Guy's and St Thomas' NHS
NHS Foundation Trust

FULL PROTOCOL TITLE OF THE STUDY

Exacerbation Prevention in chronic obstructive pulmonary disease (COPD) – obstructive sleep apnoea (OSA) overlap syndrome: The clinical and health economic impact of treating patients with COPD-OSA overlap syndrome and a high risk of future exacerbations with positive airway pressure therapy (PAP) a multicentre randomised controlled trial

SHORT STUDY TITLE and ACRONYM

Exacerbation Prevention in COPD-OSA (EPIC-OSA)

Chief Investigator:
Dr Patrick Murphy
Academic Lead/Key Collaborator:
Dr Swapna Mandal

Sponsored by:
Guy's and St Thomas' NHS Foundation Trust (GSTT)

Funded by:
NIHR Health Technology Assessment Programme

Protocol version number and date:
V0.14, 14Oct2024

Name and address of Co-Investigator(s), Trial Manager and key study contacts, Funder, Statistician, Laboratories etc.

Name:	NIHR
Address:	Alpha House, Enterprise Road, Southampton, SP16 7NS
Email:	isla.henderson@nihr.ac.uk

Name:	Dr Swapna Mandal - Academic Lead/Key Collaborator
Address:	Royal Free Hospital NHS Foundation Trust
Email:	swapnamandal@nhs.net

Name:	Dr Chris Turnbull – Co App (PPIE Lead)
Address:	Nuffield Department of Medicine, University of Oxford
Email:	Christopher.turnbull@ouh.nhs.uk

Name:	Professor Najib Rahman – Co App
Address:	Oxford Respiratory Trials Unit (ORTU)
Email:	Najib.rahman@ndm.ox.ac.uk

Name:	Dr Sophie West – Co App
Address:	Newcastle Upon Tyne Hospitals NHS Foundation Trust
Email:	Sophie.west13@nhs.net

Name:	Susan Elsey – Co App (Retired)
Address:	Royal Free London NHS Foundation Trust
Email:	sueelsey@googlemail.com

Name:	Emma Hedley – Senior Trial Manager
Address:	Oxford Respiratory Trials Unit (ORTU)
Telephone:	01865 282952
Email:	Emma.hedley@ndm.ox.ac.uk

Name:	Nicola Williams – Senior Trial Statistician
Address:	Primary Care Clinical Trials Unit (PC-CTU)
Email:	Nicola.williams@phc.ox.ac.uk

Name:	Yaling Yang – Health Economist
Address:	Primary Care Clinical Trials Unit (PC-CTU)
Email:	yaling.yang@phc.ox.ac.uk

PROTOCOL VERSION NUMBER AND DATE

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Detail the key protocol update
Current	*V1.0*	*14Oct2024*	*Dr Patrick Murphy*	*First Version*
Previous				

Guy's and St Thomas' NHS
NHS Foundation Trust

SIGNATURE PAGE

The Chief Investigator and the R&D (sponsor office) have reviewed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the UK policy Framework for Health and Social Care research, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator Dr Patrick Murphy	P Murphy 23/Oct/2024 17:57:29	23/10/2024
	Signature	Date

This Protocol template is intended for use with UK sites only.

CONTENTS PAGE

1. LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
AHI	Apnoea-hypopnoea Index
AR	Adverse Reaction
BTS	British Thoracic Society
CAT	COPD Assessment Tool
CI	Chief Investigator - The overall lead researcher for a research project
COPD	Chronic Obstructive Pulmonary Disease
COPD-OSA	Chronic Obstructive Pulmonary Disease – Obstructive Sleep Apnoea
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
eMRCD	Extended Medical Research Council Dyspnoea Score
EQ-5D-5L	EuroQol-5 dimension 5 level score (with respiratory and sleep bolt ons)
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HRA	Health Research Authority
ICF	Informed Consent Form
LTOT	Long term oxygen therapy
NHS R&D	National Health Service Research & Development
ORTU	Oxford Respiratory Trials Unit
OSA	Obstructive Sleep Apnoea
PAP	Positive Airway Pressure
PC-CTU	Primary Care Clinical Trials Unit
PI	Principal Investigator- An individual responsible for the conduct of the research at a research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.
PPIE	Patient and Public Involvement and Engagement
QA	Quality Assurance

QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SATA	Sleep Apnoea Trust Associated
SOP	Standard Operating Procedure
Sponsor	The organisation or partnership that takes on overall responsibility for proportionate, effective arrangements being in place to set up, run and report a research project.
TMG	Trial Management Group
TSC	Trial Steering Committee

Glossary of Definitions and Terms

AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease is a clinical diagnosis made when a patient with COPD experiences a sustained deterioration in their COPD symptoms (including breathlessness, cough, and/or sputum production) beyond normal day-to-day variability.

FEV_1: Forced Expiratory Volume in one second – the volume of air exhaled in the first second of the **FVC** (Forced Vital Capacity) manoeuvre.

Vital observations: measurements including heart rate, blood pressure, respiratory rate, peripheral oxygen saturation and temperature. May be combined to produce an aggregate score such as in the NEWS2 (National Early Warning Score).

2 SUMMARY/SYNOPSIS

Title	Exacerbation Prevention in chronic obstructive pulmonary disease (COPD) – obstructive sleep apnoea (OSA) overlap syndrome: The clinical and health economic impact of treating patients with COPD-OSA overlap syndrome and a high risk of future exacerbations with positive airway pressure therapy (PAP) a multicentre randomised controlled trial
Protocol Short Title/Acronym	Exacerbation Prevention in COPD-OSA (EPIC-OSA)
Study Phase if not mentioned in title	Phase III
Is the study a Pilot?	Embedded 1 year pilot
IRAS Number	332000
REC Reference	
EDGE reference	161181
Study Duration	27 months recruitment, 12 months follow-up (39 months total duration)
Methodology	Randomised controlled trial
Health condition(s) or problem(s) studied	COPD and OSA
Purpose of clinical trial	To assess the clinical and cost-effectiveness of PAP therapy in patients with COPD-OSA overlap syndrome with a high risk of exacerbations.
Primary objective	The primary outcome is the frequency of moderate and severe COPD exacerbations in the 12 months post randomisation.
Secondary objective (s)	Health care utilisation Hospital admissions (all cause and respiratory related) Health related quality of life (COPD assessment test, eMRCD, EQ-5D-5L) Sleep quality (Pittsburgh sleep quality index) Lung function (FEV_1, FVC)
End of study definition	The End of Study will have been reached when the database has been locked.
Number of Participants	600 total, randomised 1:1
Study Type	Multi-centre randomised controlled trial
Data collected/storage (if applicable)	Data will be stored by ORTU with analysis completed by the PC-CTU statistical and health economic team.

3 INTRODUCTION

Patients with chronic obstructive pulmonary disease-obstructive sleep apnoea (COPD-OSA) overlap syndrome have higher rates of COPD exacerbations compared to patients with similar severity COPD without OSA[1].

It is currently unknown whether treating OSA in those with COPD-OSA overlap reduces COPD exacerbation rates.

Exacerbations in COPD

COPD exacerbations are characterised by acute transient worsening of symptoms such as dyspnoea, sputum production, sputum purulence and cough which are above the normal day to day variation in symptom burden and are usually associated with escalation of medical therapy[2, 3].

Exacerbations are significant events impacting on patient quality of life, lung function, future exacerbation risk and survival[7, 8]. Exacerbations are recognised as a significant concern by patients[9], with exacerbation prevention ranked the number 1 research priority by COPD patients[4]. Exacerbations are significant for the health service accounting for >120,000 hospital admissions (1 in 8 of all hospital admissions) annually[10] each costing an estimated £3,726[11]. Reducing exacerbations has the potential to improve: outcomes, patient and carer experience, and to reduce costs to the health service.

Obstructive Sleep Apnoea (OSA)

OSA is a condition where the upper airway collapses and breathing stops repeatedly during sleep leading to intermittent hypoxia, sleep disruption, excessive daytime sleepiness and increased long term cardiovascular risk[12, 13].

OSA is common and it is estimated that up to 23% of women and 50% of men suffer moderate to severe OSA[14], however it is not commonly screened for in patients with chronic respiratory diseases such as COPD.

