



Decongestants in Obstructive Sleep Apnoea

Trial Title: Randomised controlled trial of nasal decongestants versus placebo to prolong treatment free periods from continuous positive airway pressure therapy in mild to moderate obstructive sleep apnoea

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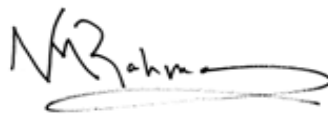
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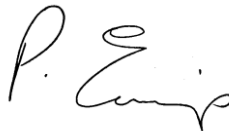
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The investigators have no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. LAY SUMMARY

This study is looking at patients with diagnosed sleep apnoea who have already been using CPAP treatment for at least 3 months. Participants will be asked to stop using their CPAP treatment and be randomised to either a real nasal spray or placebo. Participants will then be advised to spray the nasalspray into each nostril and either side of their throat prior to bed every night. The primary outcome of the study to see how long it takes for the participants' sleep apnoea symptoms to return. This treatment will be given for a maximum of 28 days at which time the patient should re-start their CPAP treatment. If the participant feels that their symptoms have returned or we see their symptoms have returned via the remote monitoring system they will be wearing on a nightly basis, we will contact the participant to initiate restarting their CPAP treatment. The aim of the study is to have an alternative temporary therapy for those patients wishing to have a "break" from traditional sleep apnoea treatments for things such as holidays.

3. SYNOPSIS

Trial Title	Randomised controlled trial of nasal decongestants versus placebo to prolong treatment free periods from continuous positive airway pressure therapy in mild to moderate obstructive sleep apnoea	
Internal ref. no. (or short title)	Decongestants in Obstructive Sleep Apnoea (DOSA)	
Clinical Phase	3	
Trial Design	Double blind drug- placebo randomised control trial	
Trial Participants	Patients with obstructive sleep apnoea established on continuous positive airway pressure for over three months	
Planned Sample Size	232	
Treatment duration	28 days	
Follow up duration	7 days	
Planned Trial Period	35 days	
	Objectives	Outcome Measures
Primary	To compare the effect of Xylometazoline versus placebo on the time to return of OSA in patients with mild to moderate OSA following withdrawal of CPAP therapy	Comparison of the number of days to a return of OSA (ODI >15 on 3 consecutive nights by remote oximetry data or the patient restarts CPAP for recurrence of symptoms.)
Secondary	To assess the effect of Xylometazoline versus placebo on subjective daytime sleepiness in patients with moderate OSA following withdrawal of CPAP therapy To assess the effect of Xylometazoline versus placebo on sleep fragmentation in patients with moderate OSA following withdrawal of CPAP therapy	Patient reported sleepiness on ESS score at baseline, and weekly (day 0, 7, 21 and 28) until 5 week follow-up Overnight every night pulse oximetry during 28 day withdrawal of CPAP
Investigational Medicinal Product(s)	Xylometazoline 0.1% (Sudafed congestion relief)	
Formulation, Dose, Route of Administration	0.1%, one spray into each nostril and onto either side of the pharynx once daily 10 minutes before bed and after teeth brushing	

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnoea
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Medicinal Product Characteristics

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group

5. BACKGROUND AND RATIONALE

Obstructive Sleep Apnoea ('OSA') is a very common condition in around 1 in 20 adults. When you relax during sleep the throat tends to narrow. In OSA patients this narrowing leads to collapse and pauses in breathing. During these pauses the oxygen level falls and the patient wakes up. These events can occur every minute in severe cases and so patients sleep very badly. They wake unrefreshed and are sleepy in the daytime. OSA is best treated with a Continuous Positive Airway Pressure ('CPAP') machine. These machines blow air into the throat through a mask worn when asleep. CPAP keeps the airway open. The breathing is stable and sleep is not disrupted. Patients awake refreshed and do not fall asleep in the daytime.

CPAP can also help snoring, blood pressure, mood and going to the toilet too often at night.

Although CPAP machines work well they are not always comfortable. Around one in 10 patients do not use CPAP very well. Patients who don't like CPAP ask if there are any other treatments or if they can stop CPAP machines for short breaks.

We know that snoring is worse if the throat is swollen or the nose is blocked. This can also lead to OSA. Snoring may be improved by nasal decongestants. We hope these decongestants will also treat OSA so that patients can come off their CPAP for short breaks. We will ask patients who have been treated with CPAP to stop their CPAP for up to 28 days and see how long it takes for OSA to return. Half the group use a real decongestant spray in their nose and throat and half use an inactive dummy spray. We will see if the decongestant spray stops OSA coming back so quickly. If the nose spray stops OSA coming back for a week or more this will help people to decide if they can go away for a few days without having to take their machine.

Background

Obstructive sleep apnoea (OSA) is a common condition for which the most effective treatment is continuous positive airway pressure (CPAP) [1]. In the UK it is estimated that there are about 230,000 patients who use CPAP, and many more as yet undiagnosed who would benefit from this therapy. Using CPAP involves wearing a mask over the nose (or nose and mouth) preferably for most nights, and for most of the night. It is a tribute to its efficacy, despite the unattractiveness of the therapy, that average compliance rates are 5 hours or so a night, with over 90% of patients with more severe OSA using the treatment long-term [2].

Because of the cumbersome nature of CPAP, patients reasonably look for alternatives for either temporary or permanent use [3]. However no other therapy is as effective, although intra-oral devices that hold the lower jaw forward during sleep can be almost as effective in some patients [4]. There have been studies looking at other alternatives, but these do not seem adequate replacements [5].

It has recently been observed that if patients stop their CPAP, then the OSA does not always return immediately [6]. In a recent study, 125 patients with previously diagnosed and CPAP-treated OSA (Oxygen desaturation Index (ODI) >10), stopped their CPAP for four nights. In 29% of these patients the OSA did not return. This 29% then went on to

stop their CPAP for a further two weeks. Of these patients, nearly a half still did not experience a return of OSA. Thus overall, 15% of patients remained OSA-free for two weeks despite no treatment.

The explanation for only a partial or gradual return of OSA in some, versus a virtually full and immediate return in others, is not understood. Rapid OSA return was more likely in those with originally more severe OSA, greater obesity, and in current smokers, although these were relatively weak associations [6]. Smoking is thought to worsen OSA through pharyngeal oedema [7].

