Study Title: The **F**easibility of supplemental **OX**ygen in patients with resistant hypertension and **O**bstructive **S**leep **A**pnoea (FOX OSA)

Internal Reference Number / Short title: Feasibility of oxygen in resistant hypertension and OSA

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Chief Investigator:	Dr Chris Turnbull NIHR Clinical Lecturer University of Oxford, Nuffield Department of Medicine, Level 5, Room 5800, John Radcliffe Hospital, Oxford OX3 9DU christopher.turnbull@msd.ox.ac.uk Tel: 01865228209
Investigators:	Professor Paul Leeson Professor of Cardiovascular Medicine University of Oxford Professor John Stradling Emeritus Professor of Respiratory Medicine University of Oxford Dr Jamie Kitt DPhil student and Cardiology Registrar University of Oxford
Sponsor:	University of Oxford Clinical Trials and Research Governance, Joint Research Office, 2nd Floor Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7LQ, email: ctrg@admin.ox.ac.uk
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Chief Investigator Signature:	

No potential conflicts of interest

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 CONTACTS

Chief Investigator	Dr Chris Turnbull NIHR Clinical Lecturer University of Oxford, Nuffield Department of Medicine, Level 5, Room 5800, John Radcliffe Hospital, Oxford OX3 9DU christopher.turnbull@msd.ox.ac.uk Tel: 01865 228209
Sponsor	Clinical Trials and Research Governance University of Oxford Joint Research Office Churchill Hospital Old Road Headington Oxford, OX3 7GB Telephone: 01865 616480 Email: ctrg@admin.ox.ac.uk
Funder(s)	Oxford Health Services Research Fund (Research Project 1334) Catherine King Oxford Hospitals Charity OUH Cowley 3rd Floor Unipart House Business Centre Garsington Road Oxford OX4 2PG 01865 743340 Catherine.king@ndm.ox.ac.uk Academy of Medical Sciences Dr Clare McVicker Head of Grants 41 Portland Place London W1B 1QH 020 3141 3200 info@acmedsci.ac.uk
Clinical Trials Unit	Oxford Respiratory Trials Unit, University of Oxford Churchill Hospital Old Road Headington Oxford OX3 7LE 01865 225205 respiratorytrialsunit@ouh.nhs.uk

2. LAY SUMMARY

Obstructive sleep apnoea (OSA) is common affecting 1 in 4 adults to some extent. Whilst sleeping, patients with OSA have repeated episodes of narrowing of their throat leading to loud snoring, pauses in breathing, and disturbed sleep. Patients with OSA often feel sleepy in the daytime and often have high blood pressure. OSA is particularly common in patients who have persistently high blood pressure despite the use of three or more medications, a condition called resistant hypertension. Resistant hypertension affects up to 1 in 20 adults and increases the risk of heart attack and stroke.

The standard treatment for OSA is a tight-fitting face mask, called CPAP. Whilst CPAP is very effective, patients often struggle to use CPAP, especially those with few symptoms, such as many of those with resistant hypertension and OSA. New treatments to reduce blood pressure are needed for patients with resistant hypertension and OSA to reduce the risk of heart attacks and stroke. Overnight oxygen is easier to deliver than CPAP, not requiring a tight-fitting face mask and it was recently shown that overnight oxygen can improve morning blood pressure in patients with OSA. However, it is not known whether oxygen can be used as a treatment for resistant hypertension in OSA. The aim of this study is to see if overnight oxygen is feasible, acceptable and suitable for use in patients with OSA and resistant hypertension. It is important to know this to help design larger studies to test if it is an effective treatment.

3. SYNOPSIS

Study Title	The feasibility of supplemental oxygen in patients with resistant hypertension and obstructive sleep apnoea
Internal ref. no. / short title	FOX OSA
Study registration	The study has not yet been registered but will be prospectively registered prior to commencement of the study
Sponsor	Clinical Trials and Research Governance University of Oxford Joint Research Office Churchill Hospital Old Road Headington Oxford, OX3 7GB
Funder	Oxford Health Services Research Fund (Research Project 1334) and The Academy of Medical Sciences
Study Design	Feasibility study
Study Participants	Patients with resistant hypertension
Sample Size	20
Planned Study Period	12 months total study length. Maximum of 15 weeks for any individual participant from completion of home polygraphy to last follow-up.

