Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to assess the effect on Health and Wellbeing in Older and Younger People.

Clinical Trial Protocol

Short Study Title/Acronym: The POSA Trial

REC Reference: 19/YH/0222 (Yorkshire and the Humber – South Yorkshire REC)
IRAS Reference: 252494

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Signature Page

The Chief Investigator (CI) and the Research Office have discussed and agreed this study protocol. The investigators agree to perform the investigations outlined in this study protocol and to abide by this protocol except in the case of medical emergency that will be notified to the Research Office.

The Investigator agrees to conduct the study in compliance with the study protocol and/or any subsequent amendments approved by the Sponsor and HRA, the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent as applicable), the Research Governance Framework for Health & Social Care, 2nd Edition (2005), the Sponsor's SOPs, and any other applicable regulatory requirements.

This protocol has been written in accordance with the Sponsor's guidance for writing non-CTIMP protocols.

Dr Julia Kelly

POSA

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1. LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AE	Adverse Event
AHI	Apnoea-hypopnoea Index
AR	Adverse Reaction
BMI	Body Mass Index
CE	Conformité Européene (a symbol applied to products to indicate that they conform with relevant EU directives regarding health and safety or environmental protection)
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019 pandemic
CPAP	Continuous positive airway pressure
CRF	Case Report Form
ESS	Epworth Sleepiness Scale
EQ-5D	EuroQol 5D
EU	European Union
FOSQ	Functional Outcomes of Sleep Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
ID	Identification
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised
mCTA	Model Clinical Trial Agreement
NHS R&D	National Health Service Research & Development
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
ORTU	Oxford Respiratory Trials Unit
OSA	Obstructive sleep apnoea
PI	Principal Investigator
PIS	Participant Information Sheet
POSA	Positional obstructive sleep apnoea
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QALY	Quality Adjusted Life Years
RBHT	Royal Brompton and Harefield Trust (NHS Foundation Trust)

RCT	Randomised Control Trial
RDS	Research Design Service
REC	Research Ethics Committee
RRAMP	Risk Assessment and Monitoring Plan
SAE	Serious Adverse Event
SATA	Sleep Apnoea Trust Association (UK OSA patient charity)
SDV	Source Document Verification
SF-36	Short Form 36
SOG	Safety Oversight Group
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USA	United States of America
VAS	Visual Analogue Scale

2. STUDY PERSONNEL AND FACILITIES

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3. STUDY SYNOPSIS

Full study title:	Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to assess the effect on Health and Wellbeing in Older and Younger People.
Short study title:	The POSA Trial
Chief Investigator:	Dr Julia Kelly
Medical condition/disease under investigation:	Positional obstructive sleep apnoea (POSA)
Study duration:	45 Months
Primary Objective:	• To determine the change in OSA severity, defined by final AHI (adjusted for baseline AHI) 3 months post Positional Therapy in patients with positional OSA, compared to Sham-Positional Therapy
Secondary Objective:	• To determine the difference in treatment effect between older (≥65 years) and younger patients • To determine the change in quality of life and symptoms of OSA, from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients • To determine the change in sleeping position and objective sleep-disordered breathing from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients • To compare treatment adherence and comfort in older compared to younger subjects • To determine the partner/ carers' perspectives of positional therapy • To investigate the cost-consequences of positional therapy in patients with positional OSA, compared to Sham-Positional Therapy • In a RBHT subgroup; to determine the change in sleep quality and efficiency, including arousals and awakenings
Study population:	Patients with positional OSA will be invited to take part through the UK Respiratory Sleep Research Network when attending their local service for investigation and treatment of OSA. Using data from our clinics we estimate that approximately 25% of patients with OSA will be eligible for the study.
Recruitment Target	n=104. We will recruit 116 patients, powered to detect superiority of Positional Therapy compared to Sham at 80% power and 5% significance level, assuming within-group standard deviation of 9.05 events/hour, accounting for a 10% drop-out rate.
Recruitment Window (Months)	45 months; Recruitment rate approximately 6 patients/month, across 4-8 centres equals 35 months. Follow-up is 3 months (+/- 7 days). Analysis and reporting 3 months
Methodology:	Prospective, randomised, double-blinded parallel trial; Patients with POSA will be randomized to receive either Positional Therapy or Sham-Positional Therapy for 3 months
Eligibility criteria:	***Inclusion criteria:*** • Aged ≥18

	• Ability and willingness to provide informed consent • AHI >5 events/hour (AASM 2012 scoring criteria) with events occurring at a frequency of 2:1 when supine, compared to non-supine; total % supine sleep >10, <90% of total sleep; respiratory events predominantly obstructive; recording of ≥4 hours of analysable signals • Ability to fit and tolerate wearing the device around the neck during treatment demonstration and initiation
	Exclusion criteria: • Unstable cardiac disease • Cardiac arrhythmia corrected with an artificial pacemaker • Supplemental oxygen • Secondary sleep pathology e.g. Periodic Limb Movement Syndrome, Narcolepsy, Circadian Disorder, Obesity Hypoventilation Syndrome; or shift workers • Concerns about sleepy driving or any other potentially dangerous symptom from physician • BMI ≥40Kg/m^2 • Inability to sleep in a non-supine position • Skin sensitivity or an open wound around neck • Neck circumference <12inches (30cm) or > 22inches (55cm) • Tics or tremors of the head • Sleep with head in upright position • A female of child-bearing potential that is pregnant or intends to become pregnant

Study treatment:

Patients with OSA will be randomised to receive either Positional Therapy or Sham-Positional Therapy for 3 months.

The Positional Therapy will be delivered by the **Night Shift™ Sleep Positioner:** (Advanced Brain Monitoring, USA) which has been developed for adult patients with positional OSA and snorers. Worn on the back of the neck, it begins to vibrate when the patient starts to sleep in the supine position and increases in intensity until the patient changes position. An internet-based Report Portal enables monitoring of the adherence and effectiveness of therapy with detailed data, including nights used, number of supine attempts, and number and intensity of successful feedback attempts, sleep/wake behavioural data, sleep efficiency, sleep position and snoring. The Night Shift™ device and computer software to be used in this trial are commercially available, CE marked, and appropriately encrypted and protected.

4. INTRODUCTION

4.1 BACKGROUND

Obstructive sleep apnoea (OSA) is a common condition affecting approximately 10% of all middle-aged males; rising to over 30% in older people(1). Older people of both genders are particularly susceptible to OSA, due to age-related changes in the pharyngeal airway(2-5). In both older and younger people OSA causes brief episodes of pharyngeal airway narrowing or closure, resulting in frequent dips in oxygen saturation and fragmented sleep. Many patients with OSA experience profound daytime sleepiness, fatigue, and cognitive dysfunction making them more prone to accidents when driving, as well as increasing risk of cardiovascular morbidity. Additionally, in older people, OSA contributes to general frailty(6) and cognitive impairment.

NICE guidelines recommend continuous positive airway pressure (CPAP) treatment for moderate and severe OSA. CPAP is a continuous positive pressure of air applied to the pharynx, generated by a small machine that is connected to the patient by a mask on the face. The air acts as a pneumatic splint to maintain airway patency. Our NIHR HTA trial (ISRCTN:90464927) extended the evidence-base for beneficial use of CPAP into older people. In OSA patients 65 years and over, CPAP reduced sleepiness, improved quality of life and was marginally more cost-effective than conservative treatment over 12 months(7, 8).

Despite the proven benefits of CPAP, up to one third of patients find using it burdensome, and adherence to treatment is generally low(9), especially in older patients(10). In UK RCTs, CPAP adherence levels have been low; 2.3-3.5 hours/night(11), falling to 1.5hrs/night in patients 65 years and older(7). Patients frequently ask for alternative treatments that are less cumbersome(12).

Positional therapy is an alternative method of preventing the pharyngeal airway from collapsing during sleep. It is especially useful for people who find breathing difficult when sleeping supine, this is called **positional OSA (POSA)(13)**. It occurs because the pharyngeal airway is more likely to collapse during supine-sleep due to gravitational forces pushing the tongue backwards and the increased soft-tissue pressure. Moreover, functional residual lung capacity is reduced, leading to reduced caudal traction effect, thereby increasing pharyngeal compliance and hence collapsibility(14). Remarkably, positional OSA seems to be exacerbated in older patients probably because their pharyngeal airway is more compliant(2). Traditional positional therapy prevents supine sleep using physical deterrents such as pillows or tennis balls behind the back, but can be uncomfortable, ineffective and poorly tolerated. New generation positional therapy works by using vibro-tactile feedback, applied to either the neck or chest, which vibrates when the patient attempts to sleep in the supine position thereby making them turn over. To our knowledge there have been few controlled studies of vibro-tactile positional therapy, and none that have included older people. It is possible that the positional therapy could work better in older patients who have a more compliant pharyngeal airway that is potentially more responsive to position change. On the other hand, the vibration feedback could disturb their sleep more, be awkward to use or older people could be less able to turn over in bed. **We want to determine whether a reduction in supine sleep**

time, leads to clinically important reductions in OSA severity and improved daytime symptoms for both older and younger patients, and if the treatment effects are similar.

OSA contributes to co-morbidities that are commoner in older people: The strength of the pharyngeal muscles and the genioglossus negative pressure reflex are reduced in older people(4). The size of the upper airway lumen is also decreased(4, 15) leading to an increase in pharyngeal resistance, independent of body mass index in older people(3). These physiological changes contribute to the increased prevalence of OSA in older people(16). Co-morbidities and their associated polypharmacy are also increased in older people with OSA. E.g it is estimated that both obstructive and central sleep apnoea are common in patients with chronic heart failure(17) and older people with atrial fibrillation(18). Moreover, it is becoming increasingly apparent that OSA is associated with cognitive decline, including poor memory and reduced executive functioning(19-22). OSA severity has recently been linked with an increased amyloid burden over a 2-year follow-up period(22). Depression, impaired social function, and nocturia(20, 23) are also issues that adversely affect older people, for which OSA may offer a modifiable factor. Additionally, for patients who are housebound, or have reduced mobility, OSA-related risks include repeated falls(24) or accidents within the home, which are also hallmarks of frailty. These can further increase patients' dependency levels.