It is thus likely that one of the relevant factors influencing the return of OSA post CPAP withdrawal is pharyngeal oedema. OSA and heavy snoring do produce sore throats in the morning and visibly swollen mucosa; in addition, histology of resected pharyngeal tissue from OSA sufferers shows oedema and inflammation suggestive of traumatic damage [8-11]. It is known that after CPAP treatment, MRI measured oedema in the pharynx decreases [12], and measures of the pharyngeal volume increase [13, 14]. Diuresis in patients with OSA and diastolic heart failure reduces the AHI and increases pharyngeal volume [15]. After a period on CPAP the pressure abolishing apnoeas can usually be reduced [16]. Fluid accumulation in the neck tissues over the night (redistributed from the legs) increases the degree of OSA, and may explain some of the observed night-to-night variation in severity [17]. There is also anecdotal experience that OSA may be provoked by a period of heavy snoring or an upper respiratory tract infection, that may then become self-sustaining or remain until the pharyngeal oedema resolves.

This is not just an academic issue over the pathophysiology of OSA, but has significant implications for the way patients on CPAP for OSA are managed in the long-term. It is possible that patients with mild to moderate OSA may be able to stop their CPAP for short periods which they would find useful, for example when going away from home for week-ends or holidays [3, 6]. If there were a way to extend the period free of OSA, this would be very valuable.

Nasal decongestants have been used for a very long time to improve nasal flow. These are usually sympathomimetics that work by vasoconstricting blood vessels and reducing tissue fluid content, thus shrinking the volume of the mucosa. [21]. There has always been concern that long-term use can be associated with tachyphylaxis and rebound hyperaemia with mucosal congestion (so-called rhinitis medicamentosa). However some of this mucosal effect was shown to be due to the previous usual preservative, benzalkonium [22] and is less likely with once daily usage rather than the usual two or three times daily [23]. Recent studies and a recent review concluded there was poor evidence to support the concept of rhinitis medicamentosa, [24 25]. The Medicines and Healthcare Products Regulatory Agency (MHRA) has recently re-issued licenses to several companies to sell over-the-counter preparations of both Oxymetazoline and Xylometazoline with recommendations regarding certain contraindications, potential drug interactions and length of use (e.g.

<http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2023529.pdf>)

There is already some evidence that nasal decongestants alone will improve snoring and OSA [26 27] [1 28 29]. Nasal administration of decongestants will inevitably lead to some of the liquid reaching the pharynx, and thus it is unclear whether some of the effect seen in these studies might be due to additional partial decongestion of the pharynx.

In three clinical trials, on a total 60 of healthy volunteers, nasal decongestant sprays were used for at least 4 weeks without demonstrating symptoms of worsening or rebound nasal congestion (Peterson & Hansson, 1982; Watanabe et al., 2003; Yoo, Seikaly, & Calhoun, 1997). Treatment is usually advised for a period of only 7 days due to concern over worsening nasal mucosal oedema with longer term use. However, the presence of benzalkonium chloride, previously used as an additive in the manufacture some nasal sprays, has been shown to worsen the rebound

congestion effect and is the likely cause of this phenomenon historically (Graf, 1996, 1999). A recent review article analysing current evidence refuted the concept of rebound congestion and rhinitis medicamentosa. For this reason we feel it is justified to ask patients to use nasal decongestant sprays for a 28 day period (Mortuaire et al., 2013).

It is thus considered reasonable to test the hypothesis, in patients with mild-to-moderate OSA currently on CPAP, that pre-sleep administration of a nasal and pharyngeal decongestant will prolong the OSA-free period following CPAP-withdrawal. Oxymetazoline (e.g. Vicks Sinex) and Xylometazoline (e.g. Otrivine/ Sudafed) are both non-prescription over-the-counter decongestants with proven efficacy (up to 12 hours, [30]) and safety, and we would propose using xylometazoline in a spray device suitable for application to the pharynx (Sudafed congestion relief nasal spray) versus a suitable placebo equivalent Saline Nasal Spray).

Public and Patient Involvement

This study was suggested by patients who often ask in clinic if Continuous Positive Airway Pressure ('CPAP') can be avoided or if there are alternative treatments. In particular we are asked about travelling away from home or short breaks off CPAP. In Taunton we ran a patient focus group to define local issues around CPAP treatment. A number of themes emerged around the use of CPAP at home and when travelling, including inconvenience to the patient during use, issues related to device (mask or machine), inconvenience to bed partner (noise, leaks) and sleep during long air flights or when travelling. We collated these in a questionnaire which was edited by our patient representatives and tested with routine CPAP follow up patients. The themes reflect usual experience and the follow up cohort identified some other patient concerns for which a short break may be appreciated.

We designed the study protocol with patient representatives involved in previous withdrawal trials and research naive OSA patients who are co-applicants on this submission. Further to the feedback on our applications we have strengthened our patient participation. We have 2 PPI representatives on the trial steering committee.

The study plan was discussed with the patient support Sleep Apnoea Trust Association and feedback adopted into the protocol. The protocol has been reviewed by our PPI representatives with supportive feedback from both Taunton and Oxford sites. We asked 30 patients attending the Taunton CPAP follow up clinic over a 1 month period June 2017 for feedback on the protocol and if they would be interested in taking part. We had responses from 18. This survey has shown a widespread acceptability to research naive patients; 83% said they would be interested in taking part. The median length of time the patients suggested that would be useful to be off CPAP was around 7 days. The main perceived benefit of doing the trial was to be able to not wear a mask where a reason was given. We have included questions about acceptability and tolerability of the spray alongside the patient diary.

Our PPI representatives have kindly reviewed the protocol and patient literature, they will help resolve any patient related trial issues and support preparation, editing and dissemination of the results through disease specific support groups and social media content. Following feedback from the NIHR RFPB committee we have appointed two independent lay members to the Trial Steering Committee for the trial.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the effect of Xylometazoline versus placebo on the time to return of OSA in patients with mild to moderate OSA following withdrawal of CPAP therapy	Comparison of the number of days to a return of OSA (ODI >15 on 3 consecutive nights by remote oximetry data or the patient restarts CPAP for recurrence of symptoms.)	Overnight every night pulse oximetry during 28 day treatment/CPAP withdrawal.
Secondary Objectives To assess the effect of Xylometazoline versus placebo on subjective daytime sleepiness in patients with moderate OSA following withdrawal of CPAP therapy To assess the effect of Xylometazoline versus placebo on sleep fragmentation in patients with moderate OSA following withdrawal of CPAP therapy	The change in Epworth sleepiness score a validated measure of daytime sleepiness Overnight pulse rate rises of more than 6 bpm per hour as a marker of autonomic arousal during sleep fragmentation.	Patient reported sleepiness on ESS score at baseline, and weekly (day 0, 7, 21 and 28) until 5 week follow-up Overnight every night pulse oximetry during 28 day withdrawal of CPAP

7. TRIAL DESIGN

This study is a double blind; placebo-controlled, randomised controlled trial. This study will take place in at least 2 hospitals in the UK with established sleep services.