Planned Recruitment period	1st January 2021 until 31st January 2022		
	Objectives	Outcome Measures	Timepoint(s)
Coprimary	To assess prevalence of OSA in screened participants with resistant hypertension To assess the feasibility of supplemental oxygen usage by participants with resistant hypertension and OSA	% of participants with an AHI >15 % of participants using supplemental oxygen for an average of ≥6 hours/night	Screening Home polygraphy 2 week follow-up visit
Exploratory Objectives	1. Explore the effect of supplemental oxygen on sleep apnoea related quality of life 2. The effect of supplemental oxygen on overnight oxygen levels 3. Change in blood pressure with supplemental oxygen 4. The effect of supplemental oxygen on carbon dioxide and base excess levels	1. Change in Sleep Apnoea related Quality of Life Index (SAQLI) 2. Change in the oxygen desaturation index 3. The mean and standard deviation of the change in blood pressure from triplicate recordings 4. Change in average capillary PCO_2 and base excess with supplemental oxygen	1. Baseline and 2 week follow-up visits 2. Screening polygraphy and night 14 oximetry 3. Days -2, -1 and 0, and Days 12, 13, 14 4. Baseline and 2 week follow-up visit
Intervention(s)	Supplemental oxygen supplied via an oxygen concentrator (NewLife, Airsep) at a flow rate of 5L/min via a loose fitting face-mask for 14 nights.		

4. ABBREVIATIONS

AHI	Apnoea hypopnoea index
BP	Blood Pressure
CI	Chief Investigator
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HR	Heart Rate
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
RES	Research Ethics Service
ORTU	Oxford Respiratory Trials Unit
OSA	Obstructive sleep apnoea
OUH	Oxford University Hospitals NHS Foundation Trust
PCO_2	Partial pressure of carbon dioxide
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

An estimated 1 billion people worldwide are affected by OSA to some extent [1], with 5% of adult males and 2.5% of adult females in Western populations having moderate to severe OSA and excessive daytime sleepiness [2]. OSA is associated with cardiovascular disease, particularly hypertension [3-5]. Continuous positive airway pressure (CPAP) is the standard treatment for OSA and improves daytime sleepiness, quality of life and blood pressure [6, 7].

Single agent anti-hypertensive regimens are as effective as CPAP in controlling blood pressure in OSA [8]. However, approximately 10% of patients with hypertension, and 2-5% of the general population, have

resistant hypertension not controlled by at least three anti-hypertensive agents [9-11]. Resistant hypertension increases the risk of cardiovascular disease [12]. OSA affects 80% of patients with resistant hypertension [13], and treating OSA with CPAP, when tolerated, has been shown to be effective in reducing blood pressure in these patients [14, 15]. However, CPAP is often poorly tolerated [16], and CPAP usage has been shown to be particularly low in minimally symptomatic patients when treated to reduce cardiovascular-metabolic risk [17-19]. Furthermore, patients with untreated OSA have an increased risk of cardiovascular complications [20].

It is important to develop new treatments for co-existent resistant hypertension and OSA, given the prevalence of these conditions, the increased cardiovascular risk, and the low usage of CPAP in those treated primarily for cardiovascular risk. Supplemental oxygen can greatly attenuate intermittent hypoxia in OSA [21], and has been proposed as an alternative to CPAP [22]. However, whilst patients are keen to explore alternatives to CPAP [23], it is not known if it is feasible to treat patients with coexistent resistant hypertension and OSA with supplemental oxygen.

Intermittent hypoxia has been shown to elevate blood pressure in animal and human models [24-28]. We showed, for the first time, that intermittent hypoxia is the dominant cause of raised morning blood pressure in OSA, rather than the often profound sleep fragmentation [29]. Supplemental oxygen abolished the substantial rise in morning blood pressure normally associated with CPAP withdrawal and return of OSA. Conversely other studies have not shown an effect of supplemental oxygen on blood pressure in treatment naïve patients with milder OSA [30]. Supplemental oxygen has not been assessed in patients with resistant hypertension and OSA, although treating OSA with CPAP has been shown to be efficacious [14, 15].