Treatment of OSA has been shown to improve morbidities, such as hypertension, stroke, low mood and accident rates(25) in patients with OSA. Nevertheless, traditional CPAP treatment may add further complexity to the burden of aging as well as increasing NHS costs. **We postulate that effective treatment of OSA in a subset of patients with a simpler, better tolerated and cheaper device could more effectively reduce co-morbidity in older people that promotes health, particularly with respect to blood pressure, cardiovascular and cerebrovascular effects as well as mental and physical health.**

The economic impact of treatment: The 2008 NICE Health Technology Appraisal concluded that in middle-aged people, CPAP was effective and highly cost-efficient at <£4,000 per QALY gained; owing to changes in sleepiness, quality of life, vascular risk and driving performance(25). Research from our group has found CPAP is also a cost-effective treatment for older OSA patients(7, 8). However, despite these findings UK commissioning groups have been faced with the task of streamlining access to CPAP, due to overwhelming needs, compared to prior NICE estimates. E.g. in Bristol, North Somerset and South Gloucestershire the cost of issuing CPAP machines in 2016/17 was over £1 million, more than ten times the estimated cost and activity levels. **New proposals recommend that OSA patients should be able to access CPAP treatment where appropriate, but greater emphasis should be attached to other management treatment options, earlier in their care pathway.**

Enhanced treatment tolerability and adherence: Although CPAP is an effective treatment, it can be burdensome and difficult to tolerate. Our patients frequently ask about other, simpler treatments. In those who are prescribed CPAP the nightly usage is often less than 3 hours/night(7, 11), with older patients showing even lower levels of CPAP use(10). Up to 30% of patients prescribed CPAP do not use the machine 2 years after therapy initiation(26). This low usage and high rejection rate wastes resources. Indeed, during our trial we realised that some older patients with multiple co-morbidities

found CPAP treatment particularly challenging. Age-related conditions including frailty, dyspnoea associated with heart failure or respiratory disease, frequent nocturia, skin fragility, diminished fine motor control and neurocognitive dysfunction, all adversely affected CPAP tolerance. **Alternative, more acceptable treatments for OSA are urgently needed.**

4.2 PRE-CLINICAL DATA/CLINICAL DATA

Traditional positional therapy includes methods to stop patients sleeping supine, such as positional pillows, and tennis balls attached to the back of sleepwear. A meta-analysis, carried out in 2014, compared positional therapy to CPAP in 71 patients with positional OSA. CPAP treatment was found to be superior to positional therapy in reducing the severity of OSA(27). A more recent systematic review and meta-analysis, comparing traditional positional therapy to either no treatment or to CPAP treatment, only included randomised studies(28). Positional therapy was found to reduce OSA, although less than the changed that occurred with CPAP; however, long-term compliance was often low due to discomfort and sleep disruption.

New generation positional therapy provides vibro-tactile feedback to deter patients from sleeping in the supine position. A small device, worn either on the back of the neck or chest, vibrates to induce a positional change. A short-term, prospective study in 30 patients wearing neck positional therapy, found 4 weeks of treatment reduced the severity of OSA (measured by the apnoea-hypopnoea index: AHI) by more than half; from mean(SD) 24.7(14.7) to 7.5(7.7) events an hour ($p<0.00001$)(29). Subsequent data in 135 patients showed good adherence with >4 hours usage for over 70% of the nights(30). Positional therapy devices have also been compared to another non-CPAP therapy for OSA; mandibular advancement splint therapy. Positional therapy was as good as the mandibular advancement splint therapy, and improvements were maintained over 12 months with good adherence to both therapies(31). However, it should be noted that mandibular advancement splint therapy can be limited in its application due to reliance on good dental health. A systematic review and meta-analysis of positional therapy, carried out in 2017, included both prospective cohort studies and randomised trials of new generation devices(32). The vibro-tactile positional therapy devices were effective in reducing the severity of OSA in younger patients and short-term compliance (3-4 weeks) was high. **In older patients, the pathophysiology, co-morbid and symptom profile of both sleep and OSA differs from that which occurs in younger patients, which may lead to differences in their ability to tolerate and respond to positional therapy. These factors have not yet been investigated**.

Currently in the market there are 2 main vibrational positional therapy devices which apply vibration feedback (in response to a change in position) to different areas; the chest (Sleep Position Trainer™, Night Balance) and the neck (Night Shift™, Advanced Brain Monitoring). We believe that while they both use similar technology, there may be significant differences in the likelihood to cause arousal. The gentle noise associated with vibration on the neck, near to the ear, may add to the success of inducing movement, as multi-modality sensory stimulation is more effective than single modality(25). When selecting our monitor, we reasoned that the chest strap may be less effective as it is sited in a less sensitive area with less dense vibration receptors, and it may work less efficiently in patients with obesity, and trunk adipose tissue. For these reasons, we believe that there is

advantage to be gained by investigations of different devices; this information will be important for patients and clinicians when selecting devices.

The chest-worn device, Night Balance Luona Sleep Position Trainer™, is currently being investigated in a multi-centre (UK and Netherlands) randomised cross-over study with the Position Trainer being compared to CPAP in 200 patients with POSA (ClinialTrials.gov Identifier: NCT03061071). Efficacy, assessed by the change in AHI, and the adherence to therapy will be compared after 3 months of each treatment. Symptoms, Quality of Life, and cost-effectiveness will also be assessed. However, patients will be included if they are CPAP naïve or if they are CPAP non-adherent (<3 hours/night). Patient eligibility is also based on an overall AHI >15 and a lateral AHI <10 events/hour. Compared to our study, the patients will have more moderate to severe disease that is 'corrected' when keeping the patient off their backs in the lateral position. The inclusion of non-adherent CPAP users may also introduce bias towards the positional device. There are also other ongoing trials also comparing various devices to CPAP eg: BuzzPOD supine avoidance device (ACTRN12613001242718, Australia).

There are two ongoing trials using vibration to the neck via the NightShift™ device. The first trial, being conducted in Hong Kong is 'A Crossover Case Control Study Using the NightShift™ Vibration Positional Device for Treatment of Position Dependent Obstructive Sleep Apnoea' (NCT02613975). The investigators are focusing on 2 groups of patients; 1) those who refuse CPAP or tolerate CPAP poorly and 2) those who are using dental devices, but with poor tolerance or treatment response. In the proposed study we plan to recruit CPAP naïve patients, since those who have already refused CPAP or been intolerant, might represent a group of patients with complex issues that may be resistant to any intervention- this is a separate question that we know our patients would like us to answer in another study. We are aiming to recruit all patients with positional OSA, including patients who are using CPAP well, but might be looking for an alternative, less burdensome therapy. The trial in Hong Kong also differs from ours in that it uses a crossover case control design, where each patient will experience the vibrational device switched on, and switched off, for 15 days each, with a one-week washout period in between. It is our opinion that it will be harder to 'blind' the patients to the therapy if they experience it in both modes. The short duration of only 15 days in the Hong Kong Trial (15 days) in a small sample size of 40 patients will provide a useful and necessary 'proof of concept' for use of positional devices in a challenging patient group who have not tolerated other therapies, but not provide definitive evidence to guide clinical practice. Our trial will recruit and follow up 138 patients over 3 months.

The second trial, being conducted in Singapore, is also a crossover trial comparing the NightShift™ Vibrational Positional Therapy Device to CPAP for Treatment of Positional Obstructive Sleep Apnea (NCT03125512). The primary outcome is the difference in sleepiness measured by the Epworth Sleepiness Scale (ESS) after 8 weeks of device use. However, the investigators are only including a sub-set of patients who are considered excessively sleepy (ESS 10-16), and these patients are therefore more likely to experience symptomatic improvement. This trial differs from the proposed trial because we plan to recruit all patients with positional sleep apnoea, regardless of their baseline symptoms. We have chosen this approach as we have previously shown that minimally symptomatic OSA patients experience an improvement in their quality of life, with a reduction in ESS and an

increase in their energy and vitality when treated with CPAP(11); specifically, 71% of minimally symptomatic OSA patients went on to continue their CPAP therapy after the trial.

Neither of the trials using the Night Shift™ device are being conducted in the UK, therefore they are not entirely relevant to the pragmatic treatment approach that we use for OSA in the NHS. In addition, we know that the risk of OSA in far eastern races has a greater contribution from cranio-facial differences, rather than obesity(33, 34). Additionally, it is our aim to determine the effectiveness of the NightShift™ Vibrational Positional Device in older as well as younger patients, including males and females. The efficacy might differ with age due to anatomical and physiological differences, as well as sleep quality and symptomatology. Also, the tolerance of the therapy may also differ with age.

Patient and Public Involvement: The trial has also been informed by our collaboration with the patient charity, Sleep Apnoea Association Trust (SATA). Their members have generously given us their views on the Positional Device Therapy via an online survey. The trust has 1402 members and the email was sent to 1237 (165 are postal only). A total of 496 (35%) members completed the survey. We found that 98% thought that The Royal Brompton and Harefield NHS Foundation Trust and the Oxford University Hospitals NHS Foundation Trust should test the device. Of those that answered, 72% would be willing to try the device if it was offered to them as a treatment. A selection of patient quotes:

- 'Anything that helps sleep apnoea and avoids the use of a CPAP machine must be worth investigating.'
- 'It could be used without CPAP, and would be a quieter, cheaper alternative if it works.'
- 'Before starting CPAP, I (and my wife) found sleeping on my side helpful. My awoken wife would nudge me to get me off my back and she could then sleep. Presumably when not snoring, my apnoea episodes were also reduced.'
- 'Anything that helps patients to get a good sleep is worth looking at, especially if they are small inexpensive items and fairly non-intrusive'.

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

Study Rationale: The initial premise for this study was borne out of our clinical experience, because patients in our clinics constantly request 'other' treatment options, compared to the gold standard CPAP therapy: "Anything is better than a CPAP machine!". OSA patients across a range of disease severity, socio-economic status and UK location are keen to have new therapeutic options, even those who are treated and well-controlled on CPAP therapy. This study also fits with directives from commissioning groups to put greater emphasis on other treatment options and earlier treatment. Moreover, many patients have told us that positional therapy is an appealing, less burdensome therapy.

Anticipated Clinical Benefit: Patients may experience a reduction in the severity of their OSA, and therefore their symptoms and quality of life based on treatment of their OSA.

Risk Analysis: The device used in this study is a commercial Positional Therapy device for the treatment of POSA in adults - The Night Shift™ Sleep Positioner: (Advanced Brain Monitoring, USA). There are no major side effects reported. In a previous study of the Night Shift™ device for prescription use, both brief arousals, as well as awakenings, were significantly reduced because patients slept more deeply. Users recalled position avoidance therapy on average twice per night, yet they attempted to sleep supine on average seven times per night (29). Positional Therapy is known to be a safe treatment that is well tolerated with very few side effects. Occasionally patients have reported discomfort in the neck or shoulders as a result of the vibration, or from having to sleep in a new position (30). There are no residual investigational device risks.

