD and asthma<sup>25</sup>. While it is unclear if these scores can be extrapolated to OSA, this gives a reasonable indication that a score change of 6.6 points in this clinical trial considered to have a positive benefit on patients' lives

### 11.2.3 Sample required to adequately power the primary endpoint.

The sample size calculation shows that 224 randomised patients are required to show a change in energy and vitality in Mild OSA (AASM 2012). However, as participants in this study based on their AASM 2007 scoring classification and then all studies are rescored as per AASM 2012. Therefore an additional number of participants are required to be enrolled in the study.

#### A note about AASM 2007 and 2012 scoring

It is not exactly known how many participants will move from Mild OSA as per AASM 2007 to Mild OSA as per AASM 2012. Previous studies which have rescored sleep studies with different criteria have been reviewed to assist with predictions<sup>7,8,26,27</sup>. The most relevant study, conducted by Bahamman *et al*<sup>8</sup> found that up to 45% of patients would have not been diagnosed with OSA using AASM 2007 criteria, but were diagnosed when using AASM 2012 criteria. In our study we expect a higher rate of participants who score no OSA with AASM 2007 to be diagnosed with OSA using AASM 2012, because these patients have presented at the sleep clinic with symptoms, and other sleep disorders have been excluded.

**Using data from previous trials to estimate occurrences of OSA, we originally predicted that a minimum of 264 participants are would be needed to be enrolled in this study to have the required 224 participants in the Mild OSA (AASM 2012) group for primary analysis. This also allows for a 10% drop-out rate.**

These estimations were checked both after the pilot phase (n = 20), and after 50% of enrolment was complete, and the planned sample size.

Based on this updated data, we anticipate that 300 participants are needed to be recruited in order to meet the required number (224) in Mild OSA 2012 group for primary outcome analysis.

Recruitment will continue until 224 participants are enrolled in the mild OSA group (as per AASM 2012).

#### 11.2.4 Participants with moderate or severe OSA as per AASM 2012

Participants with mild OSA (AHI 5-15) or no OSA (AHI 0-4) as per AASM 2007 who have moderate or severe OSA (AHI >15) when re-scored as per AASM 2012 will be analysed as per the secondary outcomes. As this group is likely to be quite small, all analysis will be exploratory only.

## 12 Statistical Analysis Plan

A separate Statistical Analysis plan will be developed and published prior to the end of the trial.

## 13 Risks and Benefits

### 13.1 Anticipated Clinical Benefits

Participants may experience an improvement in quality of life based on treatment of their OSA.

### 13.2 Anticipated Adverse Device Effects

CPAP is known to be safe and is routine standard of care for the treatment of sleep disordered breathing

- Known side effects which can result from masks are:
  - Skin marks and irritation around the nose from the mask
  - Eye irritation, caused by leakage of air from the mask
- With careful fitting of the mask the risks are minimised

The common CPAP side effects are:

- Drying of the nose, mouth, or throat
- Nosebleed
- Bloating
- Ear or sinus discomfort
- With correct therapy settings and the use of humidification the risks are minimised

### 13.3 Residual Investigational Device Risks

- The devices used in this study are commercially available CE marked CPAP devices for the treatment of OSA in adults. There are no residual investigational device risks.

### 13.4 Risks associated with Study Participation

- There are no identified risks associated with study participation. Participants randomised to the control group will wait the three month study duration before they have access to CPAP treatment. However this is deemed acceptable as CPAP treatment is not standard routine care for these patients, and, depending on the clinic, some may never be offered CPAP treatment.

- Potential participants who may pose a risk to others through excessive sleepiness or concerns about sleepy driving will be excluded from the study
- Ethics committee approval will be obtained before patient enrolment to the study

### 13.5 Data Safety Monitoring Committee (DSMC)

- Due to the low risk nature of this trial, the fact that all products are commercially available and are being used as per their intended use, combined with the short duration of subject participation, there is no requirement for a DSMC.

### 13.6 Trial Steering Committee (TSC)

A TSC will be utilised to provide overall supervision of the trial. The TSC will meet after the 20 patient pilot phase, and regularly throughout the course of the study. Members of the TSC include:

- Prof. John Stradling (Chair)
- Dr. Sonya Craig - Member
- Prof. Mary Morrell (CI)
- Dr. John O'Reilly - Member
- Ms Alison Wimms
- Prof Peter Calverley (Independent Member)
- Dr Alison McMillan - Member
- Dr Chris Turnbull - Member
- Dr Julia Kelly – Trial Co-ordinator/Lead Researcher
- Emma Hedley – Trial Manager

### 13.7 Safety Reporting

Definitions of Serious Adverse Events:

Any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization (voluntary hospitalisations 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

Important medical adverse events are those which may not be immediately life-threatening, but are clearly of major clinical significance. They might jeopardise patients' safety and might require intervention to prevent any serious outcomes listed above.