Supplemental oxygen

Long-term oxygen therapy is firmly established as a treatment for diseases causing continuous hypoxia, such as chronic obstructive pulmonary disease (COPD); thus, patients with COPD use supplemental oxygen therapy overnight. Overnight supplemental oxygen delivered by a concentrator is an easy and well-tolerated therapy, with a delivery strategy already in place in most developed countries. A previous RCT compared CPAP or supplemental oxygen (2l/min) or best-supportive care in patients with OSA and cardiovascular risk. Although CPAP reduced BP, there was no such reduction in BP with nocturnal oxygen [30]. This study contrasts with our CPAP withdrawal study [29], in that a lower flow rate of oxygen was used. This study used 2 L/min rather than 5 L/min oxygen, which would be less likely to attenuate intermittent hypoxia. Higher flow rates of oxygen can potentially cause more side-effects, such as nasal dryness, epistaxis and hypercapnia [31]. It is therefore necessary to investigate the tolerability of supplemental oxygen in patients with resistant hypertension before proceeding to larger studies of efficacy.

Patient involvement in shaping this research

This research has been directly informed from recognising the priorities of patients. We surveyed patients with OSA from the membership of the Sleep Apnoea Trust Association, a patient led OSA support group. We received 585 responses to our survey of their membership. 85% of respondents either strongly agreed or agreed that “Developing new treatments, instead of CPAP, is important” and 70% either strongly agreed or agreed with the statement “Extra oxygen can be delivered via a face-mask that does not require a CPAP machine. Whilst this will not stop symptoms of sleepiness from OSA, it

might help control blood pressure for some patients. Understanding if oxygen could be a new treatment option for OSA is important".

Aims

The aim of this study is to assess the feasibility of screening for obstructive sleep apnoea (OSA) in patients with resistant hypertension and the feasibility of supplemental oxygen treatment in these participants. The coprimary objectives are: i) To assess prevalence of OSA in screened participants with resistant hypertension. ii) To assess the feasibility of supplemental oxygen usage by participants with resistant hypertension and OSA.

Exploratory objectives include: i) The effect of supplemental oxygen on sleep-related quality of life. ii) The effect of supplemental oxygen on oxygen saturations recorded by overnight pulse oximetry. iii)The effect of supplemental oxygen on blood pressure (and the variability which will help inform future studies). iv) The effect of supplemental oxygen on venous bicarbonate as an integrated surrogate marker of hypercapnia.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Coprimary	To assess prevalence of OSA in screened participants with resistant hypertension To assess the feasibility of supplemental oxygen usage by participants with resistant hypertension and OSA	% of participants with an AHI >15 % of participants using supplemental oxygen for an average of ≥6 hours/night	Screening Home polygraphy 2 week follow-up visit
Exploratory objectives	1. Explore the effect of supplemental oxygen on sleep apnoea related quality of life 2. The effect of supplemental oxygen on overnight oxygen levels	1. Change in Sleep Apnoea related Quality of Life Index (SAQLI) 2. Change in the oxygen desaturation index	1. Baseline and 2 week follow-up visits 2. Screening polygraphy and night 14

	3. Change in blood pressure with supplemental oxygen	3. The mean and standard deviation of the change in blood pressure from triplicate recordings	3. Days -2, -1 and 0, and Days 12, 13, 14
	4. The effect of supplemental oxygen on carbon dioxide and base excess levels	4. Change in average capillary PCO_2 and base excess with supplemental oxygen	4. Baseline and 2 week follow-up visit