Due to patients being randomised to the Sham-Positional Therapy, they will wait three months before access to usual standard care treatment. This delay is deemed acceptable as many patients would wait this long for treatment, including CPAP, through the normal NHS pathway. Additionally, patients would not be offered positional therapy in their local clinics as the Night Shift™ Positional Therapy device is not a treatment funded by the NHS. Patients who pose a risk to others through excessive sleepiness and/or concerns by the physician about sleepy driving will excluded, since these patients are likely to receive fast-track CPAP through their local clinic. There are no other identified risks associated with study participation.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

Enrolment is voluntary; patients are free to withdraw at any time and will continue to be treated by their local service. Any related serious adverse events will be reported and reviewed according to GCP standards. There are no major identified risks associated with study participation. This study uses CE marked commercially available products within their intended use.

The patients in the sham arm may experience ongoing sleepiness for the duration of the trial, however this length of time (3 months) is considered acceptable for the reasons stated in 4.3.

5. STUDY OBJECTIVES

This proposal will answer three questions:

Does Positional Therapy over three months reduce disease severity in patients with positional OSA?

Is there any difference in treatment effect of Positional Therapy between older (≥65 years) and younger patients?

Does Positional Therapy over three months reduce daytime sleepiness and improve quality of life in older and younger patients?

The aim of this trial is to determine whether Positional Therapy, applied by a discrete neck-worn vibrotactile feedback device, is an effective treatment for patients with positional OSA, in reducing the severity of OSA and the associated daytime symptoms, compared to Sham-Positional Therapy.

We will also measure the interaction between treatment and age group, since pathophysiology and treatment tolerance varies with age.

Hypothesis: We hypothesise that the Positional Therapy device will reduce the severity of OSA, compared to Sham-Positional Therapy, in patients with positional OSA. Additionally, the efficacy may be influenced by age.

5.1 PRIMARY OBJECTIVE

To determine the change in OSA severity, defined by final AHI (adjusted for baseline AHI) 3 months post Positional Therapy in patients with positional OSA, compared to Sham-Positional Therapy.

5.2 SECONDARY OBJECTIVES

- To determine the difference in treatment effect between older (≥65 years) and younger patients
- To determine the change in quality of life and symptoms of OSA, from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients
- To determine the change in sleeping position and objective sleep-disordered breathing from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients
- To compare treatment adherence and comfort in older (≥65 years) compared to younger subjects
- To determine the partner/ carers' perspectives of positional therapy
- To investigate the cost-consequences of positional therapy in patients with positional OSA, compared to Sham-Positional Therapy
- In a RBHT subgroup; to determine the change in sleep quality and efficiency, including arousals and awakenings

	Objective	Outcome Measure	Timepoint		
			Baseline	Follow-up (4 days)	Follow-up (3 months)
Primary	• To determine the change in OSA severity, defined by final AHI (adjusted for baseline AHI) 3 months post Positional Therapy in patients with positional OSA, compared to Sham-Positional Therapy.	**Sleep Study Data (Apnealink Air):** • Apnoea hypopnoea index (AHI)	x		x
Secondary	• To determine the difference in treatment effect between older (≥65 years) and younger patients	**Sleep Study Data (Apnealink Air):** • Apnoea hypopnoea index (AHI)	x		x
	• To determine the change in quality of life and symptoms of OSA, from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients	**Questionnaires:** • Epworth Sleepiness Scale (ESS) • Functional Outcomes of Sleep Questionnaire (FOSQ) • Hospital, Anxiety & Depression Scale • Independent Functioning (Townsend Disability Scale) • ShortForm-36 (specifically Energy & Vitality) • Pittsburgh Sleep Quality Index (PSQI)	x		x

	• To determine the change in sleeping position and objective sleep-disordered breathing from baseline (pre-treatment) to 3 months post positional therapy in patients with positional OSA, compared to Sham-Positional Therapy, in older compared to younger patients	**Sleep Study Data (Apnealink Air):** • supine AHI • Oxygen desaturation index (ODI) • Overnight average oxygen saturation (SaO2) • % time with $SaO_2 \leq 90\%$ **Positional Therapy Data (Night Shift device):** • Number of supine attempts • Number of feedback events • % sleep time in supine • % sleep time snoring >50dB • Derived data: Sleep efficiency, Wake after sleep onset (WASO), awakenings per hour	x		x
	• To compare treatment adherence and comfort in older (≥65 years) compared to younger subjects	**Positional Therapy Data (Night Shift device):** • % nights used • Average hours used per night **Questionnaires:** • Positional Therapy Questionnaire & Visual Analogue Scale		x	x
	• To determine the partner/ carers' perspectives of positional therapy	**Questionnaires:** • Pittsburgh Sleep Quality Index (PSQI) • Positional Therapy Questionnaire & Visual Analogue Scale	x		x

	• To investigate the cost-consequences of positional therapy in patients with positional OSA, compared to Sham-Positional Therapy	**Questionnaires:** • Healthcare Utilisation Questionnaire • EuroQol EQ-5D	x		x
	• In a RBHT subgroup; to determine the change in sleep quality and efficiency, including arousals and awakenings	**Full Polysomnography sleep data and Subjective Sleep Report** • Sleep quality and efficiency • Arousals and awakenings	x		x

6. STUDY DESIGN

6.1 OVERALL DESIGN

This is an academic led, non-commercial trial which has been collaboratively designed with our trial statistician Mr Roger Newson (BSc MSc DPhil) and independently verified by the London Research Design Service.

The trial is a prospective, randomised, parallel, double-blinded trial comparing Positional Therapy (Night Shift™; Advanced Brain Monitoring, USA) with Sham-Positional Therapy, performed in older (≥65 years) and younger patients (18 – <65 years). All patients will wear the Night Shift™ device, however they will be randomised to either active mode ('TRIAL') or monitor-only mode ('MONITOR'). The trial will be analysed as 2x2 factorial; the comparison of primary interest is between patients of all ages randomised to the active treatment and patients of all ages allocated to the sham treatment, and that the old-young comparison is a matter of secondary analysis.

Adult patients with positional OSA (apnoea/hypopnea index (AHI)>5 events/hour, 2:1 when supine versus non-supine) will be recruited from centres in the UK Respiratory Sleep Research Network and randomised, minimising for age group, and OSA severity. OSA will be measured by a home study (Apnealink Air; ResMed, Australia). Patients' subjective symptoms, wellbeing and quality of life, will be assessed by questionnaires at baseline and 3 months. Partners or carers' perspective will also be captured by the Pittsburgh questionnaire. OSA treatment has been shown to improve both older and younger OSA patients' quality of life. However, their partners often also notice benefits beyond those that the patients report themselves, such as improved sleep quality, mood lability, memory and daytime functioning. Bed partners of patients with OSA also experience benefits to their own sleep quality and daytime functioning(35, 36). Improvements in relationships have also been reported(36). Adherence to therapy will also be measured by the NightShift™ device.

The primary endpoint, AHI at 3 months, will be measured by a repeat study with the device *in situ*, and compared between Positional Therapy and Sham-Positional Therapy. Analysis will be by regression of the final AHI with respect to treatment, adjusting for the baseline minimisation variables. Secondary analysis will be the interaction between the treatment effect and age. Basic health economic data and cost-consequences of Positional Therapy will also be presented.

A sample size of 104 is required to detect a clinically important treatment difference (AHI of 5 events/hour at 3 months). We will recruit 116 patients, powered to detect superiority of Positional Therapy compared to Sham at 80% power and 5% significance level, assuming within-group standard deviation of 9.05 events/hour, accounting for a 10% drop-out rate.

Study Flow:

Patients with a new diagnosis of positional OSA will be randomized to receive either Positional Therapy or Sham-Positional Therapy for 3 months (See Study Flowchart; Section 6.3)

Screening: Patients attending their local sleep service with suspected OSA, will be considered for this study. Potential participants will be identified by the clinical team who will discuss the trial with the

patient either face-to-face (during a routine clinical care visit) or remotely eg: phone/ videoconference or email (as per local clinical guidelines). During face-to-face contact, *written consent* will be obtained. Where contact is remote, a participant information sheet will be posted or emailed to the patient, along with a consent form. Designated researchers or PIs will contact patients to further discuss the trial and to *verbally consent* the patient. *Written consent* will be obtained at a later stage with the baseline data collection, either remotely via email/post or face-to-face.

Patients will be screened using the using a home sleep study (Apnealink Air; ResMed, Australia). The patient will receive the Apnoealink with instructions for use, and baseline questionnaires (see Basline Visit) in line with local clinical procedures; either by post or pick-up from a safe location at the hospital. The patient will undertake a *home sleep study* (ApneaLink) (or if patient has previous Apnoealink sleep data from a prior sleep study within 3 months, this data will be used instead). 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, until a "green light" suggests > 4 hours of meaningful data has been recorded. The participant will also complete the baseline questionnaires. Patients will return their Apnealink Air and the questionnaires to the sleep clinic in line with the local clinical procedures (eg: reply paid envelope or drop-off).

The participant's sleep study data collected by the ApneaLink Air will either be uploaded to the Trial Airview account labelled only by the participant's study number, or an Airview pdf report (labelled only by their study ID) from the site's local Airview account will be saved, scanned and emailed to the central site to add to Trial Airview data. For sites with an alternative first-line sleep monitoring device, consent will be sought before providing the trial specific ApneaLink Air home sleep study to patients with suspected positional OSA.

At this stage, some patients' sleep study data will be ineligible (ie. They will not have positional OSA). In these cases, the patient may repeat the sleep study (we expect there to be night-to-night variability). If the patient declines a repeat study or the sleep study data remains ineligible, the patient will be ineligible to continue the trial. Any questionnaire data collected as part of the screening process will not be used in any analysis and be confidentially destroyed.

All trial equipment will be cleaned in-line with local COVID-19 cleaning procedures.

Baseline Visit: Participants will be invited for a baseline visit within 3 months of their ApneaLink Air sleep study. The *baseline 'visit'* will be performed in line with local clinical procedures, either face-to-face or remotely. During face-to-face visits, participants will be given an opportunity to try the Night Shift™ device; including education on fitting and wearing, charging, and care. We have included a 10-minute run-in period where patients will self-fit the device, under instruction, and will experience the vibration sensation. The ability to tolerate the device during the run-in forms part of our study inclusion criteria. Participants may decline participation should they still have concerns about their use of the device.

Baseline demographics will be collected and a basic medical history.. Participants will be asked to complete a series of questionnaires on sleep quality, tiredness, energy, fatigue, mood and frailty, which will take 45-60 minutes to complete.