Treatment for OSA is positive airway pressure (PAP) therapy which aims to splint the upper airways and prevent intermittent hypoxia and therefore reduces daytime sleepiness and high blood pressure[5]

COPD-OSA Overlap syndrome

COPD-OSA overlap syndrome has an estimated prevalence of up to 67% in patients with COPD[17] and 1-4% in the general population[17]. Specifically, in data collected by the trial team, almost 1 in 3 (28%) patients with a hospital exacerbation of COPD had moderate to severe OSA and may therefore benefit from intervention[18].

Observational data shows that patients with COPD-OSA overlap syndrome suffer more frequent exacerbations than patients who have similar severity COPD without OSA[1] and that those who are adherent with PAP therapy have reduced severe exacerbations. However, there are no randomised trials demonstrating that treating OSA with PAP in patients with overlap syndrome reduces exacerbation frequency or improves health related quality of life. Lack of data on the effectiveness of PAP for COPD-OSA overlap has been identified as a gap in knowledge by professional societies[6].

The strong observational link between OSA and COPD exacerbation risk, the prevalent nature of this condition, and the multitude of clinical impacts of exacerbations makes exacerbation reduction an important end-point for clinical trials. The importance of exacerbation reduction is confirmed by the James-Lind Alliance[4] and the European Respiratory Society core outcome set[19].

Understanding the clinical benefit of PAP in overlap syndrome is important in shared decision making with patients because PAP therapy can be poorly tolerated[15], particularly in patients who are not sleepy. Thus deciding on continuation of therapy needs better understanding of the impact on patient relevant outcomes, as current guidance is to withdraw therapy if there is no symptomatic benefit[16]. This recommendation assumes that patients with a low symptom burden or minimal improvement in sleep symptoms will not benefit from a reduction in exacerbation risk with ongoing treatment. If PAP therapy has an impact on exacerbation frequency then this risk should be incorporated into decision making rather than symptoms alone. In the UK, patients with COPD are not routinely screened for OSA as the level of evidence available to support directing resources to this is limited.

Current UK clinical practice in patients who have OSA without significant nocturnal symptoms or daytime sleepiness is inconsistent. Despite theoretical advantages there is no clear evidence of improvement of outcomes, such as reduction in major adverse cardiovascular events with PAP in OSA[21]. The lack of evidence of benefit for broader clinical outcomes limits clinician's ability to treat patients with significant comorbidity and high risk of COPD exacerbation but who lack profound symptoms related to OSA. It also limits the ability to inform patients on the risks and benefits of PAP treatment. The decision on PAP initiation in overlap is currently suggested to be guided by sleep symptoms[16]. This recommendation is extrapolated from data regarding cardiovascular outcomes in patients with OSA and minimal sleep symptoms[21] and assumes clinical impact is limited to patients with sleep symptoms. However, the high nocturnal symptom burden in COPD makes this criteria less likely to be discriminatory, making patient selection and evaluation of PAP efficacy more challenging[22].

Active research review:

We searched clinical trial registration databases to identify active research in PAP for COPD-OSA overlap. We identified 2 trials of PAP in acute hypercapnic respiratory failure (ISRCTN57632435, ISRCTN80279999) which therefore address a different patient population. Other trials examine neurocognitive (NCT04179981) or cardiovascular (NCT05237505) outcomes with PAP and do not list exacerbation frequency as a secondary outcome. One study (NCT03766542) examines physiological outcomes comparing types of PAP therapy; another (NCT03647462) will randomise 100 patients to PAP or usual care after a hospitalised exacerbation with a primary outcome of 30-day readmission or death and is not powered for an exacerbation outcome. This study differs from the current proposal as patients will be recruited during hospital admission as opposed to during a clinic appointment. We selected this recruitment method due to concerns that diagnosing OSA may be unreliable in the initial post-exacerbation period.

Based on our review of ongoing trials and previous data in patients with overlap syndrome we have chosen to study patients at high risk of future exacerbations as indicated by 1 hospital assessed exacerbation or 2 previous clinician assessed community exacerbations within the last 12 months. These patients represent 1 in 4 patients with COPD in the UK[23]. Patients with this exacerbation

history represent a clear phenotype reliably identifying future exacerbation risk [24, 25] with large-scale data providing a robust estimate of exacerbation frequency (2-3/year)[23].

4 PATIENT AND PUBLIC INVOLVEMENT

PPI has been provided through the Respiratory Critical Care Patient and Public Involvement Group at GSTT, Respiratory PPIE group at the Royal Free and Oxford have been integral to the design of this study protocol and the Patient Information Sheets. Ongoing PPI will be coordinated through the Oxford PPIE group which will be consulted at regular intervals throughout the duration of the study to provide a patient perspective on study delivery. At the end of the study, this group will be consulted regarding the study results to assist with the production of dissemination materials. It is important to involve the PPIE group in this work to ensure appropriate non-technical language is used and appropriate dissemination opportunities are accessed. The study steering committee will include a representative who is living with COPD-OSA overlap syndrome.

5 TRIAL OBJECTIVES AND PURPOSE

The randomised control trial will aim to determine whether giving PAP therapy to patients with COPD-OSA overlap will reduce exacerbations of COPD. Patients with COPD-OSA overlap will be randomised to one of two groups: a) PAP therapy in addition to usual care for COPD compared to b) Usual care for COPD alone.

	Objectives	Outcome Measures	Timepoint(s)
Primary	To assess if 12 months of PAP therapy in patients with COPD-OSA overlap syndrome reduces exacerbation frequency	Exacerbation frequency 12 months post randomisation (hospital, community and self-treated)	Randomisation/ Baseline to 12 months
Secondary	To assess impact of 12 months of PAP therapy on quality of Life	Participant reported questionnaires (CAT, eMRCD and EQ5D5L)	Randomisation/ Baseline to 12 months

	Assess impact of 12 months of PAP therapy on patient reported sleep quality and daytime sleepiness	Participant reported questionnaire (PSQI & ESS)	Randomisation/ Baseline, 3 and 12 months
	Assess impact of 12 months of PAP therapy on Lung Function	Spirometry (Lung function)	Randomisation/ Baseline, 3 and 12 months
	Assess dose response relationship between hours of PAP use and primary and secondary outcomes	Usage hours downloaded from PAP device, exacerbation frequency, patient reported questionnaires (CAT, EQ5D, eMRCD, ESS, PSQI), spirometry, healthcare utilisation	Randomisation/ Baseline, 3 and 12 months (intervention group only)
	Assess the cost effectiveness of PAP treatment in patients with COPD-OSA overlap in the UK health system over 12 months	Health Care Utilisation and EQ5D5L	Randomisation/ Baseline, 12 months
Exploratory	To explore the relationship in primary outcome and health related quality of life based on COPD clinical phenotypes	Participant characteristics, primary and secondary outcomes (exacerbation frequency, patient reported questionnaires (CAT, EQ5D, eMRCD,	Randomisation/ Baseline, 12 months

	1. Significant sleepiness (defined as an ESS>/= 11), 2. Poor Sleep quality (defined as PSQI >5) 3. GOLD ABE grouping 4. Eosinophilic COPD (yes/no) 5. Bronchitic COPD (yes/no)	ESS, PSQI), spirometry, healthcare utilisation)	

Exacerbation definition (for primary outcome):
Definition and objective measures for the primary outcome are critical. We will use well established definitions used in published RCTs of COPD management that have impacted practice[45] and are consistent with international consensus statements[3]. The definition of the event and severity grading are pragmatic and deliverable within a clinical trial.

Moderate exacerbation of COPD: ≥2 days of worsening respiratory symptoms (including but not exclusively cough, sputum production, sputum colour change, dyspnoea, fever, malaise, coryzal symptoms) assessed by an appropriate health care practitioner to require treatment with either oral steroids, oral antibiotics or both with treatment initiated and delivered in the community.

Severe exacerbation of COPD: ≥2 days of worsening respiratory symptoms (including but not exclusively cough, sputum production, sputum colour change, dyspnoea, fever, malaise, coryzal symptoms) assessed by an appropriate health care practitioner to require treatment with either steroids, antibiotics or both whether enterally or intravenously and admission to hospital.

To fulfil the severe exacerbation category the patient will be assessed within a secondary care facility and deemed to require hospital admission. This will include admission to a virtual ward or hospital at home but not admission avoidance schemes. Individual site pathways will be reviewed at study setup and potential pathways will be allocated as indicating hospitalisation or continued community treatment based on level of clinical support provided e.g. supplementary oxygen, daily clinical review, intravenous medication, etc.