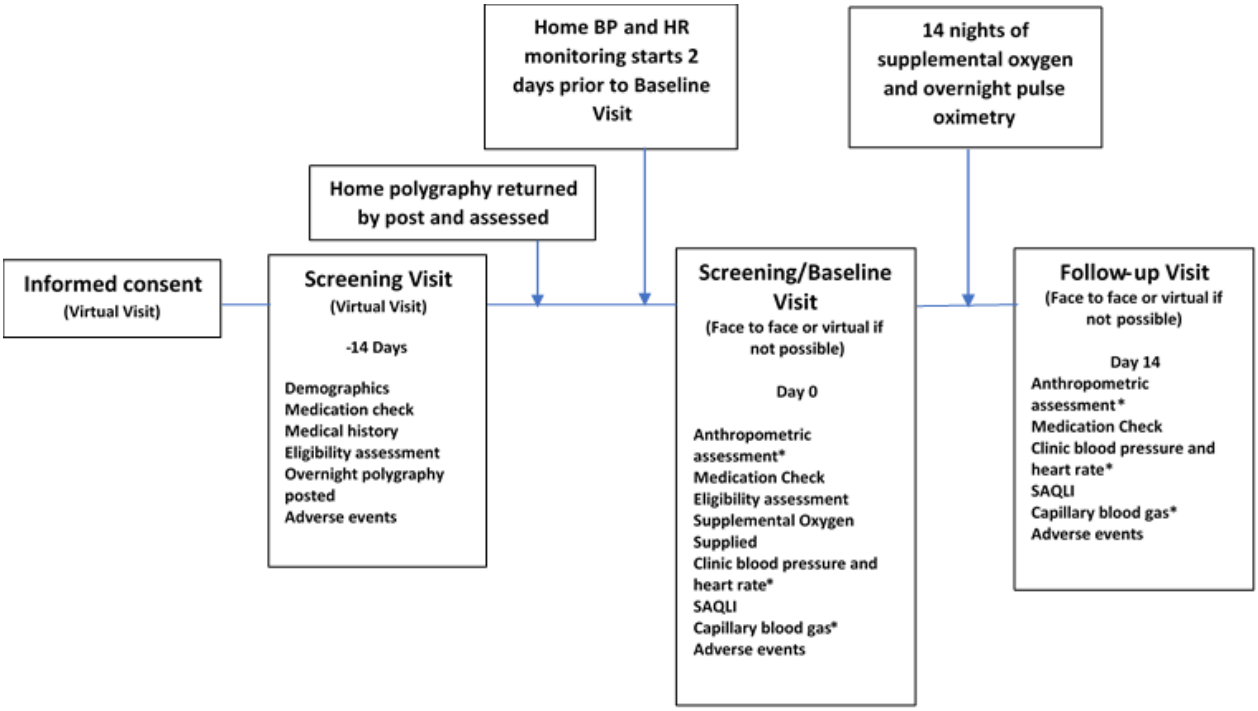
7. STUDY DESIGN

A single arm, non-blinded study assessing the feasibility of supplemental oxygen in participants with resistant hypertension and OSA. The trial will be conducted in a single UK centre, in a tertiary hospital and will recruit participants with known resistant hypertension from the Department of Cardiology in the Oxford University Hospitals NHS Foundation Trust.

The study is divided into two stages, with *Stage 1* identifying the prevalence of OSA in patients with resistant hypertension in a tertiary hypertension clinic, and *Stage 2* assessing the feasibility of supplemental oxygen in participants with resistant hypertension who were identified to have OSA in *Stage 1*.

Participants can expect to be in the study for a minimum of 15 days and a maximum of 15 weeks from the time of their home polygraphy. Participants will attend two virtual screening visits in *Stage* 1, and if eligible, will attend a face-to-face baseline visit and a face-to-face follow-up visit in *Stage 2*.

If face-to-face appointments are not possible (for example due to site guidance relating to COVID-19) *Stage 2* will be carried out virtually with two virtual visits instead of two face-to-face visits.



*Only if face to face visit possible

Figure 1 - Study flow diagram.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants with resistant hypertension undergoing screening for co-existent OSA.

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
- Current diagnosis (at time of enrolment) of resistant hypertension
- Ambulatory blood pressure monitoring showing either systolic >145mmHg or diastolic >85mmHg on ambulatory blood pressure monitoring following observed administration of medications
- Stable dose of three or more current regular anti-hypertensive medication for at least 4 weeks prior to trial entry
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Participant has access to home computer and/or other device connected to the internet and an email account

8.3. Exclusion Criteria

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

- 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 participants 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
- Secondary causes of hypertension (other than OSA)
- Excessive sleepiness with an ESS >16 (as assessed clinically prior to enrolment) or history of a sleepiness-related driving accident
- Professional drivers or vigilance critical occupation
- Any prior use of CPAP
- Current smoker or other cause of increased fire risk with oxygen therapy (i.e. relative smoking in the participants residence)
- An AHI of <=15 on both nights of screening polygraphy
- Baseline capillary blood gas PCO_2 >6.5kPa, or if unavailable, awake saturations <93% on overnight polygraphy (*assessed at the face to face Baseline visit prior to proceeding with the visit)*
- Pregnancy at enrolment or during the trial (as pregnancy related OSA is considered a separate condition to OSA outside of pregnancy)