Patients with mild to moderate obstructive sleep apnoea syndrome, already on CPAP treatment for > 3 months, and with a compliance of >3h/night will be eligible. The definition of mild to moderate OSA will be based on their original presenting diagnostic test. Patients will be eligible if they had between 15 and 40 episodes per hour with a (>4%) reduction in oxygen saturation measured by finger plethysmography.

The trial requires participants to attend two site visits and have up to two phone calls. Due to potential changes to public health restrictions and requirements to limit visits to hospital sites as a result of the COVID-19 pandemic, participants may be offered telephone calls instead of face to face visits.

When face to face visits are permitted, participants will have one (baseline) face to face visit at enrolment followed by a telephone call at day 3 (+/- 1 day) post randomisation to remind them about completing the electronic diary card and check they will inform the study team, if their symptoms return sufficiently for them to restart CPAP.

The follow up visit (visit 2) is at 28 days after randomization plus 7 days after returning to CPAP, or earlier if the primary outcome is reached before this time point. Participants will be asked to continue observing for any side effects using the electronic diary after they have completed the treatment period to look for any rebound side effects for up to 7 days post the last spray use.

If face to face visits are not possible, visit one may be split into up to three telephone calls, with equipment posted out to the participants after consent has been taken and sprays being posted out after randomisation. Visit 2 would be completed as a telephone call, with ad hoc face-to-face visits if required e.g. to assess an adverse event.

During study visits participants will be asked to complete the trial questionnaires. If physical visits are not possible, the questionnaires will be completed remotely, e.g. they may be sent electronically to the participant or be completed over the phone. Participants will be asked to wear an overnight oximeter every night they are using the sprays. In addition to this, patients will record their daily symptoms in an electronic diary including the Karolinska Sleep Scale. Participants will be asked to detail any possible side effects from the trial medication; acceptability and tolerability of the spray using a standard checklist designed for this study.

Appendix B below shows the two ways in which the visits can be conducted but participants can change between the face to face and phone visits depending on the circumstances at a given time.

Visit 1 (face to face)

- Consent
- Confirm eligibility
- Medical and drug history
- Baseline metrics
- Instruct on use of trial equipment (sprays and oximetry)
- Trial equipment issued
- Questionnaires
- Randomisation
- Start date off CPAP confirmed
- E-diary training
- Trial sprays collected from pharmacy

Visit 1 (Phone call 1 - if face to face visit not possible)

- Telephone Consent
- Written signed consent form returned via post
- Trial equipment sent out

Visit 1 (Phone call 2 - if face to face visit not possible)

- Confirm eligibility
- Medical and drug history
- Baseline metrics
- Instruct on use of trial equipment (oximetry)
- Questionnaires
- Randomisation

Trials sprays sent out

Visit 1 (Phone call 3 - if face to face visit not possible)

- Instruct on use of sprays
- Start date off CPAP confirmed
- E-diary training

Commence off CPAP – Day 1

Oximetry monitoring – Day 1 – 28 (max)

- Daily oximetry uploads
- Complete electronic diary

Follow-up Phone Call – Day 3

Return to CPAP

- Start 7 days symptom diary
- Questionnaire

Visit 2 – face to face – within 7 days of return to CPAP

- Follow-up questionnaires
- Return trial equipment and sprays

Visit 2 – within 7 days of return to CPAP – Phone call if face to face visit not possible

- Follow-up questionnaires
- Return trial equipment and sprays

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

232 patients with mild-moderate obstructive sleep apnoea will be recruited.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.
- Diagnosed with proven obstructive sleep apnoea, with an ODI > 15 and < 40 on original diagnostic sleep study
- Established on CPAP treatment for > 3 months with mean usage of > 3 hours/ night for last 3 months
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to withdraw from CPAP treatment for 28 days.
- Good mobile phone reception
- Use of Wi-Fi at home

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Significant renal or hepatic impairment.
- Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
- Professional driver or, as assessed by the local investigator, any other vigilance critical activity
- Daytime SaO₂ <93%, or any prior arterial blood gas performed on room air showing PaO₂ <8.0 kPa or PaCO₂ > 6.0,
- Significant hypoventilation on diagnostic sleep study mean saturation <92%
- Previous or current history of central sleep apnoea or Cheyne-Stokes respiration
- Previous history of a sleepiness-related accident
- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial
- Participants with a fructose intolerance
- A known hypersensitivity to Xylometazoline hydrochloride
- Previously undergone trans-sphenoidal hypophysectomy or surgery exposing the dura mater

9. TRIAL PROCEDURES

This section may be read in conjunction with the patient flow chart and schedule of procedures in appendices A and B.

9.1. Recruitment

Potential participants will be screened and identified by the clinical team at the recruiting centre from their database of all patients established on CPAP therapy or from those attending routine annual clinic follow-up appointments with the clinical team. The clinical team will screen patients' notes and their databases to establish eligibility on

initial diagnostic sleep study and most recent compliance data. The clinical team will then either send out an invitation letter along with the PIS to potential participants, give these to individuals in person at routine clinic appointments or introduce the study over the phone if any clinics are run virtually. The invitation letter will include an opt-out slip which patients can return to the research team if they do not wish to have any further involvement.

If after at least two weeks from sending out the letter, patients have not returned their reply slip or contacted the team to opt-out, the research team will then contact patients by telephone to offer them a chance to ask any questions and to participate in the trial.

9.2 Screening and Eligibility Assessment

Preliminary screening of local databases and current patients will take place. Patients' eligibility will be considered and assessed when inviting patients to participate by the clinical team. This preliminary screening will be based on medical records and sleep study data. Patients who may be eligible will also be invited for a screening visit/telephone call via a postal invitation where the full inclusion and exclusion criteria will be checked.

9.3 Informed Consent

Written Informed consent will be obtained at study Visit 1 during the participant's visit to the respiratory department.

Where contact is remote and consent is to be taken by phone, designated researchers or PIs will contact participants to discuss the trial and ensure participants have a copy of the participant information sheet and to obtain consent. The consenting researcher should initial each clause of the consent form and complete and sign the telephone consent section of the form. Two copies of the consent form should be made and sent marked "private and confidential" to the participant who will be asked to check, sign and date both copies and return one to the research team via prepaid return postage marked "private and confidential". Further trial activities should not progress until the written signed consent form is received by the research team.

On receipt of the consent form, the signed copy will be placed in the medical notes and a copy placed in the investigator site file. The consent process will be completed by a member of the research team who is both trained in taking informed consent (GCP training) and is familiar with the methodology of the trial. The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information Sheet and Informed Consent Form will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. The original consent form should be filed in the participant's medical notes, a copy should be given to the participant and a copy filed in the investigator site file. Participants will be asked to consent if they wish to be informed of the trial results and what

treatment group they were allocated to. If participants consent to this, the local trial teams will be provided with an information letter once the trial results are published.