6 STUDY DESIGN & FLOWCHART

6.1 Study Design

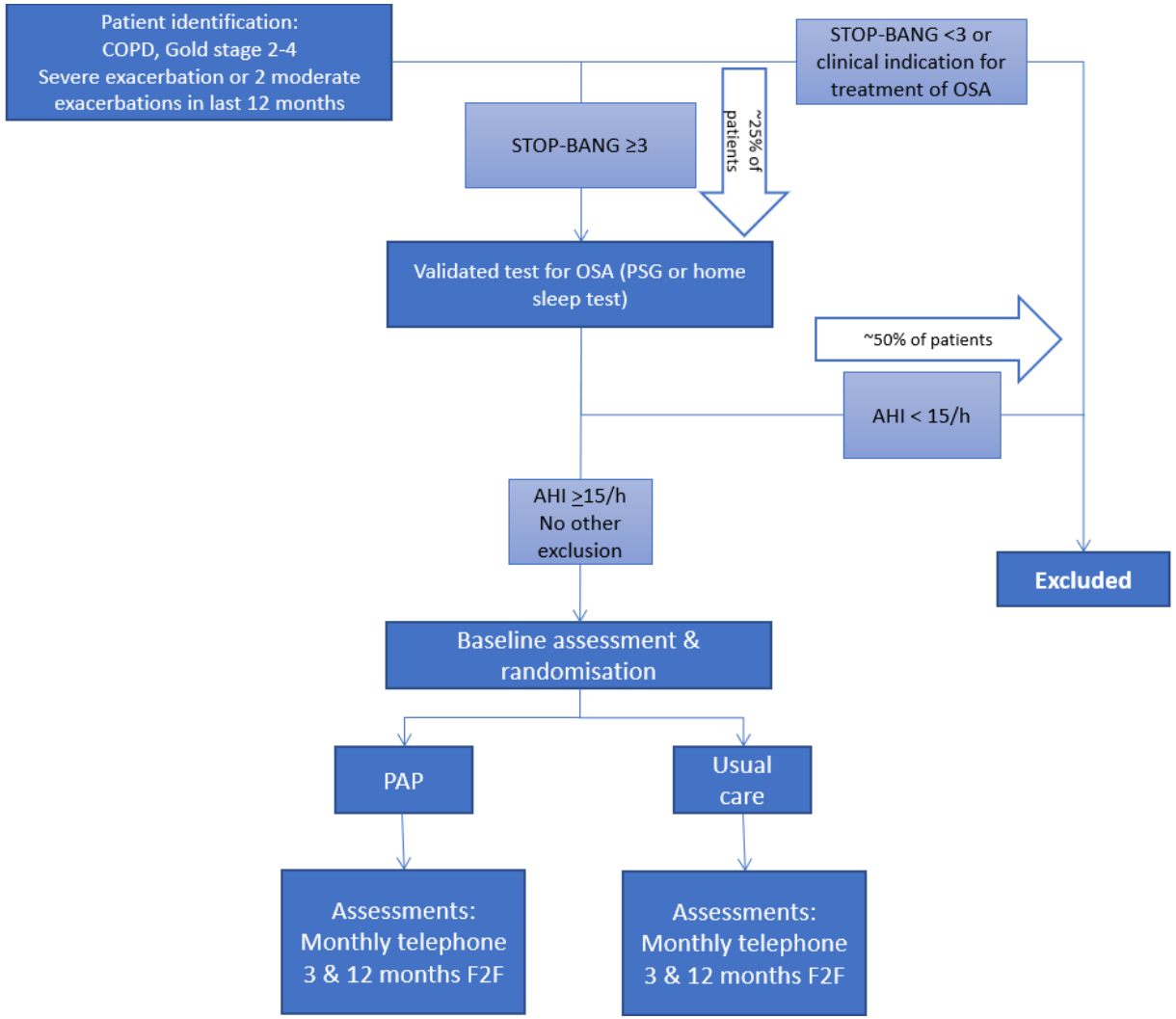
This is a multi-centre open-label randomised trial in patients with COPD-OSA overlap and a high risk of exacerbations who are not being treated clinically with PAP therapy. Participants will be randomised to receive home PAP and COPD usual care or COPD usual care alone with a 12-month follow-up period with an internal pilot. The internal pilot will run for 12 months in 4 sites (with staggered starts to facilitate site initiation visits and site support). The internal pilot will use identical processes as the main trial and will assess site set-up, screening, participant recruitment, protocol adherence, and cross over rates. Progression criteria are outlined below. All participants included in the internal pilot will be included in the final analyses.

During the 12-month pilot we will also conduct a study process evaluation (PE) (See Appendix 1). The EPiC-OSA PE will enable modification of processes affecting trial fidelity to further de-risk the trial.

Study Setting
15 centres will participate in this study.

Guy's and St Thomas' NHS
NHS Foundation Trust

Stage	Location	Assessment
Screening 1: Identification of suitable patients with high pre-test probability for OSA	COPD clinic, sleep clinic, pulmonary rehabilitation assessment, lung screening	Clinical characteristics STOP-BANG questionnaire
Screening 2: Home sleep test (WatchPAT) or validated alternative	Research centre Home or sleep centre (sleep study)	Respiratory sleep study
Baseline assessments and randomisation	Research centre	Clinical characteristics Spirometry Health related quality of life questionnaires
Follow up data collection	Research centre (3 & 21 month) Home (monthly call)	Exacerbation frequency Health related quality of life Spirometry Health care utilisation PAP therapy data



6.2 *Participant Selection*

A number of methods will be used to identify patients. Patients will be identified by clinical teams when attending clinical review in COPD clinics, rehabilitation services or sleep clinics. Where appropriate, patients who have attended community diagnostic centres for spirometry and have results consistent with COPD will be screened. Patients admitted to hospital with an exacerbation of COPD can be identified as potentially eligible and have a sleep study performed at least 6 weeks after the discharge from hospital (i.e. when clinically stable). Lastly, where possible local screening databases will be used to identify additional patients with COPD. Where possible clinical teams will be asked to record STOP-BANG and Epworth Sleepiness Score (ESS), if this is not feasible at the clinical visit, this will be done at screening. If patients meet the inclusion requirement they will be asked to consent to the study and undergo a sleep study. Following the sleep study patients with moderate to severe OSA will be randomised to PAP therapy or usual care.

Study Setting and Recruitment timeline

A total of 15 centres will be recruiting. Based on feasibility data, 2 participants will be recruited at each centre per month, with recruitment of 600 participants achieved at month 27. A site and patient recruitment plan is included below.

Month	Month	active sites (target)	cumulative total (target)
1	Jun-24	4	8
2	Jul-24	4	16
3	Aug-24	4	24
4	Sep-24	4	32
5	Oct-24	4	40
6	Nov-24	4	48
7	Dec-24	6	60
8	Jan-25	8	76
9	Feb-25	10	96
10	Mar-25	12	120
11	Apr-25	14	148
12	May-25	15	178
13	Jun-25	15	208
14	Jul-25	15	238
15	Aug-25	15	268
16	Sep-25	15	298
17	Oct-25	15	328
18	Nov-25	15	358
19	Dec-25	15	388
20	Jan-26	15	418
21	Feb-26	15	448
22	Mar-26	15	478
23	Apr-26	15	508
24	May-26	15	538
25	Jun-26	15	568

26	Jul-26	15	598
27	Aug-26	15	600

6.3 Participant inclusion criteria

- Moderate-severe COPD (GOLD grade 2-4)
- High risk of future exacerbations: 1 severe (hospital assessed) exacerbation or 2 moderate (community clinician assessed) in last 12 months
- Moderate-severe OSA (AHI ≥ 15/h)

6.4 Participant exclusion criteria

- Clinically significant or severe daytime sleepiness: Epworth Sleepiness score >15 or excessive sleepiness likely to impair safe driving in current drivers (as evidence has already established that such patients should be treated with PAP therapy)
- Significant hypercapnic respiratory failure at baseline assessment ($PaCO_2$ >6kPa, with evidence already indicating these patients should be treated with NIV)
- PAP therapy mandated by treating clinician due to severity of sleep symptom burden[16]
- Professional driver or other vigilance essential role with significant daytime sleepiness
- Currently enrolled in an interventional clinical trial

6.5 Study Procedures:

6.5.1 Screening Procedures

The electronic health record of patients attending respiratory clinic, pulmonary rehabilitation or under the care of the respiratory team will be reviewed to assess for study suitability this will include any patient who has undergone diagnostic sleep studies and are deemed suitable for study inclusion. Where applicable, research databases, screening of Lung Health Check databases and patients undergoing spirometry at Community Diagnostic Centres hosted by institutions participating in the trial will be used to identify patients with COPD.