9. PROTOCOL PROCEDURES

Procedures	Preliminary screening	Virtual Informed Consent	Virtual Screening Visit	Screening assessment	Baseline Visit (face to face if possible)	Follow-up Visit (face to face if possible)	Daily during trial
Review of medical notes/clinic databases#	X						
Informed consent		X					
Demographics			X				
Anthropometric assessment (only if face to face visit possible)					X	X	
Medication check			X		X	X	
Medical history			X				
Eligibility assessment			X		X		
Overnight Polygraphy supplied			X				
Overnight Polygraphy assessed on return of the device from participant				X			
Supplemental oxygen supplied					X		
Clinic blood pressure and heart rate (only if face to face visit possible)					X	X	
SAQLI					X	X	
Capillary blood gas (if face to face visit possible, otherwise saturations <93% on overnight polygraphy assessed)					X (participants only to proceed to baseline visit if exclusion criterion not met)	X	
Adverse event assessment			X		X	X	
Home blood pressure and heart rate reading##*							X
Overnight Pulse oximetry**							X

preliminary screening of notes and clinic databases will be conducted by the clinical team

* every morning in triplicate during the trial starting from two mornings prior to the baseline visit

** every night during the trial starting the night after the baseline visit

SAQLI=sleep apnoea quality of life index

9.1. Recruitment

Participants will be recruited from the Department of Cardiovascular medicine specialist hypertension clinic and will not have previously used CPAP. Patients will be identified by the cardiology team and invited to participate in this study (**preliminary screening including Epworth sleepiness score collected as part of standard clinical practice**). Many patients now attend the hypertension clinic virtually, and in this instance the clinical team will invite patients during this consultation and request permission to either email or post a copy of the PIS. Patients interested in participating will be provided a copy of the PIS and their permission will be sought to be contacted by the research team. Interested patients will

then be invited to meet (virtually or face to face dependent on the current OUH policies) with the research team to discuss the trial further after being given at least one week to consider the trial. As participants will have formal screening to determine if they have OSA after informed consent there is no upper limit on time from invitation to the virtual screening. The participant will be allowed as much time as wished to consider the information (at least one week), and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial.

9.2. Informed Consent

Participant informed consent will be performed virtually using video conferencing (using Attend Anywhere) or a telephone call **(Virtual Informed Consent)**. It will last about 20 minutes. At the time of the consent discussion the researcher will document the consent in the participant's notes and they will sign the consent form indicating that the participant had agreed to take part. The participant will be provided a copy of the signed consent form for their records either via email or in person at the follow-up visit if a face to face is possible. The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. The signed consent form will also be retained at the study site.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; 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 (including risks associated with oxygen therapy such as fire risk and any risks associated with study procedures e.g. blood taking which may lead to pain, bruising or tissue damage). 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.

Part of the informed consent for this trial will include consenting to sharing of information from this study with any participants GP. This will be done for all participants who provide informed consent, but is particularly important if a new diagnosis of OSA is made.

9.3. Screening and Eligibility Assessment

Following the informed consent process, participants will be posted or will collect overnight polysomnography and blood pressure device and a diary. This will include a stamped addressed envelope to return the overnight polygraphy equipment. If collecting equipment in person, participants will be required to collect it by driving to the hospital and a member of the research team will meet them in the carpark to place this equipment into the back of their car. Research staff follow current COVID-19 guidance (including but not limited to face coverings and personal protective equipment).

A **virtual screening 1 visit** (lasting about 20 minutes) will be arranged for a date after participants have received this equipment. Participants will have demographic data, current medications, Epworth sleepiness score (assessed from medical notes), and medical history assessed. Participants will be supplied with an overnight polygraphy kit and the research team will explain how to use this (either via video-call or telephone). Written instructions on how to use the sleep kit will also be provided. Participants will be instructed not to perform their overnight polygraphy if they have current symptoms of COVID-19 (as specified by the latest Department of Health and Social Care guidance) and to inform the

research team. Screening polygraphy will then be postponed until after completion of required self-isolation or the participant has had a negative COVID-19 test (as specified by the latest Department of Health and Social Care guidance). Participants will also be asked to return the polygraphy after completion in the stamped addressed envelope provided. Prior to returning the equipment patients will be requested to dispose of their single use nasal cannula and thoracic belts.

At this screening visit the research team will explain to participants (either via video-call or telephone) how to use a blood pressure machine and instructed on when to start recording their blood pressure. Written instructions on how to use the sleep kit will also be provided. Participants will be asked to start recording their blood pressure in the morning, shortly after waking. Participants will be instructed to sit quietly for 5 minutes prior to using a home blood pressure monitor record their blood pressure in triplicate with at least 1 minute between each of the three recordings. Recordings will be stored electronically on the blood pressure machine for later download (Omron M10) with participants also instructed to record blood pressure values in their diary as a back-up. This data is stored on the device and downloaded onto a hospital computer at the site once the blood pressure machine is returned. This does not use cloud based storage. Participants will be instructed to continue recording their blood pressure on a daily basis every morning until their follow-up visit.