- Epworth Sleepiness Scale
- Functional Outcomes of Sleep Questionnaire (FOSQ: disease specific)
- Hospital, Anxiety and Depression Scale
- Independent Functioning (Townsend Disability Scale)
- ShortForm-36 (specifically Energy and Vitality)
- Healthcare Utilisation Questionnaire
- EuroQol EQ-5D
- Pittsburgh Sleep Quality Index (PSQI: to determine the partners' perspective)

For remote visits, participants will have already filled in these questionnaires at home and returned them with the sleep study kit. They will be quality checked for completeness and any queries will be discussed with the participant. For participants contacted remotely, they will also be asked to weigh themselves and report their neck circumference.

Participants will then be randomised to Positional Therapy or Sham-Positional Therapy using an online computer-generated randomisation schedule, with minimisation based on age group (18 - <65: ≥65 years), and OSA severity (AHI <20: ≥20 events/hr).

For remote visits, the participants will receive the NightShift™ device in the post with instructions for use. We will ask participants to phone the central Trial Sleep Therapist on receipt of their NightShift™ device to document Night One of therapy (as there is will be a delay between randomisation and start of treatment) and to discuss set-up and useage, including education on fitting and wearing, charging, and care.

The positional devices are labelled with a POSA trial asset number and are pre-set by an unblinded researcher in the trial management team to either ''TRIAL' (first night monitoring, vibration feedback from second night onwards) or 'MONITOR' (monitoring only, no vibration feedback) according to a random number sequence provided by ORTU. Only the device numbers will identify the allocation of each device. The trial management team will manage the delivery of appropriate devices to each site, determined by the randomisation system. Each site will receive a box of pre-programmed devices with specific device numbers. At randomisation, the online system will allocate a device number to the participant. The researcher will give the participant the device allocated to them without knowing the trial arm. There is no observable feature on the device that differentiates between modes, thus the participants and researchers/clinicians will remain blinded.

Participants will be asked to wear their device nightly and will be blinded to the study arm. Lack of vibration in the sham arm will be accepted because vibration is delivered when the participant is asleep, and then the device adapts feedback intensity to minimise awakenings, therefore participants are not always aware of the delivered vibrations. Approximately one third of our patients report being unaware of the nocturnal vibrational feedback. In a previous study of Night Shift for prescription use, both brief arousals, as well as awakenings, were significantly reduced because patients slept more deeply. Users recalled position avoidance therapy on average twice per night, yet they attempted to sleep supine on average seven times per night (29).

A subgroup of Royal Brompton and Harefield Trust (RBHT) participants will be asked to consider undertaking two extra home sleep studies, one prior to treatment and one on Positional Therapy (on a night during the last week of the three months on therapy) which will both be facilitated by a

researcher from the central site, RBHT. These studies will be a more detailed sleep study, polysomnography, which measures sleep, as well as breathing. They will also fill out a subjective sleep report on these two nights. These will be performed in the participants' own homes according to local RBHT post-COVID-19 clinical guidelines and may be done remotely.

Monitoring and follow-up: To ensure consistent follow-up all participants will be contacted after 4 nights (one-night monitoring, 3 nights on Positional Therapy or Sham) by a central blinded Trial Sleep Therapist to discuss their experiences and troubleshoot difficulties. The central Therapist will receive participant contact details by secure NHSmail from the site, with consent from the patient. Contact will be made by the participant's preferred method; phone, email or text. If the designated contact day falls on a weekend or Bank Holiday, the contact will be performed the next working day. If the contact attempt is unsuccessful, this will be recorded and the Therapist will continue to attempt contact at least twice a week, until successful contact is made.

Three-month follow-up: (90 days +/- 7 days) Participants in both arms will followed up by their local service for their follow-up visit. This *'visit'* will also be performed in line with local clinical procedures; either face-to-face or remotely. Prior to this visit, participants will be posted the home sleep study kit (ApneaLink Air) to perform a repeat home sleep study while wearing the Night Shift™ device, plus the baseline questionnaires to repeat. An additional Positional Therapy Questionnaire & Visual analogue scale (VAS) to assess the comfort and tolerance of device will also be included.Patients will return their Apnealink Air, the NightShift device and the questionnaires to the sleep clinic in line with the local clinical procedures (eg: reply paid envelope or drop-off).

At the follow-up 'visit', the sleep study data and the Positional Therapy data will be downloaded.
Sleep Study Data (Apnealink Air):

- Apnoea hypopnoea index (AHI); supine AHI
- Oxygen desaturation index (ODI)
- Overnight average oxygen saturation (SaO2)
- % time with $SaO_2 \leq 90\%$

Positional Therapy Data (Night Shift™ device):

- % nights used
- Average hours used per night
- Number of supine attempts
- Number of feedback events
- % sleep time in supine
- % sleep time snoring >50dB
- Derived data: Sleep efficiency, Wake after sleep onset (WASO), awakenings per hour

Participants will repeat the baseline questionnaires plus:

- Positional Therapy Questionnaire & Visual analogue scale (VAS) to assess the comfort and tolerance of device

In the RBHT subgroup, detailed polysomnography sleep study data (SomnoScreen device):

- Sleep Quality

- Sleep Efficiency
- Sleep Stages (Wake, Stage 1, Stage 2, Slow Wave Sleep and REM Sleep)
- Arousal indices; total, respiratory and vibration-related
- Awakenings

The patient's participation in the trial is then complete. Patients will revert to routine clinical care at their local centre. At this time, after completion of all trial related activities, the researcher and the patient will be unblinded. Patients who wish to continue the treatment will be permitted to keep the device (free of charge). Patients in the sham arm will also then have the opportunity to use the device in THERAPY mode and may also keep the device if they feel it is beneficial. The NightShift device will be given back to the patient either face-to-face or by post.

6.2 TREATMENT AND RATIONALE

Participant involvement: Study duration is expected to be 13 weeks for each participant; 1 week for sleep study testing and baseline visit, plus 12 weeks of 'therapy'; either Positional Therapy or Sham-Positional Therapy. A three-month treatment period is sufficient to show changes to quality of life with CPAP therapy, with improvements in subjective and objective measures observed after 8 weeks and 6 months respectively in patients with milder OSA (11, 37). We have assumed this will also be the case with Positional Therapy as there is no reason to suggest otherwise. We expect an improvement in supine sleep time, and therefore AHI, within only 1-2 nights of using the Nightshift™ device in therapy mode, however it may take a little longer for participants to become accustomed to wearing the device, and therefore accurately report any benefit. Furthermore, longer term follow-up of 12 months in our previous trial in older patients showed a maintenance of the initial improvements in quality of life that were observed at 3 months(7).

6.3 SCHEMATIC OF STUDY DESIGN

The POSA trial flowchart

Screening and Consent:

Consenting patients (verbal or written) will be screened at local sleep centre with home sleep test by ApneaLink Air; the home sleep test can be done instead of, or as well as, routine patient screening. If ApneaLink Air test does not form part of routine care, then consent should be taken before this. Otherwise consent will be sought after eligibility confirmed. Patient eligible for study entry based on home sleep test result (automated scoring of sleep study by AASM 2012 criteria); ApneaLink Air sleep study data uploaded to Trial Airview Account.
In line with local sleep service care pathways, consultations may be face-to-face or remote eg: phone.

Baseline - Visit One (within 3 months of ApneaLink Air sleep study):

- Eligibility checked (including tolerance of Positional Therapy Device; Night Shift™)
- Demographic data (height, weight, BMI, neck circumference) and basic medical history
- Baseline questionnaires (ESS, FOSQ, HADS, Townsend Disability Scale, SF-36, Healthcare Utilisation Questionnaire, EQ-5D, PSQI)- may be posted and completed prior to visit for remote consultations
- Double-blinded randomisation (minimisation by age, gender, BMI, AHI)
- Positional Therapy Device education (fitting, charging, cleaning, downloading)

***RBHT subgroup:** Consent; Additional home sleep test by Polysomnography before first night of therapy; Sleep Reports

Positional Therapy:

- Device set in **Therapy** mode
  - Night 1= monitor
  - Night 2 onwards = vibration feedback

Participant wears the Night Shift™ device nightly for 3 months

Sham-Positional Therapy:

- Device set in **Monitor** mode
  - Monitor only
  - No vibration feedback

4 Days (1 night monitoring, 3 nights therapy) - Sleep Therapist Phone Call:

- Review adherence
- Address questions regarding Positional therapy device treatment and troubleshoot issues

***RBHT subgroup:** At 3 months; additional home sleep test by Polysomnography using Positional Therapy device; Sleep Reports

3 months - Visit Two:

- Participant receives ApneaLink Air in the post to repeat home sleep test with the Positional Therapy Device in situ
- Repeat baseline questionnaires (plus Positional Therapy Questionnaire & VAS) & weight
- Download repeat ApneaLink Air Home Sleep Test to Trial Airview Account (AHI, ODI; %TST SpO_2<90%)
- Download Positional Therapy Device (Compliance data, hours and % nights used; average nightly supine attempts, % supine time, average nightly feedback attempts, average % time snoring >50dB)

Study Completion:

Participant returned to usual clinical care at local centre: If patient had Positional Therapy and wishes to continue, they will be offered to keep device. If participant had Sham-Positional Therapy, the device will be switched to Therapy mode to try and participants may also keep the device if it is beneficial.

*RBHT subgroup = Royal Brompton & Harefield NHS Foundation Trust sub-group ♦ESS=Epworth Sleepiness Scale; FOSQ =Functional Outcomes of Sleep Questionnaire; HADS=Hospital Anxiety and Depression Scale; VAS=Visual analogue scale; SF-36=Short Form-36; EQ-5D = EuroQol 5 Dimension; PSQI=Pittsburgh Sleep Quality Index; SpO_2=oxygen saturation; BMI=body mass index; AHI=apnoea-hypopnoea index; ODI=oxygen desaturation index; TST=total sleep time; dB=decibels

7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

Inclusion Criteria
Inclusion criteria: • Aged ≥18 • Ability and willingness to provide informed consent • AHI >5 events/hour (AASM 2012 scoring criteria) with events occurring at a frequency of 2:1 when supine, compared to non-supine; total % supine sleep >10, <90% of total sleep; respiratory events predominantly obstructive; recording of ≥4 hours of analysable signals • Ability to fit and tolerate wearing the device around the neck during treatment demonstration and initiation

7.2 EXCLUSION CRITERIA

Exclusion Criteria
• Unstable cardiac disease • Cardiac arrhythmia corrected with an artificial pacemaker • Supplemental oxygen • Secondary sleep pathology e.g. Periodic Limb Movement Syndrome, Narcolepsy, Circadian Disorder, Obesity Hypoventilation Syndrome, or shift work • Concerns about sleepy driving or any other potentially dangerous symptom from physician • BMI ≥40Kg/m^2 • Inability to sleep in a non-supine position • Skin sensitivity or an open wound around neck • Neck circumference <12inches (30cm) or > 22inches (55cm) • Tics or tremors of the head • Sleep with head in upright position • A female of child-bearing potential that is pregnant or intends to become pregnant

7.3 DISCONTINUATION/ WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

Participants have the right to withdraw from the study at any time, without giving a reason and without affecting the quality of their future medical care. Participants who withdraw will continue to be treated by their local sleep service for routine clinical care. The reason for withdrawal (if available) will be recorded in the CRF, as will the participant's wishes with respect to data already collected. Unless participants request otherwise, their data will be retained and will be included in the final study analysis.