Patients meeting eligibility criteria will be approached by a member of their clinical team to assess for inclusion into the study who will then contact the research team if a potential participant is interested in taking part. Patients may be approached in person in clinic, if face to face attendance, or by telephone / email.

Patients who have not had a sleep study will be consented for the study and a sleep study performed during a period of clinical stability (i.e. at least 6 weeks from a severe exacerbation), those who have a sleep study that demonstrates moderate to severe OSA will then be randomised.

6.5.2 Participant Consent

Participant consent will be obtained by a trained member of the research team, who will discuss the study and provide the study Patient Information Sheet. Potential participants will be given sufficient time (up to one week) to consider study participation and ask questions related to the study. Written informed consent will then be obtained from the patient. Copies of the consent

form will be made for the participant, the site file and for upload to the patient's medical notes. The research team will also send a letter to their GP informing of the participation in the study.

All efforts will be made to reduce disruption of care and respect patient privacy during informed consent and study procedures. Study related procedures will commence only after written informed consent is obtained. If at any point during their study participation, participants meet an exclusion criteria, this will be documented within the CRF.

6.6 Randomisation Procedures

Participants will be randomised 1:1 into two parallel arms, PAP and COPD usual care or COPD usual care. The randomisation will be via an online system (sealed envelope), considering the following minimisation factors;

- Epworth sleepiness score (<11 or ≥11)
- Current long-term oxygen therapy (LTOT) use (Y/N)
- Study site

The randomisation system will be managed by the Oxford Respiratory Trials Unit.

6.7 Masking & other measures taken to avoid bias

6.7.1 Masking

The study will be open label with no blinding for participants or clinical teams. Participant and clinician blinding is difficult to perform in this study for ethical and practical reasons[26]. Furthermore, studies have demonstrated that patients and clinicians identify sham respiratory support, limiting the scientific justification for using sham devices[27, 28]. This unblinded design and lack of sham comparator is consistent with other clinical trials in this field[29-32].

6.7.2 Other measures taken to minimise / avoid bias

To minimise bias, the use of objective outcomes has been selected where possible.

6.8 Participant recruitment

Patients meeting eligibility criteria will be approached by a member of the clinical- team to assess for inclusion into the study. Patients may be approached in person in clinic, Participant Identification Centre (PICs), in face to face attendance, or by telephone/email.

Participants will not receive payments for study participation.

6.9 Schedule of assessments for each visit

	Screening	Baseline (up to 14 days post screening)	Monthly Phone calls 1, 2, 4-11 +/-14 Days*	3 months +/-14 Days	12 months +/-14 Days
Inclusion and exclusion criteria (including STOP-BANG and Epworth sleepiness scale if available)	X				
Patient information sheet & informed consent	X				
Sleep study screening	X				
Document from medical record: • Demographics • Anthropometrics • COPD clinical history • Use of LTOT (long Term Oxygen Therapy) • OSA parameters • Medical history • Index of Multiple Deprivation • Smoking history • Exacerbation frequency		X			
Randomisation		X			
Issue of PAP device (intervention arm only)		X			
Vital observations (inc SpO_2)		X		X	X
Patient self-reported questionnaires:					
• Chronic obstructive pulmonary disease assessment test (CAT) score		X	X	X	X
• EQ-5D-5L with respiratory and sleep bolt ons		X	X	X	X
• Extended MRC-Dyspnoea (eMRCD) score		X	X	X	X
• Pittsburgh Sleep Quality Index (PSQI)		X		X	X
• Epworth Sleepiness Score (ESS)		X		X	X
Physiological: • FEV_1 • FVC		X		X	X
Exacerbation details		X	X	X	X

Health care utilisation • Patient reported health care utilisation (via monthly telephone collection and verified at follow up visits). This will include: ○ primary care contacts ○ All secondary care contacts ○ Community service review ○ ED attendance ○ Inpatient admission (elective and non-elective)		X	X	X	X
Medication history/changes		X	X	X	X
PAP therapy data • Usage • Need for support or intervention			X	X	X
• Adverse events and Serious Adverse Events			X	X	X

* Telephone follow ups: a minimum of 3 attempts will be made over at least three days of the scheduled period of follow up, after which this the visit will be classed as a missed visit.

6.10 Schedule of assessments for each visit - Baseline

The following data will be recorded at the baseline assessment:

- Demographics & anthropometrics including: age, weight, height, ethnicity, sex registered at birth
- COPD clinical history: pack years, smoking status, emphysema/chronic bronchitic phenotype, COPD pharmacotherapy, exacerbations in last 12 months, completion of pulmonary rehabilitation in last 2 years, immunisations (influenza, pneumococcal, covid), antibiotic prophylaxis (Y/N), LTOT (Y/N), ambulatory oxygen therapy (Y/N), documentation of CT based evidence of emphysema in the last 12 months
- OSA severity: AHI, 4%ODI, mean nocturnal SpO_2, % total sleep time with SpO_2 <90%
- All known co-morbidities
- Health related quality of life: CAT, EQ-5D-5L (with respiratory and sleep bolt ons)
- Dyspnoea: eMRCD score
- Sleep quality (Pittsburgh sleep quality index)
- Epworth sleepiness score
- Spirometry

Usual Care Arm:

- If randomised to usual care the following information/advice and management will be delivered: as per NICE (https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245) and local guidance. This will include as a minimum: review of pharmacotherapy and consideration of regular, triple-inhaled bronchodilator therapy (long-acting β-agonist, long-acting anti-muscarinic, and steroid), antibiotic prophylaxis, as-needed inhaled short-acting β-agonist therapy, sputum clearance techniques where appropriate, smoking cessation support, pulmonary rehabilitation and education on COPD self-management including non-pharmacological management of COPD, including vaccination additionally advice on sleep quality will be given.

Intervention Arm:
PAP therapy for participants in the intervention arm will be delivered according to local site clinical protocols. All centres involved in the study will be asked for SOPs as part of the process evaluation. Where SOPs are not available senior members of the team will be interviewed to understand the local pathway. As a minimum the following would be expected for device setup:

- Face to face assessment for mask fitting and device training
- Mask fit and PAP tolerance check
- Use of humidification according to patient preference and symptom tolerance
- Remote review within 1st 30 days to check compliance, troubleshoot technical issues, review mask fit and leak

PAP Adherence
We will use PAP remote monitoring technology available as standard care to assess daily PAP adherence to PAP therapy. Participants will be requested to use PAP for at least 4 hours per night but ideally for the full duration of their sleep. PAP therapy adherence will be reviewed and optimised by the treating clinical team at each study visit (monthly calls and face to face visits) using the established clinical pathways (e.g. mask fit/type) at each participating centre. Adherence will also be reviewed at each follow up visit, including telephone assessments. Participants with poor adherence (less than 4 hours use per night on 70% of nights) will have reasons and barriers explored. Participants will be presented with solutions to overcome these barriers and counselled on strategies to increase usage

6.11 Follow up Procedures

All participants will undergo face to face assessments at 3- and 12-months following randomisation and will complete outcome measures assessments as outlined in the trial flow chart. Trial visits will occur ± 14 days from scheduled date. Telephone calls will be made monthly (a minimum of 3 attempts will be made over at least three days of the scheduled period of follow up, after which this the visit will be classed as a missed visit) to collect health care utilisation and PAP therapy (if in the intervention group) data and will be verified at the face-to-face visits.

Follow up data collect will include:

Monthly telephone call:

During the monthly telephone call the participants will be asked about the following

- Health care contacts including primary care (GP, nurse, other), secondary care (respiratory, non-respiratory; consultant led, nurse or other), community service (e.g. pharmacist review), ED attendance (COPD or non-COPD), inpatient admission (elective/emergency), admission duration since the last review
- Prior to the call occurring the research team will review the EHR and then validate the admissions times and cause ie confirm if AE-COPD or non-respiratory
- Exacerbations: hospital stay duration in nights
- Medication changes
- PAP usage via machine: average daily use, % of nights >4h use (via machine download)
- AE/SAE's
- During these monthly calls we will also assess the need for support for use of the PAP mask and machine use and provide this during the call. This will be documented in the CRF.
- Questionnaires will be completed with the participant CAT, EQ-5D-5L (with respiratory and sleep bolt ons) and eMRCD score

Face to face visit (month 3 and 12):

- During the face to face visits, we will collect all data collected at the monthly call and in addition;
    - A member of the research team will administer the following questionnaires (CAT, eMRCD, EQ5D-5L (with respiratory and sleep bolt ons), PSQI, ESS)
    - We will measure lung function: FEV_1, FVC, FEV_1: FVC

7 MEDICAL EQUIPMENT (DEVICES)

Please create a table for each device model to be used in the study.