Upon receipt of the overnight polygraphy, the equipment will be cleaned in line with the trust standard operating procedures. Polygraphy will be assessed against the eligibility criteria and participants will be informed by phone of their eligibility. Overnight polygraphy will be considered adequate for analysis if there is > 4 hours of adequate airflow, oximetry and effort signal from polygraphy on at least one night. Rescreening polygraphy can be re-attempted on a maximum of two occasions if these quality criteria are not met. If required, this will require postage or collection of equipment on multiple occasions. Should a participant be eligible to continue with the study, a date for attending a screening 2/baseline visit will also be arranged during this phone call. The baseline visit should occur within 12 weeks of the successful completion of the screening polygraphy.

A further inclusion criterion is required for participants to continue in the study beyond home screening polygrapahy:

- Objectively confirmed obstructive sleep apnoea with an AHI of >15 on at least one of two nights of screening polygraphy

9.4. Baseline visit

This study does not involve randomisation. Participants who meet the eligibility criteria will be enrolled following successful screening.

Participants will attend for their **baseline visit** (lasting about 1-2 hours) at least 1 day and no more than 12 weeks after completing their screening polygraphy. Assessment of any new medications will be made and eligibility criteria for Stage 2 of the study will be confirmed at that point.

Where possible, baseline assessments will be conducted face-to-face. Participants will be telephoned on the day prior to the planned face to face visit to complete a COVID-19 questionnaire in line with trust standard operating procedures. Participants will be instructed not to attend if they have current symptoms of COVID-19 (as specified by the latest Department of Health and Social Care guidance) and to

inform the research team. The visit will then be postponed until after completion of required self-isolation or the participant has had a negative COVID-19 test (as specified by the latest Department of Health and Social Care guidance). The current local trust operating procedures will be followed with respect to wearing face coverings and PPE. All equipment used will be cleaned in line with trust standard operating procedures.

Should the local site guidance not permit face-to-face appointments, this visit will be replaced with a virtual appointment and all required equipment will be collected by participants or delivered to participants ahead of the appointment.

If face to face visits are possible, participants will have capillary blood gas measurement as described in the sample handling section. Should this show a carbon dioxide level > 6.5kPa, participants will not be able to continue in the trial as there would be concerns in these individuals that supplemental oxygen might worsen carbon dioxide levels. If face-to-face visits are not possible, the capillary blood gas assessment will not be conducted. Instead, to ensure participants are not put at risk of elevated carbon dioxide levels, participants with awake oxygen saturations <93%, defined as the oxygen saturations during the first 10 minutes of overnight polygraphy on either night, will not be included. This will ensure that participants with hypercapnia are not put at risk. This virtual visit will last about 1-1.5 hours.

A further exclusion criterion will be assessed at this screening visit:

- Baseline capillary blood gas PCO_2 >6.5kPa, or if unavailable, awake saturations <93% on overnight polygraphy

Participants who meet this criterion will not be able to continue in the study.

At the baseline visit participants will have their office blood pressure and heart rate recorded in triplicate following at least 5 minutes of rest in a seated position from their left arm. At least one minute will be allowed between each blood pressure measurement. If conducted virtually, this assessment will not be conducted.

Participants will be requested to complete a Sleep Apnoea Quality of life Index (SAQLI) questionnaire. If conducted virtually, this assessment will be conducted via telephone or video-call.

Participants will be supplied with a pulse oximeter (Minolta 300i) and instructions on its use will be given. They will be asked to perform oxygen saturation measurements (and pulse rate rises) at home every night, using this simple overnight pulse oximeter.

Participants' height and weight will be recorded whilst dressed without wearing shoes. If conducted virtually, participants will be asked to provide their own height and weight if possible.

Participants' neck circumference will be measured from the level just below the laryngeal prominence using a single-use disposable tape measure. If conducted virtually, participants will be asked to record their neck circumference and will have been provided with a single-use disposable tape measure.

Participants will be shown the overnight oxygen concentrator and nasal cannulae or oxygen face mask (participant preference) usage. The baseline hours/night of operation of the oxygen concentrator will be

recorded in the CRF from the concentrators clock. Participants will be assisted in transporting this where necessary. Participants will be instructed to start using this from the evening of their baseline visit when they go to sleep for 14 nights.