In addition, the Investigator may withdraw a participant from the trial at any time if they consider it necessary to protect the patient's or others' wellbeing. If the participant is withdrawn due to an adverse event, the trial team will arrange for follow-up visits or telephone calls to monitor the adverse event until it has resolved or stabilised.

Patients may also discontinue use of their study device at any time should they wish. This does not constitute withdrawal from the study, and all study visits/calls will take place as planned.

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

8. SUBJECT/PATIENT RECRUITMENT PROCESS

Patient recruitment at a site will only commence once the *study* team has ensured that the following approval/essential documents are in place:

1. HRA approval,
2. REC Approval
3. Local Site Delegation of Duties and Signature Log is completed

All sites participating in the *study* will also be asked to provide a copy of the following:

1. Signed nMCTA
2. Confirmation of capacity and capability

All patients who wish to enter the study will be consented by the Chief Investigator (CI), Principal Investigator or someone else from the research team who is suitably qualified and delegated to do so.

Patients will be invited to take part through the UK Respiratory Sleep Research Network when attending their local service for screening for OSA. We estimate that approximately 4 -8 UK centres will participate.

Patients who visit a participating local sleep service for an overnight sleep test will be screened for the study by the direct healthcare team. Screening will involve the use of the Apnealink Air home sleep test. The Apnealink Air home sleep test can be performed instead of, or as well as, routine patient screening done at the local sleep service. If the Apnealink Air is not standard care, consent will be sought prior to the study.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Potential patients will first be approached by the direct care team at their local sleep service who will discuss the trial with the patient either face-to-face (during a routine clinical care visit) or remotely eg: phone/ videoconference or email (as per local clinical guidelines). Patients who have attended their local sleep service for obstructive sleep apnoea screening, and who have positional OSA, will be told about the study and given a written information sheet..Patients will have the opportunity to discuss the trial with their treating clinician, and/or the trial principal investigator if they prefer. Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI) and/or a delegated member of the research team as recorded on Sponsor's Delegation of Responsibilities Log. Where the consultation is remote, a participant information sheet will be posted or emailed to the patient, along with a consent form. Designated researchers or PIs will contact patients to further discuss the trial and to *verbally consent* the patient. *Written consent* will be obtained at a later stage with the baseline data collection, either remotely via email/post or face-to-face. Research staff will undertake Good Clinical Practice and consent training. Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating. Patients are encouraged to consider taking part, and discuss the trial with their physician, family, friends and whoever else they wish before making a decision.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group.

The Investigator or designee will explain that the patients are under no obligation to enter the study and that they can withdraw at any time during the study, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one filed in the Investigator Site File (ISF)).

For the RBHT subgroup, a separate written information sheet will be provided to these participants and consent for the additional two detailed home sleep studies will be obtained separately.

9.2 RANDOMISATION PROCEDURE

Patients will be randomised 1:1 (Positional Therapy or Sham-Positional Therapy) and will be performed using a bespoke web-based randomisation software package, with minimisation based

on age group (18 - <65: ≥65 years), and OSA severity (overall AHI <20 or ≥20 events/hr). All participating sites will have access to this online system.

The positional devices will be pre-programmed before arriving at sites to either ''TRIAL' (first night monitoring, vibration feedback from second night onwards) or 'MONITOR' (monitoring only, no vibration feedback) using an online portal by the sponsor, and sent to the sites. Each site will receive a box of pre-programmed devices with specific device numbers. At randomisation, the online system will allocate a device number to the participant. The researcher will give the participant the device allocated to them without knowing the trial arm. There is no observable feature on the device that differentiates between modes, thus the participants and researchers/clinicians will remain blinded, until after all trial activities are completed.

9.3 EMERGENCY UN-BLINDING

In the unlikely event of a SUSAR, then the ORTU will un-blind the participant's group for REC reporting. The Serial Numbers of the devices will be securely held at ORTU along with the device setting (MONITOR or THERAPY).

10. STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS

- Home polygraphy sleep study (Apnealink Air; ResMed, Australia) and upload to Airview
- Medical history, in particular, BMI, diagnosed sleep disorders and cardiac history
- Physician concern about sleepy driving or any other potentially dangerous symptom

10.2 BASELINE ASSESSMENTS

- Baseline demographic data (height, weight, BMI, neck circumference)
- Medical history
- Questionnaires (subjective, patient-administered)
    - Epworth Sleepiness Scale
    - Functional Outcomes of Sleep Questionnaire (FOSQ: disease specific)
    - Hospital, Anxiety and Depression Scale
    - Independent Functioning (Townsend Disability Scale)
    - ShortForm-36 (specifically Energy and Vitality)
    - Healthcare Utilisation Questionnaire
    - EuroQol EQ-5D
    - Pittsburgh Sleep Quality Index (PSQI)
- Positional Therapy (NightShift™) fitting, education, run-in

10.3 TREATMENT PROCEDURE

Participants with OSA will be randomised to receive either **Positional Therapy** or **Sham-Positional Therapy** for 3 months; both provided by the **Night Shift™** device (Advanced Brain Monitoring Ltd, USA).

Participants will be asked to wear their device nightly and will be blinded to the study arm. The devices will be pre-set to either **'TRIAL'** (first night monitoring, vibration feedback from second night onwards) or **'MONITOR'** (monitoring only, no vibration feedback).

10.4 SUBSEQUENT ASSESSMENTS

At Night One:

- For patients undergoing remote visits, the the participants will receive the NightShift™ device in the post with instructions for use. We will ask participants to phone the central Trial Sleep Therapist on receipt of their NightShift™ device to document Night One of therapy and to discuss set-up and useage.

At 4 Days:

- The central Trial Sleep Therapist will contact the participant by phone or email; to troubleshoot any issues with the Positional Therapy, encourage adherence to therapy and answer any questions the participant may have. This phone call/ email will be conducted by the Centralised Trial Sleep Therapist to ensure that all information given to participants is consistent.
- If the contact attempt is unsuccessful, this will be recorded and the Therapist will continue to attempt contact at least twice a week, until successful contact is made. If the participant is unable to be contacted after multiple attempts, the Trial Sleep Therapist will contact the participant's local sleep service and ask for assistance contacting the participant. If contact is still unsuccessful the participant will be withdrawn from the trial and deemed 'lost to follow-up'. Normal clinical care will resume, which may comprise the local clinician writing to the patient and GP.

At 3 months:

- Home polygraphy sleep study (Apnealink Air; ResMed, Australia) with the Night Shift™ device *in situ* (this will be posted to participant prior to their follow-up visit)
- Repeat demographics, weight, and medical history in last 3 months
- Repeat baseline questionnaires plus post-therapy questionnaires
    - Positional Therapy Questionnaire & VAS scale on tolerance and comfort
- Download sleep study data (Apnealink Air) and Positional Therapy data (Nightshift™)
- Refer participant back to routine clinical care at their local centre.
- Participants who wish to continue the treatment will be permitted to keep the device.
- Participants in the sham arm will also then have the opportunity to use the device (the device will be switched from MONITOR to THERAPY).

In a subgroup from Royal Brompton and Harefield NHS Trust
At baseline and at 3 months:

- Home polysomnography sleep studies (SOMNOscreen; SOMNOmedics GmbH and Co., Germany) will also be performed before device therapy and on therapy with the Night Shift™ device *in situ.* These will be performed in the participant's home with their consent, by an experienced researcher from the Royal Brompton and Harefield NHS Trust working by a Lone Worker Trial Specific Procedure.
- Participants will also complete two short reports about their sleep on the night prior to the sleep study and on the morning following the sleep study.

10.5 SUMMARY CHART OF STUDY ASSESSMENTS

Study Procedures	**Screening**	**Baseline – Visit 1**	**Follow up** *(4 days)*	**Ongoing support** *(prn)*	**Follow up** (*3 months*)
Informed Participant Consent	x				
Inclusion/exclusion criteria	x	x			
Home Sleep Study (Apnealink Air)	x				x
Medical history		x			
Demographics		x			x
Questionnaires		x			x
Positional Therapy run-in		x			
Positional Therapy initiation & education		x			
Central Sleep Therapist 4-day phone call			x		
Central Sleep Therapist support available				x	
Post-therapy Questionnaires					x
Partner/ Carer Questionnaire					x
Safety reporting			x	x	x
RB&HT Subgroup:					
Informed Participant Consent		x			
Home Sleep Study (Somnoscreen)		x			x
Sleep reports		x			x

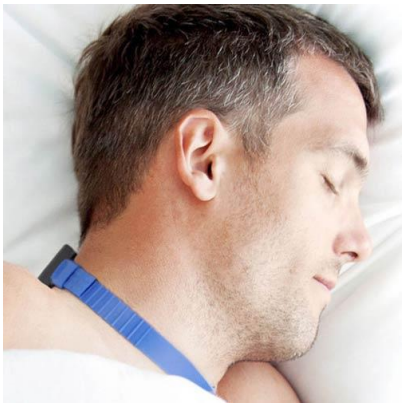
11. METHODS

11.1 Medical Devices and Tools

- **Night Shift™ Sleep Positioner**:

The Night Shift™ Sleep Positioner (Advanced Brain Monitoring, USA) has been developed for adult patients with positional OSA, and snorers. Worn on the back of the neck, it begins to vibrate when the patient starts to sleep in the supine position and increases in intensity until the patient changes.

The Night Shift™ device and computer software to be used in this trial are commercially available, CE marked, and appropriately encrypted and protected. An internet-based Report Portal enables monitoring of the adherence and effectiveness of therapy with detailed data, including nights used, number of supine attempts, and number and intensity of successful feedback attempts, sleep/wake behavioural data, sleep efficiency, sleep position and snoring. Adherence to CPAP therapy (i.e. nightly usage >4 hours/night) is required to produce quality of life improvements, with greater usage associated with increased benefits(17). We will investigate whether this level of adherence can be extrapolated to positional therapy, and also explore the adherence and efficacy between older and younger patients.