9.4 Randomisation, blinding and code-breaking

If the participant is happy to proceed, randomisation will take place at Visit 1 (Baseline), or during the equivalent telephone 'Visit 1' process if face to face visit is not possible. Some participants may request more time to consider the trial and a repeat baseline visit/telephone call may be arranged.

Randomisation will be performed using a bespoke web-based randomisation software package called Sealed Envelope. Minimised randomisation will be performed using age (≥ 60), centre and original BMI ≥ 37 . Where an up to date BMI is unavailable, the neck circumference will be used as a surrogate, with ≥ 42 cm used as the cut-off.

If unblinding is necessary, then this will be supplied for a single participant and can be accessed using the Sealed Envelope online system. The randomisation service provides a facility for emergency unblinding of treatment allocation which can be accessed by the local PI. All emergency unblinding will be at the discretion of the local investigators, when clinically indicated for the safety of the patient. Investigators should refer to the trial specific procedures (TSP) for the emergency unblinding procedure. Non-emergency unblinding can be requested via the Sealed Envelope system and will require approval by the Chief Investigator.

Participants and the researchers involved in day to day trial management and outcome assessment will be blind to the treatment allocation. Medications will be prepared by a commercial licenced manufacturer (Stockport Pharmaceuticals). We will use a proprietary over the counter nasal decongestants. These will be over labelled to preserve blinding. The commercial pharmacy will prepare placebo sprays in a similar fashion over labelling proprietary nasal saline sprays in similar bottles.

The trial participants will be shown how to use the spray during visit 1. The trial spray prescription will be dispensed from pharmacy. Instructions on use will be provided by the research team. The sprays must be returned to the pharmacy department only following the end of the participant's trial period. The pharmacy department will weigh the bottles to assess compliance. Compliance data will be returned to the research team periodically throughout the trial.

9.5 Baseline Assessments:

9.5.1 Visit 1 (Visit to take place in research department, 180 mins approx)

To confirm eligibility during visit 1 females of child-bearing potential will be asked to carry out a urine β -HCG pregnancy test and all participants' baseline daytime oxygen saturations will be checked. At baseline (visit 1) all recruiting sites will measure participant's height, weight, neck circumference and blood pressure. Participants will complete questionnaires (SF-36, EQ 5D 5L, ESS and Sleep Apnoea Quality of Life (Short SAQLI)). Participants will be asked to bring their CPAP machines with them so the compliance hours can be checked. Participants will be provided with a pulse oximeter Check me O2 pulse oximeter from Viatom. CE0197 (CE marking indicates conformance to ec directive number 93/42/eec concerning medical devices) for use overnight every night they are in the trial. This is a wrist watch device coupled with an android mobile phone with a prepaid data card for data downloading. Participants will be trained on the use of the device and shown how to connect to the mobile phone and upload the overnight data. Participants will be provided with an e-diary and be shown how to complete it.

Musgrove Park Hospital, Taunton Participants only: will have a structured examination of their nasopharynx with an otoscope, a scoring of their pharynx by Mallampati score, an assessment of competency of the nasal valve and site of snoring with mouth closed, mouth open, maximal tongue protrusion and maximal jaw advancement at baseline. Spirometry will be performed during the baseline visit unless historical spirometry data has been performed within the previous 2 years, in which case these results will be recorded.

Other recruiting sites: Will be limited to only recording the Mallampati score.

Participants will be randomised to either placebo or real nasal/pharyngeal decongestant usage pre-sleep. The participants in both groups will then be instructed to stop CPAP, and use the allocated nasal/pharyngeal decongestant nightly from that first night off CPAP for up to 28 days. Training on how to use the spray will be given by the research nurses providing written and video instructions to demonstrate the correct technique to participants, no dummy sprays will be used during this training session.

CPAP will be re-started once OSA has returned or once the participant has reached their 28 days in the trial. This will be clearly explained to the patient during the baseline visit. Return of OSA will be determined on overnight oximetry criteria ODI>15/h, on three consecutive nights or 2 nights when there has been any inadequate data, or the patient wants to restart CPAP treatment because of return of symptoms. The participants will be asked to complete a further e-diary to record any side effects for 7 days post spray use. The electronic device will be returned at visit 2. The trial for each patient will last a maximum of 35 days (28 days treatment, 7 days side effect monitoring), or less if OSA has returned prior to this (reaching the primary endpoint).

The nasal/pharyngeal spray will be stopped either when OSA returns and the participant restarts CPAP or when the 28 day point has been reached. Participants may be telephoned during the trial at other times to be informed that the oximeter has shown recurrence of OSA and they should restart CPAP or in the event of data loss or poor data from the oximeters, this could be due to the patient not wearing the oximeter or incorrect positioning.

9.5.2 Visit 1 – telephone option when face to face visit not possible (remotely completing requirements of baseline visit, 2-3 telephone calls, 2-3x30mins approx.)

To confirm eligibility females of child-bearing potential will be asked to carry out a urine β -HCG pregnancy test. The test will be sent out to the participants and they will be asked to report the result to the research team during the telephone assessment.

Trial equipment will be sent out to the participant via recorded delivery postal or courier service. This will include written instructions on how to use the trial sprays and there will also be an instructional video on the mobile device for participants to watch. Similarly, there will be written and video instructions on how to use the Check-me O2 oximeter. Participants will be asked to perform a trial upload of a short recording of 5-10minutes using the oximeter during the daytime to confirm the trial equipment is functioning correctly and that daytime oxygen saturations meet the eligibility criteria. During the telephone call with participant, the research team will check that the participant is confident to use the oximeter. Participants will also be asked to measure their neck circumference with a tape measure provided.

If remote uploads of CPAP machine compliance data are not possible, the research team will ask the participant to report this information verbally over the phone.

A trial SD memory card labelled with participant ID number only, will be sent to those participants to be used in their CPAP machine for the duration of the trial. This will be used to record usage data to confirm compliance data during the off CPAP and follow-up 7 day on CPAP periods of the trial.

Medical and medication history will also be reviewed during this telephone call.

Spirometry, blood pressure and examination of the nose/throat will not be possible via this pathway but any recently documented results that are available will be recorded in the study CRFs.

Following the confirmation of eligibility, the participant will be randomized using the online system, SealedEnvelope. Once this is completed, the participant will be allocated the assigned trial sprays and these will be delivered by registered post or courier to the participant.