#### Reporting Serious Adverse Events

- 1) All known details of the SAE should be notified to the clinical trials unit as soon as becoming aware. The CTU will pass this information to the sponsor within 24 hours of being notified
- 2) The sponsor (ResMed) is responsible for sending all information to ResMed's Regulatory department within 10 days to ensure correct regulatory reporting  
The SAE is followed to completion  
A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted

within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

## 14 References

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *The Lancet* 2014;383:736-47.
2. Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006;29:381-401.
3. Monasterio C, Vidal S, Duran J, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *American journal of respiratory and critical care medicine* 2001;164:939-43.
4. Weaver TE, Mancini C, Maislin G, et al. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *American journal of respiratory and critical care medicine* 2012;186:677-83.
5. Craig SE, Kohler M, Nicoll D, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. *Thorax* 2012;67:1090-6.
6. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2012;8:597-619.
7. Guilleminault C, Hagen CC, Huynh NT. Comparison of hypopnea definitions in lean patients with known obstructive sleep apnea hypopnea syndrome (OSAHS). *Sleep Breath* 2009;13:341-7.
8. BaHammam AS, Obeidat A, Barataman K, Bahammam SA, Olaish AH, Sharif MM. A comparison between the AASM 2012 and 2007 definitions for detecting hypopnea. *Sleep Breath* 2014;18:767-73.
9. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;Cd001106.
10. Victor LD. Treatment of obstructive sleep apnea in primary care. *American family physician* 2004;69:561-8.
11. Weaver TE. Relationship Between Hours of CPAP Use and Achieving Normal Levels of Sleepiness and Daily Functioning. *Sleep* 2007;30:711-9.
12. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011;34:111-9.
13. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest* 2006;130:1772-8.
14. Patel AA, Donegan D, Albert T. The 36-item short form. *The Journal of the American Academy of Orthopaedic Surgeons* 2007;15:126-34.
15. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care* 1992;30:473-83.
16. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ (Clinical research ed)* 1992;305:160-4.
17. Chiner E, Arriero JM, Signes-Costa J, Marco J, Fuentes I. [Validation of the Spanish version of the Epworth Sleepiness Scale in patients with a sleep apnea syndrome]. *Arch Bronconeumol* 1999;35:422-7.
18. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *Jama* 2012;307:2161-8.
19. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835-43.
20. Vidal S, Ferrer M, Masuet C, Somoza M, Martinez Ballarin JI, Monasterio C. [Spanish version of the Functional Outcomes of Sleep Questionnaire: scores of healthy individuals and of patients with sleep apnea-hypopnea syndrome]. *Arch Bronconeumol* 2007;43:256-61.
21. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research* 2002;52:69-77.
22. Lee MH, Lee SA, Lee GH, et al. Gender differences in the effect of comorbid insomnia symptom on depression, anxiety, fatigue, and daytime sleepiness in patients with obstructive sleep apnea. *Sleep Breath* 2014;18:111-7.
23. Valipour A. Gender-related differences in the obstructive sleep apnea syndrome. *Pneumologie* 2012;66:584-8.
24. Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. *Sleep medicine* 2008;9:675-83.
25. Wyrwick KW, Tierney WM, Babu AN, Kroenke K, Wolinsky FD. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40:577-91.
26. Vat S, Haba-Rubio J, Tafti M, Tobback N, Andries D, Heinzer R. Scoring criteria for portable monitor recordings: a comparison of four hypopnoea definitions in a population-based cohort. *Thorax* 2015;70:1047-53.
27. Ho V, Crainiceanu CM, Punjabi NM, Redline S, Gottlieb DJ. Calibration Model for Apnea-Hypopnea Indices: Impact of Alternative Criteria for Hypopneas. *Sleep* 2015;38:1887-92.

## 15. Protocol Versions

Version	Change
1.0	Original Version
2.0	<p>Section 10 (Questionnaires)</p> <ul style="list-style-type: none"> <li>• Addition of the EQ-5D questionnaire</li> </ul>
3.0	<p>Front page Change of trial statistician</p> <p>Section 5 (Study Methods) Clarification that AHI given by automatic scoring will be used for the primary and secondary outcomes, and that AHI given by review of the central scorer will be reported as a secondary outcome Update to text and trial figures to clarify this information</p> <p>Front of page 1 and Section 13.6 (Trial Steering Committee) Updated list of TSC members</p> <p>Section 5.7 (3 month visit) Participant weight to be collected at 3 month visit.</p> <p>Section 6 Clarification of central scorer</p> <p>Section 11 Updated sample size section with new estimation of required number of participants</p>
4.0	Weight added to section 5.7, this was omitted in error in the previous amendment
5.0	<p>Section 5.3 (Home Sleep Test Scoring Review) and Section 6.1 (Study Responsibilities: Terms and Tasks) Clarification of the role of the expert Central Scorer and the review of the automated AASM 2012 scoring</p> <p>Page 1 and Section 13.6 (Trial Steering Committee) Updated list of TSC members</p>