Participants will be asked about any adverse events with any adverse events being recorded in the CRF.

9.5. Subsequent Visits

Participants will attend a follow-up visit 14-17 days after the baseline visit starting on supplemental oxygen.

This visit will repeat the measures taken at the baseline assessments as detailed in section 9.4 with the following exceptions: height, weight and neck circumference recordings will not be repeated, capillary blood gas measurements will be recorded but will not be used to assess eligibility at the follow-up visit, demonstration of equipment use will not be repeated, if an ESS is repeated for clinical reasons within +/- 5 days of this subsequent visit it will be recorded on the CRF from the medical notes. All equipment (oxygen concentrator, blood pressure machine, pulse oximeter) and patient diary will be returned. If performed virtually arrangement to collect all equipment will be made.

9.6. Blinding and code-breaking

This is an unblinded study so does not require blinding or code breaking.

9.7. Description of study intervention(s), comparators and study procedures (clinical)

9.7.1. Description of study intervention(s)

Oxygen treatment

The application of supplemental oxygen overnight for 14 days using nasal cannulae or oxygen face masks (participant preference), at a flow rate of 5L/min from a normal oxygen concentrator (AirSep Corporation Newlife Elite). Participants will be instructed that they can store the concentrator in another room other than the bedroom to reduce disturbance from noise and will be supplied with up to 15m of oxygen tubing to allow this. Participants will be instructed to ensure the oxygen tubing is stored out of the way when not in use. Participants will be instructed to turn on the oxygen concentrator immediately prior to going to bed and to switch the concentrator off immediately when they awaken in the morning.

9.7.2. Description of comparator(s)

As a feasibility study there is no comparator.

9.8. Sample Handling

The only samples that will be collected from participants (if the face to face visit is possible) will be a capillary blood gas measurement at both the baseline and follow-up visit. This will enable recording of capillary carbon dioxide and bicarbonate levels to assess if there is any change in these measurements following using supplementary oxygen.

Capillary blood gas measurements provide a more accurate assessment of carbon dioxide levels than venous blood gas sampling, with results being comparable to arterial blood gas samples. Capillary blood

gas sampling is no more painful than a venous blood sample and is much less painful/ invasive than arterial blood gas sampling [32]. Capillary blood gas sampling involves taking a small amount of blood from the earlobe (<1ml) after application of a vasodilator to the earlobe and will be conducted in accordance with the OUH Sleep Unit SOP. At both baseline and follow-up visit <1ml samples will be taken.

Capillary blood gas samples will be analysed immediately using point of care testing (bedside blood gas analyser) with any excess blood being disposed of in accordance with local procedures.

After analysis all samples will be destroyed in line with the Human Tissue Act; no samples will be stored in this study.

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to discontinue the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE
- Inability to comply with trial procedures
- Participant decision

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Participants can withdraw at any time but any data collected will be kept and analysed. This will be fully explained in the PIS.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial intervention or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial intervention or results in inability to continue to comply with trial procedures

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

If treatment is discontinued due to pregnancy the pregnancy will be followed-up to outcome. See the Safety Reporting section below.

9.10. Definition of End of Study

The end of the trial will be the last virtual or face to face visit of the last participant.

10. SAFETY REPORTING

Safety data will be collected for any events that occur from the participant's screening visit until their follow-up visit.

10.1. Procedure for Recording Adverse Events

Adverse Events that are judged by the investigator to possibly be related to the intervention (including but not limited to nasal dryness, mild nosebleeds and morning headache) will be recorded as part of the CRF for the study. Adverse events that are judged by the investigator not to be related to the intervention will not be recorded unless constituting an SAE (see 10.3).

10.2. Definition of Serious Adverse Events

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.

10.3. Reporting Procedures for Serious Adverse Events

There are no expected SAEs in this study. Any SAEs that occur must be reported on the ORTU SAE reporting form to ORTU as soon as possible site study team becoming aware of the event. ORTU will perform an initial check of the report, request any additional information, and ensure a nominated Medical Reviewer provide a review. It will also be reviewed at the next Trial Safety Oversight Group meeting. All SAE information must be recorded on an SAE form and scanned and emailed, to ORTU respiratorytrialsunit@ouh.nhs.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.