After receipt of the sprays, the research team will contact the participant again via telephone to ensure they know how to use the trial spray and to confirm the start date for using the sprays and coming off CPAP. Baseline sleep and quality of life questionnaires will be completed at this point along with any necessary training on how to use the daily electronic symptom diary.

9.6 Subsequent Visits

Telephone Calls

A telephone follow-up will remind the participants to complete their e-diary on day 3 (+/- 1 day) post randomization (or off CPAP start period if there is a delay between randomization and the IMP start/start of off CPAP period) and feedback the results of the first 3 nights overnight oximeter recording. This is also to check the participants are happy in how to use the trial sprays correctly.

Telephone calls will be made to patients if the overnight oximeter data shows recurrence of OSA or if there is no data uploaded.

Daily E - Diary

Participants will be given a home daily symptom e-diary to complete from visit one until one week post stopping trial medication including ESS (on days 7, 14, 21 and 28 and days 1 and 7 after restarting CPAP), daily Karolinska sleep scale and trial specific questionnaires of potential expected adverse effects from CPAP withdrawal or use of nasal decongestants. The e-diary instructions will request they report any possible treatment related side effects in this e-diary. Or if they have any concerns about other symptoms to call their local research team. These diaries will be remotely checked by the research registrar on a frequent basis. There will be a checklist on possible side effects from CPAP treatment withdrawal and use of nasal decongestants.

Participants will be asked to continue their e-diary for 7 days after restarting CPAP and return their android device at visit 2.

Visit 2 (day 35, or 7 days following CPAP restart if endpoint reached, visit to take place in research department, 60 mins approx)

At visit 2 the participant's height, weight, neck circumference and blood pressure will be recorded. Participants will complete questionnaires (SF-36, EQ 5D 5L, ESS and Sleep Apnoea Quality of Life (Short SAQLI)). The research team will collect the pulse oximeter and mobile device from the participant. We will ask direct questions of the participant about side effects and snoring, reporting expected and any other symptoms. We will also ask open questions about

any possible complications and look for any unforeseen concerns that the patients and partners have about their disease or its treatment.

Participants should return all trial sprays directly to the pharmacy department that they were originally dispensed from where they will be weighed by the pharmacy department and disposed of.

CPAP use will be checked by review of the machines compliance record. The CPAP devices will be reviewed to ensure no use over the trial period and to review data on hours per night usage before the trial and since restarting CPAP.

Visit 2 - telephone option if face to face visit not possible (telephone call, 30-60 mins approx.)

Participants will be asked to complete the trial questionnaires (SF-36, EQ 5D 5L, ESS and Sleep Apnoea Quality of Life (Short SAQLI)). They may be sent these electronically along with the ON CPAP diary at day 7 of CPAP restart or these can be completed over the phone with a member of the research team entering responses directly into the electronic CRF.

Participants will also be asked questions about side effects and snoring, reporting expected and any other symptoms. They will also be asked open questions about any possible complications and any unforeseen concerns that the participants and partners have about their disease or its treatment.

The participant will then be asked to return all trial equipment by pre-paid postage/courier. This will include the oximeter, trial mobile phone, CPAP SD memory card (if applicable) and all the spray bottles (used or unused). Trial sprays will be returned to pharmacy by a research staff member independent of the trial, to avoid unblinding.

CPAP usage data will be checked by reviewing the trial SD memory cards.

Daily review of oximeter data

The Research fellow will review the downloaded oximeter data each day for each participant. If data confirms the recurrence of OSA and the end criteria have been reached, the site teams will be informed and asked to contact the participant to instruct them to recommence CPAP (the Research fellow will only directly contact patients recruited in their own centre, where they will be part of the site team – in other centres, local site staff will contact patients). A study appointment will also be made for visit 2 within 7 days. If there is no data recorded on the overnight oximeter, the study teams will also be informed and asked to contact the participant to remind them to complete this.

9.7 Withdrawal of Participants from the Trial

Each participant has the right to withdraw their consent to continue the trial at any time. The investigator may discontinue a participant and withdraw them from the trial if the Investigator considers it necessary for any reason including:

- Pregnancy
- Significant protocol deviation
- Significant non-compliance with the trial requirements, for example if there is no oximetry data downloaded despite telephone contact and requests to do so
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.8 Definition of End of Trial

The end of trial is the date the last participant's seven day e-diary card has been returned.

10 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

10.1 IMP Description

At randomisation participants will be randomised to a treatment of which they will be instructed to take one spray into each nostril and onto each side of the pharynx once at night. The trial sprays should be taken until the return of their sleep apnoea symptoms or for a maximum of 28 days at this point they should be stopped. Any part-used or un-used trial sprays should be returned to the local hospital pharmacy at the participants follow up visit (Visit 2).

The investigational product, Sudafed 0.1% Nasal Spray (Xylometazoline hydrochloride) and the placebo Calpol saline nasal spray (0.9% sodium chloride) will be packaged and labelled by Stockport Pharmaceuticals, according to current EU Good Manufacturing Practice (GMP) guidelines. The label will fulfill GMP Annex 13 requirements and/or local regulatory requirements.

*Please note that that the IMP and matched placebo will be supplied in different size bottles. Trial specific procedures will be written and training will be given to sites on how to ensure that blinding is maintained.

10.2 Storage of IMP

All sprays will be stored within the local pharmacy department. These products do not require refrigeration or any special storage requirements.

10.3 Adherence to Trial Treatment

Adherence will be assessed by the patient e-diary recording of doses taken and by returning all unused and part-used medication bottles to the pharmacy departments. The spray bottles will be weighed as a measure of adherence with non-adherence defined as <70% of expected dosage used.

10.4 Accountability of the Trial Treatment

Site pharmacists will record accountability of the trial treatment allocated and returned. Accountability information will be checked throughout the study.

10.5 Concomitant Medication

At visit 1 and 2 all participants' medications will be recorded. Participants will carry on using their standard medications for the duration of the trial. Any concomitant medications will be allowed.

10.6 Post-trial Treatment

The IMP/placebo will not be provided beyond the end of the participant's individual trial treatment phase, participants will recommence using their CPAP therapy.

11 SAFETY REPORTING

11.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	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 serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

11.2 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated – Where an event is not considered to be related to the IMP / intervention

Possibly Related – although a relationship to the IMP / intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably Related – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP / intervention

Definitely Related – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the IMP / intervention is the most likely cause.

11.3 Procedures for Recording Adverse Events

Adverse events listed in the active Xylometazoline and control saline trial medications include; a burning sensation in the nose and throat, local irritation, nausea, headache, dryness of the nasal membranes, temporary and passing visual disturbance, allergic reactions, cardiovascular effects including palpitations.