Manufacturer Details			
Name:	Zoll Itamar Ltd		
Address:			
Model Details			
Name:	WatchPAT 300		
Manufacturer's Reference:			
Is the device UKCA/CE marked as a medical device?	☒ Yes ☐ No		
Regulatory Classification: *(I, IIa, IIb or III)*	Class IIa device *Based on EU MDR or UK MDD?*		
Software Version:	3.12		
Documents to Provide			
Document Type	**Title**	**Reference No.**	**Version**
Investigator's brochure	n/a		
Instructions for use	WatchPAT-300-Operational-Manual-Europe		
Declaration of Conformity	The product complies with MDD 93/42 EEC: 1993 & Amm. 2007/47/EC (Medical Device Directive) requirements and CE approved. (within operation manual)		
Risk assessment	Risk assessment document		v1

Manufacturer Details			
Name:	ResMed		
Address:	ResMed UK Ltd of Quad 1, First Floor Becquerel Avenue, Harwell Campus, Didcot, Oxfordshire, United Kingdom, OX11 0RA		
Model Details			
Name:	Airsense 10 Autoset		
Manufacturer's Reference:	TBC		
Is the device UKCA/CE marked as a medical device?	☒ Yes ☐ No		
Regulatory Classification: *(I, IIa, IIb or III)*	IIa according to Rule 9		
Software Version:	TBC		
Documents to Provide			
Document Type	**Title**	**Reference No.**	**Version**
Investigator's brochure	n/a		

Instructions for use	Airsense 10 user guide (airsense10-autoset-elite_user-guide_eur4_mul.pdf (resmed.com))		
Declaration of Conformity	Declaration of Conformity	Signed 29Jun2023	
Risk assessment	Risk assessment document		v1

7.1 Overview of device usage in research

WatchPAT

The WatchPAT will be used within its intended use to diagnose OSA in patients with a high pre-test probability identified through the screening pathway. The participants will be instructed on how to use the WatchPAT and the operational pathway and data transfer has been cleared for use within NHS trusts. WatchPATs are disposed of for recycling after use.

Airsense S10

The airsense S10 PAP machine will be used within its intended purpose and machines will be maintained during the study by the research team. At the end of the study, participants will be offered to continue with PAP therapy and the machine will then be transferred for ongoing maintenance and support to the relevant clinical service. Participants randomised to the usual care group will be offered a trial of PAP therapy at the end of the 12-month data collection period.

The process evaluation work will also be used to determine if PAP therapy is delivered as intended (appendix 7)

PAP Adherence
By utilising the remote monitoring technology, the daily adherence to PAP will be recorded. Participants will be requested to use PAP for at least 4 hours but ideally for the full duration of their sleep. Adherence to PAP therapy will be reviewed and optimised using the established clinical pathways (e.g. mask reviews) at the relevant centre. Adherence will also be reviewed at each follow up visit, including telephone assessments and participants with poor adherence (less than 4 hours use per night on 70% of nights) will have reasons and barriers explored and will be advised to increase usage.

8 END OF STUDY DEFINITION

The End of Study will have been reached when the database has been locked.

9 ASSESSMENT OF SAFETY

9.1 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.

9.2 Reporting procedures for AEs

The population of patients involved in EPiC-OSA is one in which a high number of adverse events are expected due to the underlying likely disease (COPD and OSA). Therefore, relevant adverse events will be recorded in the CRF and only those adverse events meeting the criteria to be a Serious Adverse Event and related to the study intervention (PAP) will be expeditiously reported (see 8.3).

9.3 Reporting Procedure for Serious Adverse Events

The **safety reporting period** is for participants receiving the study intervention for 12 months **post randomisation** (or the discontinued use of PAP whichever is sooner).

SAEs that are considered (by the site investigator) to be **possibly, probably or definitely related** to the study intervention (PAP) will be reported on the relevant reporting form (PM124-A Serious Adverse Event Report Form (non-CTIMPs)) and emailed to ORTU ortu@ndm.ox.ac.uk without delay. ORTU will perform an initial check of the report, request any additional information and ensure it is reviewed by a nominated Medical Reviewer. ORTU will also forward all SAE's once reviewed by the medical reviewer to r&D@gstt.nhs.uk within 24 hours.

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).

9.4 Study Management Group (SMG)

A Study Management Group (SMG) will meet monthly and will oversee the day-today co-ordination and progress of the trial, managing any key issues and tasks to be addressed.

9.5 Study Steering Committee (SSC)

A SSC will be convened to keep oversight of the trial. A charter will be written explaining the role of the SSC 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 study.

9.6 Data Safety Monitoring Committee (DSMC)

An independent DSMC will be established to assess safety signals over the course of the trial, with the expectation of meeting at least annually, and as needed in response to safety concerns from the SSC. The aims of this committee review 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
- Monitoring the safety of the study

9.7 Ethics & Regulatory Approvals

This study will be performed in line with the Declaration of Helsinki, GDPR and local procedures, including approval by the local Research and Development Departments and Research Ethics Committee.

10. COMPLIANCE AND WITHDRAWAL

10.1 Participant compliance

There will be regular review of accurate completion of the trial procedures and data fidelity, as per the study risk assessment.

10.2 Withdrawal / dropout of participants

Participants have the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

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

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Participants will have the following two options for withdrawal:

1. Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care, i.e., demographics, clinical parameters, results and evidence of COPD exacerbations on subsequent hospital visits.

2. Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data will be collected after withdrawal.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

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

10.3 Protocol Compliance

An incident 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 an incident form and filed in the study master file. A log of incidents will also be maintained in the study master file.

Standard operating procedures are in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

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.

If 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.

11. DATA

11.1 Data to be collected

Data	Source	Time point for collection	Why data is collected	Is data from standardised tool	Type of data
Demographics / anthropometrics	Electronic patient record	Baseline	Baseline characteristics	No	Categorical, Continuous
Medical (including medications) history	Electronic patient record	Baseline	Baseline characteristics	No	Categorical
Smoking history	Electronic patient record (confirmed with participant)	Baseline	Baseline characteristics	No	Categorical, Continuous
Exacerbation frequency prior to and during the trial	Electronic patient record (confirmed with participant)	Baseline and monthly through to 12 months	Baseline characteristics, risk stratification	No	Continuous
COPD phenotype	Electronic patient record (confirmed with participant)	Baseline	Baseline characteristics	No	Categorical
Vital observations	Electronic patient record	Baseline, 3 & 12 months	Baseline characteristics and monitoring	No	Continuous
Spirometry	Participant	Baseline, 3 & 12 months	Baseline characteristics and monitoring		Continuous
Questionnaires	Participant	Baseline, 3 & 12 months	Baseline characteristics and monitoring	CAT, eMRCD score, PSQI, ESS, EQ-5D-5L (with bolt ons)	Ordinal, Continuous
Questionnaires	Participant	Monthly	Baseline characteristics and monitoring	CAT, eMRCD EQ-5D-5L (with bolt ons)	Ordinal, Continuous
PAP settings, data and usage (intervention arm only)	PAP device	Randomisation and monthly through to 12 months	Therapy variables and patient therapy compliance	Yes	Continuous
Health Care Utilisation	Participant	Monthly	Primary outcome	No	Categorical, continuous
Adverse/Serious adverse events	Participant	Post randomisation, monthly through to 12 months or stopped usage of the PAP machine	Monitoring and safety	No	Categorical

11.2 Data handling and record keeping

All documents will be stored safely in confidential conditions in an appropriate area in line with local procedures. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name. Data generated by the study will be stored for 5 years. Data will be handled in accordance with data protection legislation. The site PI is responsible for ensuring accuracy of data collection, recording and quality.

All trial data will be entered onto eCRFs in a web-based database by trained site staff. Installation Qualification, Operational Qualification, Upgrade Qualification and Performance Qualification are performed. The clinical database will be designed and tested in this environment prior to recruitment and will include custom data validation rules embedded to enhance data quality management.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file other than the participants post code on the baseline CRF to measure the index of multiple deprivation.