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

10.4. Safety Oversight

The ORTU Safety Oversight Group will review all SAEs for the study 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

11. STATISTICS AND ANALYSIS

As this is a feasibility study, no formal power calculation has been conducted. The recruitment target is 6 participants receiving intervention and it is estimated that 15 participants will need to be screened. Allowing for drop outs 20 participants will be screened. The coprimary outcome measures and the two main measures of success will be the prevalence of OSA in screened participants with resistant hypertension, and the percentage of using their supplemental oxygen for an average of ≥6 hours/night. Prevalence of OSA of 40% and CPAP adherence as described above in >60% of participants are the stop-go criteria. This will validate the prevalence of OSA in resistant hypertension. Approximately 75% of resistant hypertension patients have OSA as defined by an AHI >10 using inpatient polysomnography. The study aims to identify OSA in ≥40% of resistant hypertension patients screened using polygraphy and a more stringent AHI cut-off of >15. CPAP usage is usually low at between 2.5 and 3.5 hours/night in patients without the typical symptoms of OSA. Supplemental oxygen usage in the team's previous trials was higher at 7.2 h/night over 2 weeks. In order to consider supplemental oxygen a feasible treatment in patients with resistant hypertension the majority of participants (≥66%) would need to be able to use it for the majority of the night (≥6 hours/night). In addition, exploratory outcome measures will give important safety data and information regarding size and variability of the effect of supplemental oxygen on blood pressure.

No interim analysis is planned for this study.

12. DATA MANAGEMENT

The plan for the data management of the study is outlined below. A separate Data Management Plan will be produced.

12.1. 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), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

All trial data will be entered into the REDCap research data management system in the form of an electronic case report form (eCRF).

The participants will be identified only by a unique trial-specific code in all electronic records created for the trial. The name and any other directly-identifying detail will NOT be included in any trial data stored on the electronic database.

Data will be held on a secure, backed-up server for the duration of the trial. Access to view and/or enter data will only be available via the data management system for authorised personnel (validated by individual user credentials, with different permissions granted as appropriate). The system will maintain an audit trail of all entries/modifications/deletions made to the data.

After trial completion, the study data will be archived electronically.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

The study will be conducted in accordance with the current approved protocol, GCP guidelines, relevant regulations and local standard operating procedures. The study will be monitored as per the study risk assessment.

13.2. Study monitoring

Appropriate monitoring will be performed according to the trial specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.3. Study Committees

As a feasibility study there will be no study committees. Safety reporting will be monitored by the ORTU SOG (see 10.4).

14. 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.

15. 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.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required) 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.

16.4. Other Ethical Considerations

The most common symptom of OSA is that of daytime sleepiness. An important ethical consideration is the risk of accidents, either at work in vigilance critical occupations or whilst driving. To mitigate the risk of accidents individuals with severe daytime sleepiness (ESS>16), a history of sleepiness related road traffic collisions, professional drivers and those in vigilance critical occupations will be excluded. Should circumstances change during the trial and participants develop anyone of these criteria, subjects will be withdrawn and considered for immediate treatment with CPAP, the current standard treatment of OSA.

Supplemental oxygen is not routinely given as treatment for OSA but is commonly given for other conditions. With oxygen an important ethical consideration is that of developing daytime hypercapnia with supplemental oxygen. Participants most at risk are those with an elevated baseline carbon dioxide level or low resting oxygen saturations. Those with carbon dioxide levels >6.5kPa or mean saturations <93% will be excluded. Participants will be informed of the symptoms of developing hypercapnic, particularly early morning headaches and encouraged to report these.
As supplemental oxygen is not given in routine clinical practice, participants will be unable to continue supplemental oxygen treatment at the end of the study. Participants will be asked if they would like to be referred for treatment of OSA with CPAP under the clinical team at the end of the study.
This protocol includes taking two capillary blood samples, which are taken from the earlobe, if face-to-face visits are possible. These blood tests can be slightly painful but should not be any more painful than normal blood tests. There is also a very low risk of tissue damage although this is very unlikely and the test will be conducted by an experienced clinician.

16.5. Reporting

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

16.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

Oxford Health Services Research Fund (Research Project 1334) has provided funding for this project (£9306.04). Academy of Medical Sciences Starter Grants for Clinical Lecturers (REF: SGL022\1063) has provided funding for this project (£17035.46).

17.2. 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.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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

Not applicable

19. ARCHIVING

The study documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms along with the study database) will be kept for a minimum of five years. They will archived as per the ORTU Archiving SOPs. The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the University server, and electronically archived at study completion for a minimum of five years.

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21. APPENDIX A: STUDY FLOW CHART

See text

22. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

See text

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).