Participants will be asked to report any side effects they experience during their trial period. Patients will self-report symptoms in a structured daily e-diary including questions about any symptoms they experience.

All expected AEs will be captured within the e-Diary and any additional symptoms noted by the participant will be recorded on the CRF, whether or not attributed to trial medication. Those AEs that are expected side effects of the trial medication are specifically collected as part of the e-Diary process and will not be further reviewed as part of the safety reporting process. AEs that are not expected side effects of the trial medication (as specifically listed in the e-Diary) will be reviewed for relatedness, seriousness and (if required) expectedness.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, where possible the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or until the condition becomes stable.

11.4 Reporting Procedures for Serious Adverse Events

All SAEs occurring during the trial or until 7 days post the last spray must be reported on the ORTU reporting form to ORTU within 24 hours of the Site Study Team becoming aware of the event at respiratorytrialsunit@ouh.nhs.uk. ORTU will perform an initial check of the report, and ensure the SAE is reviewed by the Medical Reviewer (including expectedness assessment). The SAE will also be reviewed at the next ORTU Safety Oversight Group meeting. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and reported to ORTU.

11.5 Expectedness

Expectedness will be determined according to the latest approved Summary of Product Characteristics (SmPC) for Sudafed 0.1% Nasal Spray (Xylometazoline hydrochloride).

11.6 SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

11.7 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

12 STATISTICS

12.1 Statistical Analysis Plan (SAP)

A detailed Statistical Analysis Plan will be developed and signed off by the Trial Statistician and Steering Committee before any analysis. Data will be presented according to ConSoRT guidelines.

12.2 Description of Statistical Methods

Baseline data will be presented descriptively by randomisation group with appropriate measures of central tendency and numbers/proportions. All primary comparative analyses will follow the intention-to-treat principle as far as possible. Per protocol analyses will also be presented where appropriate, including for safety endpoints.

Outcomes will be compared between randomisation groups by the use of appropriate regression models including fixed effect terms for the randomisation group and the minimisation variables used for the randomisation. The models will also include the corresponding baseline value of the outcome measure where appropriate. The primary outcome will be assessed by a Cox regression analysis which will compare the time to recurrence of OSA between Xylometazoline and placebo. Secondary outcomes will be compared using logistic and linear regressions (with transformation as may be necessary) according to the nature of the outcome. ORTU SOPs will be followed to account for missing, unused and spurious data. Where data remain missing, the reasons will be examined and consideration given to imputation methods if appropriate.

The trial data will be analysed by the trial statistician at Musgrove Park Hospital by Prof Paul Ewings, the current Director of the Research Design Service South-West.

12.3 Sample Size

From our previous data (6) the relapse of OSA in an untreated group at 2 weeks is 85% (15% do not relapse or 'survive' CPAP withdrawal). By four weeks we assume this will be 10% 'surviving'. We estimate that an absolute improvement of 15% in the number 'surviving' at the end of the study period, i.e. to 25%, would be clinically useful.

These survival percentages imply a hazard ratio of 0.60 (assuming an exponential distribution for relapse time) which, for 90% power, requires a total sample size of 208 patients based on a simple logrank test. If we assume a withdrawal rate of 10% this comes to a total of 232 subjects required.

12.4 Analysis Population

All participants randomised will be included in the analysis.

12.5 Decision Points

No interim analysis is planned for this study. The CI will have access to the results for analysis with the stats team in line with the statistical analysis plan.

12.6 Stopping Rules

There are no interim analyses planned and hence no early termination criteria for the trial, given the small sample size and that the duration of follow up is short and pharyngeal Xylometazoline has a track record of being used safely in clinical practice. The safety committee can advise on early termination if there are safety concerns

12.7 The Level of Statistical Significance

As there is a single primary outcome and the hypothesis is that Xylometazoline is superior to placebo in the proportion of patients surviving without return of OSA the level of statistical significance will be a two-sided alpha of $p < 0.05$.

12.8 Procedure for Account for Missing, Unused, and Spurious Data

Please see the Data Management Plan.

12.9 Procedure for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be justified in protocol and/or in the final report, as appropriate).

13 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

13.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), laboratory and pharmacy records, diaries, correspondence, questionnaire data, SD cards (when provided to participants) and overnight oximetry data.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name.

13.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13.3 Data Recording and Record Keeping

All trial data will be entered on to a web-based, trial data management system (REDCap).

The study database is bespoke and hosted on the University of Oxford server with services provided through Oxford University Medical Sciences Division IT Services. The server and database are protected by a number of measures including anti-virus and anti-spyware applications, firewalls, encryption technology and permissions. The database will be backed up on a daily basis. The Data Manager will maintain a list of personnel with authorization to edit and/or view data. All trial data will be archived for 5 years.

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 this will be kept for up to 3 years post the end of the study only if the participant consents to being informed of the study results. If participants do not consent to this, identifiable information will be destroyed once data analysis has taken place.

The participants will be identified by a unique trial specific number in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

The oximeter data will be collected by the wristwatch oximeters linked to an android phone with a prepaid data card for 1 month. Pseudonymised data using the participants trial number will be uploaded to a central server and subsequently downloaded to secure desktop computer for daily analysis by the research fellow who is blinded to the treatment allocation.

14 QUALITY ASSURANCE PROCEDURES

The data will be securely stored in line with the principles of GCP standards and the data protection Act. Standard Operating Procedures (SOPs) will be followed to ensure quality control.

The Chief Investigator and authorised staff based at the ORTU will have access to participants' data from across all sites. The Principal Investigators at individual sites will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Participant's consent to this will be sought at the time of enrolment into the study.

ORTU has extensive experience in managing large multi-centre studies (>1000 patients in the last 8 years) and has an established track record of delivering high quality trials with excellent follow-up rates.

14.1 Risk Assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2 Monitoring

The study will be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures by CTRG. A detailed Risk Assessment will be conducted by ORTU before the trial starts and an appropriate Monitoring Plan will be developed by CTRG.

14.3 Trial Committees

14.3.1 Safety Oversight Group

The Oxford Respiratory Trials Unit (ORTU) Safety Oversight Group will conduct a review of all SAEs for the trial reported during the reporting period and cumulatively. The ORTU Safety Oversight Group requires at least three clinicians to attend each meeting (this may include the Chief Investigator). The Group will provide advice to the TSC and may correspond directly with the Sponsor if potential safety concerns are raised. 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

The content and timings of the ORTU Safety Oversight Group will be detailed in a Safety Oversight Group Charter, which will be agreed with the members.

14.3.2 Trial Steering Committee

A TSC will be convened to keep oversight of the trial. The following committee members have been invited to join the committee. A charter will be written explaining the role of the TSC and each of its members. All members are required to sign a declaration of their participation. The charter will define how often the committee will meet during the course of the study.