- **The ApneaLink Air**

Portable Home Sleep Testing devices are widely used, and well validated in the screening and diagnosis of sleep apnea. The ApneaLink Air device (ResMed) is a commercially available, sleep study device which is small, simple to use and can be used in the home. Many sleep services in the UK already use the ApneaLink Air for routine screening. It contains software which allows for the scoring of apnoeas, 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.

The ApneaLink Air, and AirView 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.

The device will be downloaded and automatically scored using the electronic software (Airview). 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.

For a subgroup of patients from the Royal Brompton and Harefield Hospitals, full overnight **Polysomnography (PSG)** will be used in addition to the ApneaLink Air to measure sleep, as well as breathing events:

- **SOMNOscreen – Portable PSG**

Similar to the Apnoealink Air, this sleep test measures heart rate or electrocardiography (ECG) and breathing using respiratory airflow, respiratory effort and pulse oximetry. However, the portable PSG kit (SOMNOscreen; SOMNOmedics GmbH and Co., Germany) will also measure sleep, by using brain activity or electro-enchephalography (EEG), eye movements or electo-occulography (EOG) and muscle activity or electro-myography (EMG).

- ***Questionnaires:***

We wish to determine the effects of positional therapy over time from the patients' perspective using questionnaires that are valid and sensitive to changes in wellbeing, such as sleep quality, daytime physical functioning as well as societal interactions; all of which contribute to an older person's sense of well-being and independent functioning. We are using a battery of questionnaires that assess both the patients' and the carers' perspectives on the effects of the therapy.

  - **Epworth Sleepiness Scale**:

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(38). New generation positional therapy in younger people has produced beneficial changes in Epworth Sleepiness Scale scores and Functional Outcomes of Sleep Quality(38, 40).

- **Functional Outcomes of Sleep Questionnaire (FOSQ: disease specific)**

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(39). The FOSQ includes five subscales: activity level; vigilance; intimacy and sexual relationships; general productivity; and social outcomes(39).

The FOSQ has been shown to be a good instrument for assessing the daily impact of the symptoms of sleep apnoea(40). 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(41)

- **Hospital, Anxiety and Depression Scale**

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(42). As anxiety and depression are common in OSA, a specific measure of these conditions is considered important in this study(43).

- **Independent Functioning (Townsend Disability Scale)**

The Townsend Disability Scale is a short index of activities that assesses the physical ability in social terms. It is self-administered and includes nine items of activities of daily living and patients report their level of difficulty(44-46).

- **Positional Therapy Questionnaire and Visual analogue scale (VAS) of comfort and tolerance of device**

Patient comfort and tolerance will be measured by a standard VAS and will form an integral part of our recommendations following analysis of the sleep results.

- **ShortForm-36 (specifically Energy and Vitality)**

The SF-36 questionnaire is a well validated widely used generic health questionnaire(47). 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(48). 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(49). The Energy and Vitality domain of the SF-36 is sensitive to change after initiation of therapy in patients with OSA, particularly in mild disease(33).

- **The Pittsburgh Sleep Quality Index (PSQI)**

The PSQI measures sleep disturbance and usual sleep habits during the prior month. It has 19 items divided into seven clinically derived domains of sleep difficulties: Sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Validated in the OSA population, the PSQI relates

well to clinical evaluation, and other sleep questionnaires (eg: FOSQ) but does not relate well to objective sleep measures (eg: actigraphy, polysomnography) in community sample. It is self-administered; a score of >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% to distinguish "poor" sleepers (depressed patients) from "good" sleepers (healthy subjects). There are questions included that gain the perspective of the bed-partner.

- **Healthcare Utilisation Questionnaire**

We will collect health resource usage by a Health Utilisation Questionnaire, based on the 10 core items of Standardised Resource Use Measure (Expert Delphi Consensus Survey, 2017)(50) to capture core items of health resource use, from hospital admissions, to GP and community settings, as well as home visits and medications. This will allow us to present simple cost consequence data of Positional Therapy, which could be compared to the cost consequences of CPAP Therapy in the NHS.

- **EuroQol EQ-5D**

The EQ-5D is the subjective tool used in economic analysis of the treatment of OSA, allowing us to compare the costs and benefits to other diseases and their treatments. It contains several questions relating to health and mobility, the second part of the questionnaire asks the patients how they feel their health is on the day of the visit.

- **Sleep Reports**

Participant will be asked to complete two sleep questionnaires. The first one will be completed before and after the detailed sleep study at the beginning of the trial to check the sleep quality of the participant. The second one will be completed before and after the final detailed sleep study at the end of three months to check for the sleep quality while the participant is wearing the Night Shift device.

11.2 Definition of the End of Study

The end of trial is defined as after the last patient's 3-month follow up visit.

12. SAFETY REPORTING

12.1 Definitions

Adverse Event (AE) — any untoward medical occurrence in a patient or clinical study subject who is administered a treatment and which does not necessarily have a causal relationship with this treatment (*i.e.* any unfavourable or unintended change in the structure (signs), function (symptoms),

or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

A **Serious Adverse Event** is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.2 Recording Adverse Events (AEs)

The Night Shift™ device (Advanced Brain Monitoring, USA) is CE marked and safety data has already been established therefore this trial will not be looking at the safety of the device. Based on our previous 2 trials (MERGE and PREDICT) (7, 11), AEs are minimal when using CPAP or Standard Care in similar patients. Considering that Positional Therapy has fewer expected adverse events than CPAP, for the duration of this trial, expected AEs, along with any device issues, will be recorded in CRFs but these will not be reported.

At all follow ups, participants will be asked about any issues/ side effects as a result of the positional therapy and these will be recorded in the CRF. The research team will also aim to resolve any device issues where possible.

Expected adverse events and device issues might include:

- discomfort from neck strap
- discomfort from side-ling
- neck or shoulder pain
- hip pain
- clasp unfastens
- intolerable sleep disruption by vibration
- difficulty in falling asleep
- vibration too strong or too loud
- vibration disturbing partner
- continued symptoms despite wearing device eg: snoring
- problems with charging the device

12.2 REPORTING AND Assessment of SAEs

In the event of a Serious Adverse Event (SAE), the Site Principal Investigator (PI) is only required to report **related** SAEs from consent until the end of the participant's involvement in the trial. These should be reported on the ORTU SAE reporting form to ORTU as soon as possible from the Site Study Team becoming aware of the event.

Classification and causality of related SAEs will be conducted by local PIs and reviewed by the CI. ORTU will perform an initial check of the report, request any additional information, and ensure it is reviewed by a nominated Medical Reviewer (including Expectedness Assessment). The site PI's classification cannot be downgraded and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The SAE will also be reviewed at the next Trial Safety Oversight Group meeting at ORTU. All SAE information must be recorded on an SAE form and scanned and emailed to ORTU ORTU@ndm.ox.ac.uk. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and scanned/emailed to ORTU.

SAEs that are unrelated, as determined by the PI, do not need to be recorded or reported for the purpose of this trial.

12.3 Reporting of SAEs to the Sponsor and the REC

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) that gave a favorable opinion of the study (the 'main REC'), the study Sponsor (RB&HFT Research Office) and the local R&D Office where in the opinion of the PI/Medical Reviewer the event was:

- **'related'**: that is, it resulted from administration of any of the research procedures; and
- **'unexpected'**: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted within 15 days of the CI/PI becoming aware of the event; using the SAE reporting form for non-CTIMPs published on the HRA website and entitled non-CTIMP safety report to REC. The form should be completed in typescript and signed by the Chief Investigator (CI) prior to submission to the REC.

Reports sent to the REC of SAEs in double-blind studies should be un-blinded.

The coordinator of the main REC will acknowledge receipt of safety reports within 30 days. It is the responsibility of the CI and his/her research team to send a copy of the SAE notification and acknowledgement receipt to the Research Office.

12.4 The type and duration of the follow-up of subjects after SAEs

Related SAEs will be reported for the duration of the device use by the participant during their trial period. All unexpected SAEs will be followed up until resolution or the end of the trial when the patients will return to routine clinical care.

12.5 Pregnancy

Females of child-bearing potential that are pregnant or intend to become pregnant will be excluded from participation as OSA in pregnancy is a different disease process.

12.6 ANNUAL PROGRESS REPORTS (APRS)

The Chief Investigator or delegate will prepare and submit APR's for the study. It will be reviewed by the RO and sent to the REC by the CI within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the study is declared ended.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act 1998, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, 2nd Edition (2005), and the condition of the REC approval.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's study Identification Number (ID) will be used for identification.

13.2 DATA COLLECTION TOOL

Case Report Forms (CRF) will be designed by the CI in conjunction with ORTU. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry, handling and managing the database.

Researchers and patients will complete paper-based versions of the CRFs and questionnaires, which will then be scanned and sent to ORTU via a secure nhs.net email. ORTU are responsible for data entry into an electronic database, and also the ongoing data monitoring and associated data validation. They will provide support to the researchers and PIs at each site for data queries and technical support for the research database. The Airview sleep study data and the Night Shift data will be managed by the central site.

13.3 DATA HANDLING AND ANALYSIS

Data will be entered from paper CRFs onto a secure, validated, GCP-compliant electronic data management system. All staff performing data entry will be appropriately trained prior to access being granted. Access to the data management system is controlled by individual user accounts, and

a full audit trail is kept of all modifications made to data. The study database will be hosted on a University of Oxford server with hosting services provided by the University's Medical Sciences Division IT Unit (MSD-IT). The database will be backed up at least daily. Further details will be in the Data Management Plan.

Standard Operating Procedures (SOPs) and best practice in design of data collection instruments will be followed to ensure quality control. The processes for validation of study data will be detailed in the study RAAMP, data management plan, and other associated documents. The Chief Investigator and/or Principal Investigator will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Patients' consent to this will be sought at the time of enrolment into the study. The Chief Investigator will act as Data Custodian for the trial. Relevant ORTU staff will have overview of all entered data.

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.

Sleep study data will be uploaded from the apnoea-link device to a secure data server. The data server (known as AirView) is compliant with EU 95/46/EC and national data privacy laws. Data is encrypted and all database accesses are logged and can be re-traced. Data stored in AirView will be via a study participant ID code, and contain no identifiable information.

Night Shift™ Positional Therapy data will be uploaded from the device to a secure data server via an online portal (https://cportal.b-alert.com/night-shift/home).