The data entered onto the database and will be regularly monitored for quality by ORTU. Queries will be sent to sites as part of data management activities. Final data cleaning will happen after last patient's last visit with confirmation of completion from sites.

Preliminary data exports will be shared with the trial statistician(s) for planned DSMC meetings, data cleaning and prior to database lock for an opportunity to raise queries and a final dataset export will be planned after database lock. This data will be sent in a pre-agreed format using secure FTP (onedrive or similar).

Data (TMF and database) will be retained in accordance with ORTU/Sponsor SOP's/local procedures, any other data including the qualitative interviews will be combined with the TMF at the end of the study and retained through an archiving service as outlined by the sponsor, Iron Mountain, and will be retained in accordance with regulatory requirements for a minimum of 5 years after termination of the trial. After publication, anonymised data will be shared upon responsible request to the CI from researchers with bone fide research proposals (e.g. for a systematic review). If required, the sponsor will be granted access to documents within the trial master file which is held on the Oxford Respiratory Trials Units network.

11.3 Data sharing

Data Sharing Statement

Deidentified individual participant data, alongside study protocol, statistical analysis plan and health economic analysis plan will be available after trial publication. Access to these data will be via request to the SMG, who will consider requests with sound methodological proposal for inclusion in individual meta-analyses and or secondary exploratory analyses. Data sharing will require completion of an appropriate data access agreement with the primary data controller (Guy's & St Thomas NHS Foundation Trust).

11.4 Personal Data Breaches

GDPR broadly defines personal data breaches as a security incident that has affected the confidentiality, integrity or availability of personal data. In short, there will be a personal data breach whenever any personal data is lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable, for example, when it has been encrypted by ransomware, or accidentally lost or destroyed. Any personal data breach must be reported to ORTU in the first instance who will then report on further to sponsor.

12 MONITORING AND AUDITING

Regular meetings of the SSC (per recruitment target; 25%, 50%, 75%, 100% and at least 6 monthly) and DSMC (per recruitment target; 25%, 75%, and at least 12 monthly)) and compliance with any Sponsor-led audits will ensure adequate monitoring and quality control of this study. The principles of Good Clinical Practice and research governance guidelines will be adhered to throughout.
Monitoring will be performed if required, according to the trial specific Risk Assessment and 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 Risk Assessment and Monitoring Plan.

13 STATISTICAL CONSIDERATIONS

13.1 Sample size calculation

COPD patients with 1 severe exacerbation have a mean number of moderate-severe exacerbations of 2.8 (SD 2.5) per year[23]. We have selected an effect size of 25% (0.7 exacerbations per patient per year) as this has been suggested as the minimally clinically important difference for COPD and is used in trials of other interventions[31, 32]. This effect size is consistent with observational data indicating COPD-OSA overlap syndrome doubles the rate of severe exacerbations[1]. Therefore, a reduction of 25% is a plausible treatment effect. A sample size of 514 will allow detection of a ratio of negative binomial rates of 0.75. This is based on a reduction from 2.8 exacerbations per patient per year in the usual care group to 2.1 in the intervention group, a sensitivity of 5% and power of 90%. The dispersion factor has been estimated from previous COPD exacerbation data at 0.60[33]. Accounting for drop-out and loss to follow-up of 17% (based on previous trials conducted by our group[33, 34]), we will target a sample of 600 patients (300/group).

13.2 Statistical analysis plan

A detailed statistical analysis plan will be drafted and finalised before the recruitment of the final participant). Baseline characteristics will be summarised by group and overall.

Continuous data will be presented as mean (standard deviation) or median (interquartile range) as appropriate and binary/categorical outcomes as number and percentage. All available data will be included and analysed by allocated group, regardless of intervention received. We will analyse the primary outcome using a negative binomial regression model adjusting for minimisation variables (centre, baseline severity of sleepiness and long-term oxygen therapy use). This analysis method accounts for both skewed distribution of exacerbation rates and variance between patients and is recommended analysis for this outcome.[46] We will calculate the incidence rate ratio with associated 95% confidence interval and p-value. The mechanism of missing data will be explored and covariates found to be predictive of missingness (based on logistic regression) will be included in the analysis

model as a sensitivity analysis. Continuous secondary outcomes measured at follow-up will be analysed using a mixed effects linear regression model. The model will include a random intercept for each participant to account for the repeated measures on the same participant and an interaction term for the treatment by visit interaction to allow the treatment effect to differ at each visit. The model will include fixed effects for group and minimisation variables. Study site will be included in the model as a random effect. Adjusted mean differences between randomised groups at each time point will be estimated from the model with their associated 95% confidence interval and p value.

A per-protocol analysis will be carried out, restricted to patients in the PAP group who were compliant with therapy (defined as mean use >4h per night) and those in the control group who did not receive PAP.

Subgroup analyses will be carried out to determine whether the intervention effect differs depending on the following subgroups:

1. Significant sleepiness (defined as an ESS≥ 11),
2. Poor Sleep quality (defined as PSQI >5)
3. GOLD ABE grouping
4. Eosinophilic COPD; this will be defined as a blood Eosinophil count >0.3x10^9 cells/L (yes/no)
5. Bronchitic COPD; as defined by a CAT score >2 in questions 1 & 2 (yes/no)

This will be determined by including an interaction term between intervention group and the subgroup of interest in the primary analysis model.

Health-economic

We will conduct a full economic evaluation to examine the impact of PAP on cost effectiveness among patients with COPD-OSA overlap following methods recommended by NICE[47]. The primary evaluation will take the NHS and Personal Social care perspective therefore relevant health care and social health cost will be included in the analysis. We plan to conduct an economic evaluation alongside the proposed clinical trial to examine the short-term impact of PAP on cost and effectiveness, and a model-based economic evaluation to examine the long-term impact of PAP on cost and effectiveness by developing a decision analytical model to extrapolate the within trial cost effectiveness to the patient's lifetime based on disease progress of COPD and OSA. Incremental cost per Quality-adjusted life year (QALY) gained will be obtained as the principal outcome of the within trial and model-based economic evaluation, and will be compared with the established NICE cost effectiveness threshold of £20,000 per QALY gained.

Embedded in the clinical trial, health care resource utilization data and health related quality of life data (i.e. EQ-5D-5L and CAT) will be collected at monthly telephone contact with the patients. A data collection form will be developed to include relevant and important health resource utilization items based on discussion with the clinical team, consultation with patient groups, and suggested by the literature. The provisional list of cost items include community care (e.g. GP visits (including home visits), GP walk-in centre appointments and district nurse visits), hospital care (e.g. outpatient COPD clinical appointments, A&E visits, inpatient admissions and length of hospital stay, etc.), and interventions (e.g. medications, diagnostic tests, medical devices). Data on items relating to the cost of delivering PAP will also be identified and collected, and include in economic analysis.

For the within-trial cost-effectiveness analysis, we will obtain a health utility value based on participants' scores on the EQ-5D-5L using recommended mapping approach recommended by NICE[47]. We will calculate QALYs using the area under the curve method. Costs associated with health care resource utilisation will be calculated using data collected and unit costs obtained from standard national sources such as the British National Formulary, NHS Reference Costs and Unit Costs for Health and Social Care. To identify relevant unit costs and assess accuracy and completeness of data collected, a preliminary review of data on outcomes relating to health care resource utilisation will be performed when the internal pilot study is completed. We will estimate the incremental cost per acute exacerbation avoided by calculating the difference in mean costs and number of acute exacerbations between the two trial arms. We will estimate the incremental cost per QALY gained by calculating the difference in mean costs and QALYs between the two trial arms as incremental cost-effectiveness ratios (ICERs) for the intervention versus usual care. The latter will be used to determine whether the intervention is likely to be cost-effective for the NHS by comparison with the NICE threshold. Potential differences in participants' social demographics between the trial arms will be accounted for using regression models. Missing data will be handled using multiple imputation techniques. Bootstrapping will be used to evaluate the uncertainties.

Based on the within-trial analysis, supplemented by the findings from a quick review of literature, we will develop a decision analytic model to extrapolate the impact of the PAP on both cost and effectiveness over the course of a COPD patient's lifetime. Deterministic and probabilistic sensitivity analysis will be conducted to explore uncertainties in the model and parameters, and the results presented by estimating cost-effectiveness acceptability curves. We will also explore structural uncertainties in our sensitivity analysis to examine alternative assumptions regarding the long-term impact of PAP therapy on economic outcomes. The study team has previously involved in the development of COPD model[48] which we could use as a starting point for further investigation with input from our clinical team.