Chairman

Independent Member

Non-Independent Member

Patient Representative

Independent Statistician

PI and Grant Fund Holder

Non-Independent Member

Patient Representative

Chief Investigator

14.3.3 Trial Management Group

The TMG will meet frequently during the study to discuss the day to day management of the study

PI

Research Fellow

Trial Manager

CI

Data Manager

15 PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) 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 trial master file.

16 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –
(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial".

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 REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted through the HRA to an appropriate Research Ethics Committee (REC) and the MHRA and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.5 Participant Confidentiality

The trial staff will ensure that the participants' confidentiality is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and

authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR) and associated Data Protection Act (2018), which encourages pseudonymisation of data to the maximum extent practical.

Participant's data will be pseudonymised by the oximetry device number with no participant details. The data will be stored in a cloud-based server outside the UK. Participants will consent to their data being used in this way according to recent GDPR regulations. Data will be downloaded from the server to a secure computer for subsequent revalidation and analysis.

17.6 Expenses and Benefits

Reasonable travel expenses for the 2 additional visits will be offered to trial participants on production of receipts, or a mileage allowance will be provided as appropriate.

17.7 Other Ethical Considerations

With using the CPAP withdrawal model there is the potential for participant's symptoms to re-occur both in those receiving Xylometazoline and those receiving placebo. Participants may have a return of sleepiness during the day. Participants will be supported and advised about what to do if they become sleepy particularly around avoiding driving if they feel sleepy. In our experience from our previous trials using this model (over 130 patients) there have not been any serious events associated with this but participants will be advised of this theoretical risk.

Patients will not be enrolled if it is clinically advised by their clinical sleep physician that is not suitable for them to stop CPAP treatment.

It is possible that during the study we will find unrelated conditions. This is unlikely but if we do find these we will discuss these with the participants and their GP and refer them on to the appropriate specialist if needed.

18 FINANCE AND INSURANCE

18.1 Funding

Funding for the conduct of this study is provided by the Research for Patient Benefit grant through the NIHR. PB-PG-1216-20038

18.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

19 PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study is funded by NIHR. Dr Pepperell will be the senior author. The research fellow will be the first author on the primary paper. Other outputs authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

21 ARCHIVING

All trial documents will be archived for at least 5 years following the end of the trial. Documents will be stored in a secure archiving facility as required by ORTU SOPs

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APPENDIX A: TRIAL FLOW CHART