RBHT subgroup sleep study data from the Somnoscreen device will be uploaded to an encrypted RBHT memory stick and transferred to the secure RBHT computer network for manual analysis and storage, plus daily back-up. All data stored will be via a study participant ID code, and contain no identifiable information.

13.4 Archiving Arrangements

The study documents (including the Trial Master File (TMF), and Case Report Forms (CRFs), along with the study database) will be kept for a minimum of five years. The TMF will be the responsibility of the sponsor but recruiting sites will be responsible for their own archiving of their local CRF's and Informed Consent Forms.

At the end of the trial all ORTU documents (electronic and paper) will be sent to the Sponsor for archiving. The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the RB&HFT computer network, for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&HFT patients is Box-It Storage UK. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

14. STATISTICAL DESIGN

14.1 SAMPLE SIZE AND RECRUITMENT

Power calculation: The final AHI after 3 months of therapy, will be compared between Positional Therapy and Sham-Positional Therapy. We will also measure the interaction between treatment and age group. We will use the final AHI as our primary outcome and include age as a blocking factor as well as including baseline AHI as a linear predictor which will slim the confidence intervals and reduce bias caused by unfortunate randomisation. In the most recent meta-analysis of randomised trials and cohort-studies using new generation devices(32) a mean reduction in AHI of 11.33 events/hour occurred with a mean SD of 9.05 events/hour.

The sample size has been calculated(51); a **sample size** of 104 is required to detect a treatment difference in final AHI of 5 events an hour, based on data from a recent meta-analysis(32). We will therefore recruit 116 patients to be powered to detect superiority of Positional Therapy compared to Sham with 80% power and a 5% significance level, assuming a within-group standard deviation of 9.05 events per hour for 3-month AHIs, and accounting for a 10% drop out rate. CPAP studies usually allow for a 10% drop-out rate but in previous studies of Positional Therapy, intolerance of only 3% has been observed.

14.2 ENDPOINTS

14.2.1 Primary endpoints

Primary outcome: Final AHI after 3 months (adjusted for baseline AHI) of patients treated with Positional Therapy, compared to Sham-Positional Therapy

14.2.2 Secondary endpoints

Secondary Endpoints:

- Final AHI after 3 months (adjusted for baseline AHI) of patients treated with Positional Therapy, compared to Sham-Positional Therapy, **in older compared to younger patients**.
- Final scores after 3 months (adjusted for baseline scores) of patients treated with Positional Therapy, compared to sham-treated controls, in older compared to younger patients in:
    - Epworth Sleepiness Scale
    - Functional Outcomes of Sleep Questionnaire
    - Hospital Anxiety and Depression Scale
    - Independent Functioning (Townsend Disability Scale) and Rate of Accidents
    - Short Form-36 (specifically Energy and Vitality)
    - The Pittsburgh Sleep Quality Index (PSQI: to determine the perspective of the partner/ carer)
    - Health Utilisation Questionnaire
    - EuroQolEQ-5D
- Visual analogue scale (VAS) of comfort and tolerance of device

- Adherence to positional therapy
- A change from baseline to 3 months post Positional Therapy, compared to sham-treated controls, in older compared to younger patients in:
    - Sleep Study Data (Apnealink Air):
        - Supine AHI
        - Oxygen desaturation index (ODI)
        - Overnight average oxygen saturation (SpO2)
        - % time with $SpO_2 \leq 90\%$
    - Positional Therapy Data (Night Shift device):
        - Number of supine attempts
        - Number of feedback events
        - % sleep time in supine
        - % sleep time snoring >50dB

In a RBHT subgroup

- Final scores after 3 months (adjusted for baseline scores) of patients treated with Positional Therapy, compared to sham-treated controls, in older compared to younger patients in:
    - Sleep Quality
    - Sleep Efficiency
    - Sleep Stages (Wake, Stage 1, Stage 2, Slow Wave Sleep and REM Sleep)
    - Arousal indices; total, respiratory and vibration-related
    - Awakenings

14.3 STATISTICAL ANALYSIS PLAN

Statistical support will be provided by Mr Roger Newson, Statistician and Advisor for the London Research Design Service, Imperial College, and co-applicant on this Trial. With his further support, a full statistical analysis plan will be developed prior to the end of the trial.

Data will be presented according to CONSORT guidelines. All primary analyses will be performed on an intention-to-treat principle. Analysis of the primary endpoint will be performed by regression of final AHI with respect to treatment adjusting for baseline AHI and age group. All secondary data (objective sleep data and subjective quality of life data) will be analysed in the same way. Adherence to Positional Therapy will be measured by the device allowing us to determine its role in the treatment effect.

Our trial will be analysed as a 2x2 factorial design. The comparison of primary interest is between patients of all ages randomised to the active treatment and patients of all ages allocated to the sham treatment, and that the old-young comparison is a matter of secondary analysis. We will use the final AHI as our primary outcome and include age as a blocking factor as well as including baseline AHI as a linear predictor which will slim the confidence intervals and reduce bias caused by unfortunate randomisation. We will continue to use age as a binary (older versus younger) variable rather than continuous as we are less certain that the effect of age is linear. Because age is not correlated with treatment, but is correlated with outcome, (ie. AHI - severity of OSA) this will act to

further slim the confidence intervals. We will measure interaction between treatment and age group as a secondary analysis.

Health resource usage data will be presented to allow basic evaluation of the cost and effects of the Positional Therapy device, and enable the reader to form their own opinion on the relevance and relative importance in context(52). We will also collect EQ-5D data which could allow us to compare the costs and benefits to other diseases and their treatments. If the primary outcome of this Trial is positive, a more in-depth cost consequences analysis, including the budget impact for the NHS, could be considered; however, this would require further funding. Health Economic data collection, therefore, is a hypothesis generating aspect of this trial.

14.3.1 Primary endpoint analysis

Analysis of the primary endpoint will be performed by regression of final AHI with respect to treatment adjusting for baseline AHI and age group. All primary analyses will be performed on an intention-to-treat principle.

14.3.2 Secondary endpoint analysis

All secondary data (objective sleep data and subjective quality of life data) will be analysed in the same way as the primary analysis. Adherence to Positional Therapy will be measured by the device allowing us to determine its role in the treatment effect.

Health resource usage data will be presented to allow basic evaluation of the cost and effects of the Positional Therapy device, and enable the reader to form their own opinion on the relevance and relative importance in context(52). We will also collect EQ-5D data which could allow us to compare the costs and benefits to other diseases and their treatments.

14.4 RANDOMISATION

Patients will be randomised 1:1 (Positional Therapy or Sham-Positional Therapy) and will be performed using a bespoke web-based randomisation software package with minimisation based on age group, and OSA severity. All participating sites will have access to this online system.

14.6 OTHER STATISTICAL CONSIDERATIONS

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

15. COMMITTEES INVOLVED IN THE STUDY

1. **Trial Management Group (TMG)** -includes those individuals responsible for the day-to-day management of the trial, i.e. CI, statistician, ORTU trial manager, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard patients and the quality of the trial itself.

The TMG will also meet after a pilot phase of the first 10 participants have completed to review the trial methodology and flow. Additional changes to the protocol may also be made based on these findings, and will be recommended for approval by the Trial Steering Committee.

2. **Trial Steering Committee (TSC)** - will provide overall supervision of the trial and ensures that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will agree the trial protocol and provide advice to the Investigators on all aspects of the trial. Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC. The TSC will meet regularly throughout the course of the trial. A TSC charter will be written which will provide further details of the role of this committee. Members include:

- Chair
- CI
- Members
- SATA member
- Independent member

Details of roles and persons in the TSC Charter

3. **ORTU Safety Oversight Group -** The Oxford Respiratory Trials Unit (ORTU) will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

16. MONITORING AND AUDITING

The requirement for study monitoring or audit by the Sponsor will be based on ORTUs risk assessment procedure and applicable Sponsor Standard Operating Procedures (SOPs). It is the responsibility of the RO to determine the monitoring risk assessment and explain the rationale to the study research team.

Study monitoring and/or audit will be discussed with the CI before arrangements are made to conduct the visit.

17. DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

18. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the study protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and any patient facing documentation have been approved by the Health Research Authority (HRA) which includes Research Ethics Committee (REC) approval, prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for HRA approval prior to implementation.

Before site(s) can enrol patients into the study confirmation of capacity and capability must be issued by the institution hosting the trial (unless HRA specifically has confirmed in the HRA approval letter that this is not required). It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals by the participating site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the study, the CI will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply a final summary report of the clinical study to the REC and the Sponsor in parallel within one year after the end of the study.

19. FINANCE

The study is Funded is National Institute for Health Research (NIHR) Government Funding Stream – Research for Patient Benefit. The research is sponsored by The Royal Brompton and Harefield NHS Foundation Trust. The Study is coordinated on behalf of the Sponsor by Oxford Respiratory Trials Unit which is a Clinical Trials Unit.

20. INSURANCE AND INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

The Night Shift™ Sleep Positioner (Advanced Brain Monitoring, USA) has been developed for adult patients with positional OSA and snorers, and conforms to health and safety regulations and is available on the open market. Advanced Brain Monitoring Inc has made a gift of 150 Night Shift devices and 30 neck straps for use in this trial. The company will maintain Products Liability Insurance in the amount of $3 million USD with $1 mm per incident. This is covered under a letter of commitment and certificate of liability insurance with the company.

21. PUBLICATION POLICY

Data ownership rights will lie with the institution.

22. STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, ORTU's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK Policy Framework for Health and Social Care Research.

This study will be conducted in compliance with the protocol approved by HRA and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and HRA except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the REC as soon as possible.

22.1 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.
A standard operating procedure should be in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

22.2 SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the trial subjects; or
(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

23. LIST OF PROTOCOL APPENDICES

Appendix 1 Night Shift product characteristics
Appendix 2 Night Shift CE mark certificate

24. REFERENCES

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25. PROTOCOL VERSIONS

Version	Date issued	Author(s) of change	Details of changes made
V2.0	29/08/2019	Julia Kelly	The process of sending Airview data has been updated in the screening section to allow sites to send it in PDF format as well as uploads. Randomisation procedure updated to remove the need for an unblinded person to perform the randomisation procedure. TMG to review trial methodology and participant flow after completion of the first 10 participants
V3.0	13/12/2019	Julia Kelly	PSG subgroup: Addition of a RBHT subgroup in who detailed sleep study data will be collected on sleep quality and efficiency by home polysomnography
V4.0	26/06/2019	Julia Kelly	In line with the COVID-19 revised provision for clinical sleep services, the POSA trial protocol will now have the option to be delivered remotely in order to remove additional patient visits to the hospital sites. The protocol will vary between sites in accordance with local revision of clinical procedures and processes. All trial equipment will be cleaned in-line with local COVID-19 cleaning procedures. For transfer of home sleep study equipment and anonymised questionnaires, the patients will receive reply-paid, addressed envelopes.
V5.0	28/01/2021	Julia Kelly	Change of contact details for Trial Statistician as moving institutions. Amendment to the inclusion criteria from total % supine sleep >20, <90% of total sleep to total % supine sleep >10, <90% of total sleep. Amendment to Statement of Compliance in line with UK leaving the EU. Optional remote delivery of home sleep studies for the RBHT subgroup in line with COVID-19 care provision.
V6.0		Julia Kelly	TSC meeting decision to change the power of the study

			from 90% to 80%, thus reducing the sample size from 132 to 104. Change of ORTU email address for safety reporting Updated Sponsor name from Royal Brompton & Harefield NHS Foundation Trust to Royal Brompton and Harefield Hospitals, part of Guy's and St Thomas' NHS Foundation Trust (after merger on 1 February 2021).