13.3 Interim analysis and data monitoring

Internal pilot study

We will run a 12-month internal pilot with staggered site initiation. The pilot will start with 4 sites with 2 sites added per month from month 6 until 15 sites are recruiting. The pilot feasibility criteria will have red (do not proceed), amber (review process evaluation data, protocol and consider alternatives (i.e. primary care recruitment, expanded trial site number) and green (proceed) thresholds. Feasibility criteria:

PROGRESSION CRITERIA AT MONTH 12	RED	AMBER	GREEN
	<50%	50 to <100%	100%
PROPORTION OF SCREENED PATIENTS RECRUITED	<5%	5-10%	>10%
TRIAL RECRUITMENT PER SITE	<1	1 to <2	≥2
NUMBER OF OPEN SITES	<8	8-14	15
TOTAL RECRUITS	<89	89-177	178
DROPOUT RATE (ALTER % THRESHOLDS)	>28%	14-28%	<14%

Table 1: Internal pilot study feasibility criteria

At month 12 there will be an interim analysis and DSMC convened to determine whether the trial continues.

13.3.1 Stopping / discontinuation rules and breaking of randomisation code

No pre-specified stopping criteria are set that would require premature discontinuation of the trial. The appointed Trial Steering Committee and Data Safety Monitoring Committee will review blinded data throughout the study with pre-specified analysis points of 25%, 50% and 75% of participant recruitment and are able to stop the trial if there are safety concerns.

14 PEER REVIEW

This study has been peer-reviewed by the London Respiratory Muscle Group and the NIHR Health Technology Assessment programme.

15 FINANCING

The study is being funded by the NIHR HTA.

16 INSURANCE AND INDEMNITY

This study is sponsored by Guy's and St Thomas' NHS Foundation Trust (GSTFT) and indemnity is provided through NHS Resolution's Clinical Negligence Scheme for Trusts (CNST) which provides indemnity for clinical negligence. In the case of negligent harm, health care professionals undertaking clinical trials or studies on volunteers, whether healthy or patients, in the course of their NHS employment are covered by NHS Resolution. In the case of non-negligent harm, legal liability does not arise where a person is harmed but no one has acted negligently. In exceptional circumstances NHS bodies may consider whether an ex-gratia payment could be offered.

17 DATA CONTROLLER

Guy's and St Thomas' NHS Foundation Trust is the Data Controller as defined by UK general data protection legislation (UK GDPR) for this study and as such agrees to comply with the obligations placed on a Data Controller by the UK GDPR. This is not limited to, but includes, being responsible for and able to demonstrate compliance with the principles relating to Processing of Personal Data (Article 5 UK GDPR).

18 INTELLECTUAL PROPERTY (IP)

N/A

19 REPORTING AND DISSEMINATION

We have devised a dissemination plan with our PPI group to ensure that key stakeholders at a local, national and international level are informed of the study results. This includes a study website (managed by the CIs and core research team) and social media strategy tailored to patients, clinicians, NHS managers and researchers. A study summary will be produced in an easy-read format with appropriate figures and images to support patient understanding of the trial outcome and implications. This will be made available at the study sites. We aim to publish the results in a high ranked international journal in line with the acknowledged importance of this clinical question.

The research is intended to produce several scientific manuscripts that will detail the trial protocol and then subsequent clinical and health economic results. These publications will target high impact journals with open access to maximise visibility and impact. We will work with our patient advisory group to develop accessible output suitable for wider dissemination. We will target local, national and international engagement with relevant patient advocacy groups such as Asthma-Lung UK and the Sleep Apnoea Trust Association (SATA). We will use traditional media for dissemination as well as social media and an established clinical trial website to highlight study progress and findings. We will work with professional organisations such as the British Thoracic Society (BTS) to apply pressure for adoption of any clinically relevant benefits of the intervention.

Patients and service users will be engaged throughout the trial process and our extensive PPIE will ensure they are embedded in the dissemination of study results. We will use the established PPIE groups to develop lay summaries of the trial protocol and any results. We will use infographics and other media content to increase accessibility. Summaries will be translated into the common languages in the local areas of trial centres. An executive summary and report will be produced and sent to participating centres along with a virtual presentation with subsequent Q&A for interested clinicians and decision makers. Lay summaries will be distributed by patient advocacy groups as above. Members of the group have a track record of supporting dissemination of findings from clinical trials and supporting patient access to health care. Dr Murphy and Prof Rose are members of Home Mechanical Ventilation in partnership (hmvip.co.uk) which was established to help support patients with respiratory failure obtain the care they need.

Any major clinical benefits of the trial will be highlighted via press release using the communications department and media team at Guy's and St Thomas NHS Trust.

Our trial group is multidisciplinary and covers regional variation within England. We have already approached sites from within Wales and Scotland to ensure representation from other areas of the UK. Members of the trial team are senior clinicians active within care pathways with integrated care boards and can support generation of new clinical pathways through these organisations. Members are also involved in supporting professional organisations such as the BTS as members of specialist committees and patient organisations such as SATA. Many members of the trial team have already contributed to national and international guidelines on the management of patients with sleep disordered breathing.

The study website will provide regular updates on study progress including recruitment rates and sites participating. Information on the website will be structured in lay language and developed with the patient advisory group. We will ask for participant's contact details during consent if they wish to receive a lay summary/infographic of the study findings at the end of the trial.

20 REFERENCES

1. Marin, J.M., et al., *Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome.* Am J Respir Crit Care Med, 2010. **182**(3): p. 325-31.
2. Kim, V. and S.D. Aaron, *What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement.* Eur Respir J, 2018. **52**(5).

3. Celli, B.R., et al., *An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal.* Am J Respir Crit Care Med, 2021. **204**(11): p. 1251-1258.
4. Alqahtani, J.S., et al., *Research priorities for exacerbations of COPD.* Lancet Respir Med, 2021. **9**(8): p. 824-826.
5. Pengo, M.F., et al., *Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis.* Eur Respir J, 2020. **55**(5).
6. Malhotra, A., et al., *Research Priorities in Pathophysiology for Sleep-disordered Breathing in Patients with Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Research Statement.* Am J Respir Crit Care Med, 2018. **197**(3): p. 289-299.
7. Hurst, J.R., et al., *Temporal clustering of exacerbations in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2009. **179**(5): p. 369-74.
8. Donaldson, G.C., et al., *Airway and Systemic Inflammation and Decline in Lung Function in Patients With COPD.* Chest, 2005. **128**(4): p. 1995-2004.
9. Zhang, Y., et al., *A systematic review of how patients value COPD outcomes.* Eur Respir J, 2018. **52**(1).
10. National Institute for Clinical Excellence. *Health and social care directorate quality standards and indicators briefing paper*. 2015 [cited 2022 30.10.22]; Available from: https://www.nice.org.uk/guidance/qs10/documents/briefing-paper.
11. McLean, S., et al., *Projecting the COPD population and costs in England and Scotland: 2011 to 2030.* Sci Rep, 2016. **6**: p. 31893.
12. Yaggi, H.K., et al., *Obstructive sleep apnea as a risk factor for stroke and death.* N Engl J Med, 2005. **353**(19): p. 2034-41.
13. Gottlieb, D.J., et al., *Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study.* Circulation, 2010. **122**(4): p. 352-60.
14. Heinzer, R., et al., *Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study.* Lancet Respir Med, 2015. **3**(4): p. 310-8.
15. Sterling, K.L., et al., *Impact of Positive Airway Pressure Therapy Adherence on Outcomes in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2022. **206**(2): p. 197-205.
16. National Institute for Health and Care Excellence. *Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s [internet]*. NG202 2021 [cited 2022 27.11.22]; Available from: https://www.nice.org.uk/guidance/ng202/chapter/3-COPDOSAHS-overlap-syndrome.
17. Shawon, M.S., et al., *Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: A systematic review.* Sleep Med Rev, 2017. **32**: p. 58-68.
18. Dave, C., et al., *Development and Relevance of Hypercapnia in COPD.* Can Respir J, 2021. **2021**: p. 6623093.
19. Mathioudakis, A.G., et al., *ERS statement: a core outcome set for clinical trials evaluating the management of COPD exacerbations.* Eur Respir J, 2022. **59**(5).
20. Adler, D., et al., *Symptomatic response to CPAP in obstructive sleep apnea versus COPD-obstructive sleep apnea overlap syndrome: Insights from a large national registry.* PLoS One, 2021. **16**(8): p. e0256230.
21. McEvoy, R.D., et al., *CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea.* N Engl J Med, 2016. **375**(10): p. 919-31.
22. Price, D., et al., *Impact of night-time symptoms in COPD: a real-world study in five European countries.* International journal of chronic obstructive pulmonary disease, 2013. **8**: p. 595-603.
23. Whittaker, H., et al., *Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study.* Int J Chron Obstruct Pulmon Dis, 2022. **17**: p. 427-437.