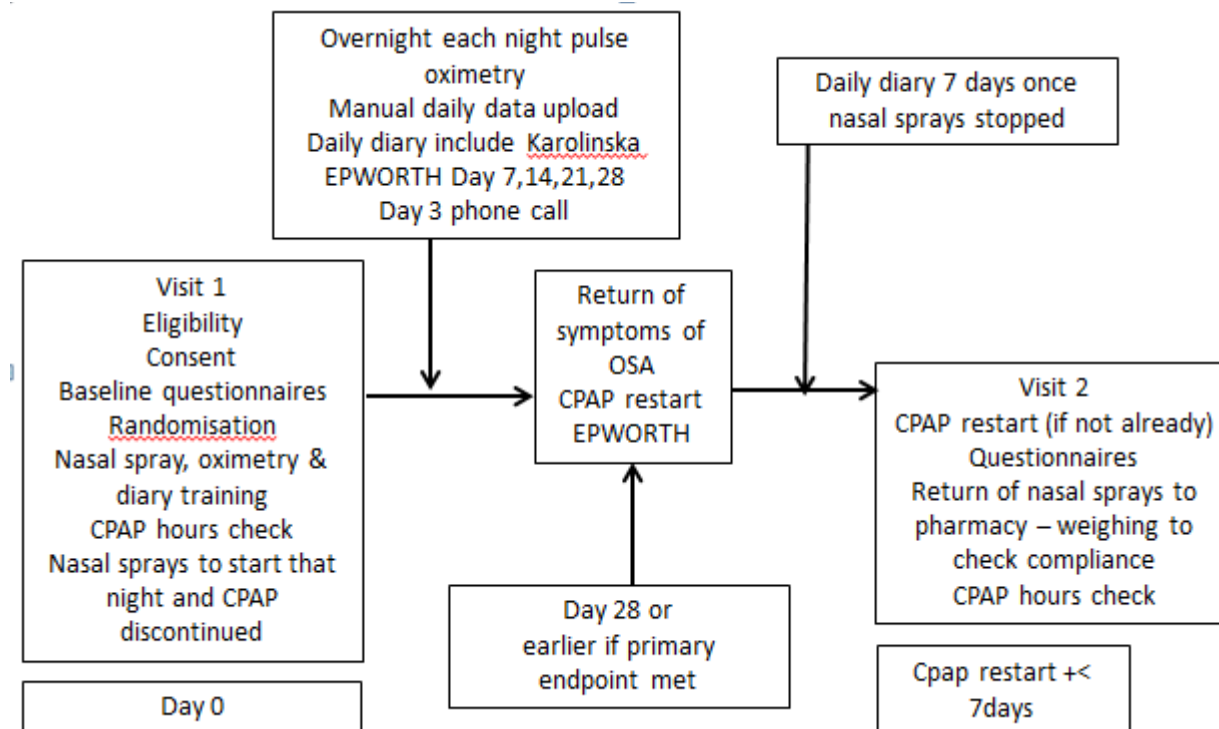
Pre trial

Screening of database and clinic attendances

Letter of invitation sent to suitable patients

Review of patients in routine CPAP follow up clinics

Arrange Visit 1 if patient decides to participate

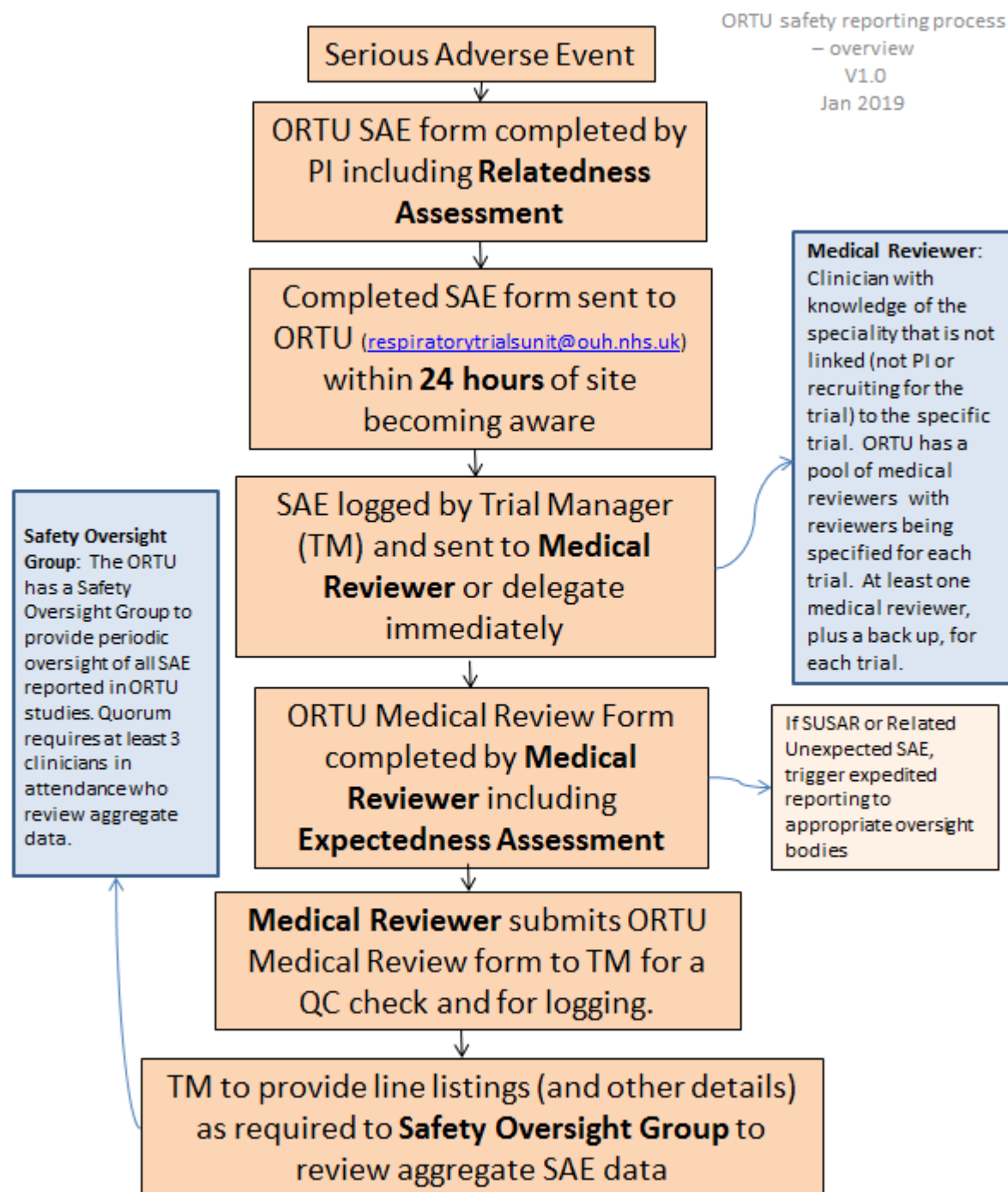


APPENDIX B: SCHEDULE OF PROCEDURES

Procedures									
	Pre study contact	Visit 1	Visit 1 (Telephone Call 1 - if face to face not possible)	Visit 1 (Telephone Call 2 - if face to face not possible)	Visit 1 (Telephone Call 3 - if face to face not possible)	Daily	Daily	Visit 2	Visit 2 (Telephone Call - if face to face not possible)
	Screening	Day 0				Day 1-28 (or until CPAP restart)	7 days after CPAP restart	Day 7 after CPAP restart (latest day 35)	Day 7 after CPAP restart (latest day 35)
Introduction to study provision of information	X	X	X						
Eligibility assessment	X	X		X					
Informed consent		X	X						
Demographics		X		X					
Medical history		X		X				X	X
Concomitant medications		X		X				X	X
Physical examination		X	N/A	N/A	N/A			X	N/A
Pregnancy test (Females of child-bearing potential only)		X		X					
E- Diary card initiation/ review		X			X			X	X
Quality of life and symptom questionnaires		X			X			X	X
Randomisation		X		X					
Dispensing of trial drugs		X		X					
IMP start						X (day 1-28 or until CPAP restart/ OSA return)			
CPAP hours check	X			X				X	X
Trial drug compliance (by pharmacy)								X	X
Adverse event assessments					X			X	X

Test oximetry recording			X						
Overnight oximetry						X			
E-diary card (Karolinska index daily, side effects daily, ESS weekly)						X	X	X	X
Telephone call	X					X (day 3)			
Adhoc telephone calls if inconsistencies seen at data download						X			

APPENDIX C: SAE REPORTING FLOW CHART



APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1 (MHRA)	2.0-3.0	06Nov2018	Emma Hedley	3. Synopsis: amended nasal spray dose from up to 2 sprays to one spray 8.3 Exclusion criteria added: A known hypersensitivity to Xylometazoline hydrochloride Previously undergone trans-sphenoidal hypophysectomy or surgery exposing the dura mater 9.2 Screening added: During visit 1 females of child-bearing potential will be asked to carry out a pregnancy test. 9.4 Randomisation, blinding and code-breaking: Paragraph two added regarding emergency unblinding. Appendix B: Pregnancy test added to the schedule of procedures
2	3.0-4.0	06Feb2018	Emma Hedley	2. Lay Summary, 7. Trial Design and 8.2 Inclusion Criteria: Amended CPAP treatment from 6 months to 3 months. 8.3 Exclusion Criteria: clarification on daytime oxygen saturations. 11.2 Causality, 11.4 Reporting Procedures for SAEs and 14.3.1 Safety Oversight Group: updated as per internal SOP and process. 12.3 Sample Size: clarified the power in paragraph 2. Appendix C: Updated SAE reporting flowchart.
3	4.0-5.0			8.2 Inclusion Criteria: Amended ODI range from 15-30 to 15-40, CPAP usage requirement reduced from 4 hrs/night to 3 hrs/night over the last 3 months. 9.5 Baseline assessments clarified, that the Oxford will only perform the Mallampati score and Taunton will perform, Mallampati, structured examination of their nasopharynx with otoscope, a scoring of their pharynx by Mallampati score, an assessment of competency of the

				nasal valve and site of snoring with mouth closed, mouth open, maximal tongue protrusion and maximal jaw advancement at baseline. In addition at Taunton Spirometry will also be performed at baseline.
5	5.0-6.0	04Dec2020	Dr James Davidson/Magda Laskawiec-Szkonter/Prof Najib Rahman	COVID-19 changes – to allow virtual visits to be carried out when the face to face visits cannot be completed due to COVID-19 restrictions. Removal of “nasal” throughout the protocol as clarification due to how the IMP is administered. Clarification that on review of oximetry data, participants will be contacted by their local teams only and not the research fellow.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.