1: Night Shift™ Product Characteristics

Intelligent, Interactive Monitoring

Night Shift is worn around the neck; it uses and measures the effectiveness of vibration feedback to discourage back-sleeping.

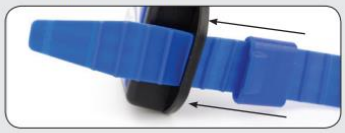
Using the Night Shift:

- Prior to first use, completely charge the device.
- Fit the strap so it is adjusted evenly on both sides. If worn too tight, the magnetic clasp will detach during the night. If worn too loose, incorrect positional feedback will occur when not centered on the back of your neck.
- Just after you turn the device on, it will provide feedback to confirm sufficient battery capacity to record and provide feedback for at least eight hours. Remember to recharge the battery at least once every three days.
- When the Night Shift recognizes you are sleeping on your back, it will vibrate with increasing intensity until you change position.
- Night Shift records your position, sleep quality, and snoring so you can print reports to monitor your response to positional feedback.

Fitting the Night Shift: Step-by-step

The Strap

1 Begin by feeding one end of the strap through one of the slots on the side of the enclosure. The strap should be fed through from the back to the front of the device, and with the ridged side facing out.

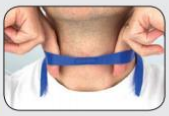


2 Loop the strap back and slide it through the retention band. Pull the strap through the band just enough to hold it in place. Repeat the process with the other side.

3 With the blue label right-side up, center the Night Shift on the back of your neck. **The blue label must be facing away from the neck and the On/Off button facing down.**

4 Re-fasten the magnetic clasp and tighten both sides of the strap evenly, keeping the enclosure centered on the back of your neck and the magnetic clasp centered on the front.

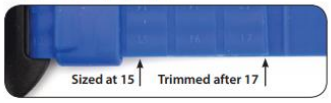
5 The Night Shift strap should be just tight enough to prevent it from sliding around the neck. Two fingers on each side should fit between the strap and the neck without causing the magnets to release.



6 Use the numbers provided on the strap as a guide to help even out each side.

7 With the straps evened out, try the Night Shift on again and verify the fit is still comfortable and snug.

8 Once a good fit is determined, excess length can be trimmed off the ends of the strap. Leave at least 2 extra sizes in case you need to loosen the strap later. The Night Shift is now properly fit.



9 Unclasp the strap by bending at a 90° angle, like snapping a stick. To avoid damage, do not pull apart.

⚠ **Caution:** Replace the strap immediately if the clasps become demagnetized and do not retain during the night.

Night Shift Features

Starting the Night

- Hold the On-Button down for 1-second.
- The LED indicator and vibration feedback patterns will confirm if there is sufficient battery capacity to record and provide feedback for the entire night:

Battery charge sufficient for	LED indicator pattern	Vibration feedback
3 nights	Green - 3 blinks	3 times
2 nights	Green - 2 blinks	2 times
1 night	Green - 1 blink	1 time
Needs charging	Yellow - 1 blink per second	1 time every 5 seconds

- When the device is powered on for a study, the LED indicator will blink green for 5 min. After 5 min. the LED will become solid green.
- Place the device on the neck and go to sleep.
- Vibration feedback will not begin for the first 15 minutes to allow adequate time to fall asleep.
- To turn the Device off, quick-press the On-Button and the Green LED will turn off.
- Note: if the device has not been used for more than 29 days the date and time may be incorrect; connect the device to the portal and follow the on-screen instructions to adjust the date and time.

Explanation of symbols:

Follow Instructions for Use · Adults Only · Dispose Properly · Keep Dry · -25C +70C Storage Temperature · IP22 Limit Objects, Water Ingress

Charge Between Uses · CE 0482 European Conformity · Type BF Applied Part · Rx Only USA Only · REF Catalog Number · SN Serial Number

Manufacturer: Advanced Brain Monitoring, Inc. 2237 Faraday Ave, Suite 100, Carlsbad, CA, USA 92008 P 760.720.0099 | F 760.476.3620 | info@advanced-sleep.com

EC REP: European Representative: MPS Medical Products Service GmbH, Borngasse 20, 35619 Braunfels, Germany

For technical support, or to obtain a replacement neck strap, please contact your Night Shift healthcare provider.

www.NightShiftTherapy.com

Charging the Night Shift:

- See Warnings associated with charging the device.
- Insert the small cable connector into the USB port of the device.
- Connect the large cable connector into a computer or recommended USB wall charger.
- If the device does not appear to charge or hold a charge, try using a new USB cable.

LED Indicators while Night Shift is charging	
Charging	Green on – for up to three hours and LED will turn off when charging is complete
Charging error	Green and yellow on - check power supply and cable connections
Device failure	Yellow on - return the devices for servicing

Cleaning the Night Shift:

When cleaned as described below, the Night Shift can be reused on the same or different patients.

Strap: Detach the straps from the device. Wash each strap separately by submerging in solution of 1 teaspoon (5 ml) of mild dish detergent (e.g. Dawn) per gallon (4 liters) of water. Agitate slightly for one to two minutes. Rinse with clear warm tap water for one minute. Dry with a clean paper towel.

Device: Wipe all surface areas of the device enclosure with a 70% isopropyl alcohol wipe. All surface areas should remain wet for at least 15 seconds. Using a new alcohol wipe, repeat the cleaning; allow to remain wet for 15-seconds. If any visible soil remains, repeat as needed. Allow to air-dry.

Using www.NightShiftTherapy.com:

Go to www.NightShiftTherapy.com and click the Portal link to register the device. Then you can:

- Generate and print daily, monthly, or annual reports to monitor how often you're sleeping on your back, how well you are sleeping, and how loudly you are snoring.
- Update date, time, and firmware on your device
- Change the delay of delivery of positional feedback from 15-minutes after the device is powered on to 30-minutes.

Indications for Use:

The Night Shift is indicated for prescription use for the treatment of adult patients with positional obstructive sleep apnea with a non-supine apnea-hypopnea index <20, and to reduce or alleviate snoring. It records position, movement, and sound so that positional changes in sleep quality and snoring can be assessed.

⚠ Warning: Do not wear the device while it is being charged. To avoid permanent damage: a) charge with a medical IEC 60601.1 compliant wall charger (maximum 5 volts and 1.5 amps), b) avoid use of rapid or fast wall chargers, and c) do not use USB cables with exposed wires or bent pins.

⚠ Cautions:

- Night Shift users should NOT:
  - have Cardiac Arrhythmia corrected with an artificial pace-maker;
  - have skin sensitivity or an open wound around their neck;
  - have a neck size that is very small (less than 12 inches/30 cm) or a very large (greater than 22 inches/55 cm);
  - sleep with their head in a near-upright position;
  - suffer from tics or tremors of the head.
- You may initially feel more tired during the day if your sleep is disrupted while you learn to not sleep on your back.
- The measured signal will be influenced by a snoring bed partner.
- Do not wear the Night Shift upside down – the reported sleep time on your left and right sides will be reversed.
- Do not wear the strap too loose – position feedback will be inaccurate if the device is NOT on the center of your neck.
- Do not wear the strap too tight – the strap may become detached during the night.
- US Federal law restricts this device to sale by or on the order of a physician.
- Dispose of the device that includes a Lithium Polymer battery properly.
- To avoid damage not covered by warranty, keep the device dry and clean, and out of reach of children and pets.
- Selection of an appropriate pillow for non-supine sleep may reduce the occurrence of neck, shoulder, or back pain. Discontinue use of the device and contact your physician or the device manufacturer in case of any significant pain.

Warranty: Twenty-four (24) month warranty for assembly workmanship and electronic components and twelve (12) month warranty for haptic motors and battery. Warranty does not cover the strap or damage attributed to improper use by the customer. The warranty will be voided if an attempt is made to open the enclosure or change the battery.

The treatment efficacy of Night Shift was demonstrated in a study of 27 patients diagnosed with positional obstructive sleep apnea with a pre-treatment non-supine apnea-hypopnea index < 20. The results showed:

	Pre-treatment				95%
	≥5 AHI <15	≥15 AHI < 30	AHI ≥ 30	Total	Confidence Interval
Treatment outcome	n = 11	n = 10	n = 6	n =27	
AHI ≥50% decrease, % (n)	81.8 (9)	80.0 (8)	100.0 (6)	85.2 (23)	71.8–98.6
AHI ≥35% decrease, % (n)	9.1 (1)	0.0 (0)	0.0 (0)	3.7 (1)	-5.4–10.8
Non-responder, % (n)	9.1 (1)	20.0 (2)	0.0 (0)	11.1 (3)	-0.8–23.0

US and International Patents, Patents Pending

MED / CERT
Certification. Medical Only.

EC Certificate of Conformity

The Notified Body

MEDCERT Zertifizierungs- und Priifungsgesellschaft for die Medizin GmbH Pilatuspool 2 — 20355 Hamburg — Germany

herewith certifies that the company:

Advanced Brain Monitoring, Inc.
2237 Faraday Avenue, Suite 100
Carlsbad, CA 92008
United States of America

with locations listed in the appendix

has introduced, applies and maintains a quality assurance system for the products / product categories listed in the appendix.

The compliance of this quality assurance system with the below mentioned requirements of the **Council Directive 93/42/EEC** was verified by an audit:

Annex II without section 4

This certification is subject to surveillance by MEDCERT.

Effective date:	**2020-11-25**
Expiry date:	**2023-12-07**
Report No.:	3309PS18F
Process No.:	QS - 3309
Certificate N	3309GB410201125A

Hambur 20- 1-25

MEDCERT Certification Body
(Markus Bianchi)