24. Hurst, J.R., et al., *Susceptibility to exacerbation in chronic obstructive pulmonary disease.* N Engl J Med, 2010. **363**(12): p. 1128-38.
25. Hurst, J.R., et al., *Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review.* Respir Res, 2022. **23**(1): p. 213.
26. Neugebauer, E.A.M., et al., *Specific barriers to the conduct of randomised clinical trials on medical devices.* Trials, 2017. **18**(1): p. 427.
27. Djavadkhani, Y., et al., *Ethics, consent and blinding: lessons from a placebo/sham controlled CPAP crossover trial.* Thorax, 2015. **70**(3): p. 265-9.
28. Gruis, K.L., et al., *Evaluation of sham non-invasive ventilation for randomized, controlled trials in ALS.* Amyotroph Lateral Scler, 2006. **7**(2): p. 96-9.
29. Clini, E., et al., *The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients.* Eur Respir J, 2002. **20**(3): p. 529-38.
30. Kohnlein, T., et al., *Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial.* Lancet Respir Med, 2014. **2**(9): p. 698-705.
31. Struik, F.M., et al., *Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study.* Thorax, 2014. **69**(9): p. 826-34.
32. Murphy, P.B., et al., *Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial.* JAMA, 2017. **317**(21): p. 2177-2186.

APPENDIX 1

Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE (related and unexpected)	Chief Investigator	-Report to ORTU upon learning of the event -	ORTU SAE Report form available from ISF	ORTU and Sponsor
Urgent Safety Measures	Chief Investigator	Contact ORTU Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator/ORTU	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC with a copy to be sent to the Sponsor
Declaration of the conclusion *or* early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the HRA website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator/ORTU	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

APPENDIX 2

EPIC-OSA Process Evaluation

We will conduct a study process evaluation during the 12-month internal pilot. The EPiC-OSA PE will enable modification of processes affecting study fidelity. This in turn will help to reduce the risk of Type III error in interpretation of the study results, (40) i.e., determination that the EPiC-OSA intervention is ineffective in the case where inadequate study fidelity has resulted in the lack of effect on study outcomes. This has the potential to prevent research waste and improve return on NIHR investment.

Our process evaluation aims are to explore:

1. Fidelity of study methods and intervention delivery.
2. Barriers and enablers to delivery of the study as intended including adherence to the PAP therapy intervention.

A priori, we hypothesize the following potential threats to study fidelity

1. Reach: Failure of clinicians to refer potentially eligible patients to the research team for screening.
2. Reach: Potentially eligible patient declining to participate in home screening processes.
3. Reach: Challenges with at home screening processes (home sleep study; 1 hour daytime trial of PAP in the home) prior to randomisation.
4. Intervention fidelity: Poor compliance with prescribed PAP therapy.
5. Outcome fidelity: Poor compliance with patient self-reported questionnaire completion (intervention and control arms).
6. Patient response: Negative experience with PAP therapy.
7. Clinician response: Negative clinician experience with study recruitment.

The EPiC-OSA PE will provide the following outputs:

1. Quantitative and qualitative evaluation of study recruitment processes including barriers and facilitators to recruitment
2. Quantitative and qualitative data on study fidelity including barriers and facilitators to intervention delivery and outcome assessment
3. Quantitative and qualitative data on clinician and patient response (acceptability and barriers and facilitator to study participation (patient) and study recruitment (clinicians)

Methods

The EPiC-OSA PE will employ a mixed methods design. We will use a combination of analysis of routinely collected study data (screening/recruitment logs; outcome assessment), remote downloads of PAP use, quantitative questionnaires, semi-structured interviews, and site observation (recruitment processes) to monitor study fidelity and processes at each site.

Reach 1: To assess potential threats to fidelity in terms of failure to refer potentially eligible patients we will examine clinic attendance records and monthly screening logs of the four sites participating in the internal pilot.

At each site we will identify which specialised COPD or general respiratory clinics potentially eligible patients attend. Research staff will then review the electronic medical record of all patients attending these clinics to assess the number of eligible patients/month. To assess for missed patients we will compare this independent eligibility assessment to the site screening logs.

Reach 2: To assess patient refusal to participant in pre-randomisation screening processes which includes a diagnostic home sleep study we will examine and collate reasons for declining to participate on the screening log.

Reach 3: To assess challenges to these home screening processes, we will conduct brief semi-structured interviews with patients and clinic/research team members involved in these processes. These interviews will be conducted via Teams by a qualitatively trained researcher, digitally recorded, and professionally transcribed. Interviews with patients will be conducted within one-month of the home sleep study to minimize recall bias.

Intervention Fidelity: We will review the monthly download data from PAP devices and compare to prescribed PAP use. We will categorise participants as high, moderate and low levels of compliance. We will recruit a purposive sample (participants with high, moderate and low levels of compliance for each of the four internal pilot sites) and conduct semi-structured interviews at the three month data collection point focusing on acceptability, barriers and facilitators to PAP use. These interviews will be conducted via Teams by a qualitatively trained researcher, digitally recorded, and professionally transcribed. We will administer the Theoretical Framework of Acceptability questionnaire to gain further understanding of intervention acceptability.

Outcome Fidelity: We will obtain a report of missing outcome data (monthly health service utilisation and 3 and 6 month questionnaire completion) from the study database to assess for missing outcome data in both the intervention and control arm. We will contact participants with low completion rates at 12 months to qualitatively explore barriers to completion and collect suggestions as to how to make questionnaire completion easier for participants.

Patient response: We will explore patient experiences of PAP therapy and study participation during the semi-structured interviews exploring intervention fidelity conducted at three months.

Clinician response: We will explore clinician experiences of referring patients to the study and their clinical management during the study using semi-structured interviews on completion of the 12 month internal pilot. We will administer the Theoretical Framework of Acceptability questionnaire to gain further understanding of study acceptability.

Sample Size

We will assess quantitative data on intervention fidelity for all 52 intervention participants and outcome fidelity for all 104 participants recruited during the internal pilot. We will aim to recruit a purposive sample of a minimum of 6 participants (2 each of high, moderate and low PAP therapy compliance) from each of the 4 centres to participate in qualitative interviews. We will aim to recruit a minimum 2 clinicians from each site for qualitative interviews.

Analysis Methods

We will use descriptive statistics to summarize reach and fidelity data overall and for each site. We will analyse qualitative data using directed content analysis methods. We will use the following methods to ensure credibility of the results. Participation of two research team members throughout all phases of data analysis. Frequent team to discuss sequential interviews, data codebook, data coding, and the content of reflexive interviewer memos. We will establish dependability and confirmability using a third research team member. We will develop a study specific logic model using the data collected as described above which will help support ongoing implementation throughout the study.

Prior to study commencement we will consult our patient advisory group as to strategies to enhance these processes from a patient perspective. Throughout the process evaluation we will provide reports of reach, fidelity and response to our patient advisory group and ascertain guidance as to how to optimize our study processes

Envelope Details

Title	EPiC-OSA Protocol V1.0
Author	Emma (emma.hedley@ndm.ox.ac.uk)
Envelope Created on	Wed, 23 Oct 2024 16:40:01
Envelope ID	a43633ad-d5d5-4b01-974b-ff42c39afe0a

Document Details

Title	EPIC-OSA_Protocol_GSTFT_RCT_V1.0_14Oct2024_FINAL_CLEAN.docx.pdf
Digital Fingerprint	296a6bcd-e53f-48ee-bd92-cc5dc7205fa5

Document Signers Scan/Click the QR Code to view signature information

Name	Patrick Murphy
Email	Patrick.Murphy@gstt.nhs.uk
Status	**SIGNED** at Wed, 23 Oct 2024 17:57:29 BST(+0100)
Signature Fingerprint	465eea3b-263c-4bcb-a72b-9e70a4df03c6

Document History

Wed, 23 Oct 2024 17:57:30	**Patrick Murphy** Signed the Document (IP: 161.17.0.1)