Protocol details

1.1 PROTOCOL TITLE:

Can Mandibular Advancement Device Treatment For Obstructive Sleep Apnoea Reduce Nocturnal Gastro-Oesophageal Reflux: A Feasibility Study

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1.3 Protocol details

Version number: 3.0
Final/draft: draft
Date: 22/09/2022

2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed 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 (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

[Insert name of CI]

Signature Date

Sponsor Representative

R&D to Add
GSTFT

Signature Date

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3 List of Abbreviations and Definitions

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
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
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

4 Summary/Synopsis

Title	Can Mandibular Advancement Device Treatment For Obstructive Sleep Apnoea Reduce Nocturnal Gastro-Oesophageal Reflux: A Feasibility Study
Protocol Short Title/Acronym	MAD-REFLUX
Protocol Version number and Date	v3.0 15/09/2022
Study Phase if not mentioned in title	Feasibility study
Is the study a Pilot?	Yes
IRAS Number	304665
REC Reference	22/EM/0157
Sponsor Reference	146614
Study Duration	20 months
Methodology	Unblinded randomised controlled study
Sponsor name	Guy's and St-Thomas' Foundation Trust and King's College London
Chief Investigator	Dr. Saoirse O'Toole
Funder Name	NIHR RfPB
Medical condition or disease under investigation	Gastro-Oesophageal Reflux Disease
Purpose of clinical trial	To determine the feasibility of a fully trial investigating the impact of Mandibular Advancement Devices (MADs) on nocturnal reflux
Primary objective	To determine the acceptability of this protocol to patients in order to assess if MADs reduce reflux to the same extent as CPAP therapy
Secondary objective (s)	To obtain a sample size calculation for a definitive trial
Number of Subjects/Patients	44
Trial Design	Feasibility study for a randomised controlled clinical trial
Endpoints	Adequate patient recruitment and retention rates
Main Inclusion Criteria	Adult patients diagnosed with both mild-moderate obstructive sleep and gastro-oesophageal reflux disease
Statistical Methodology and Analysis	Determining differences in clinical outcomes between the arms is not the primary purpose of this feasibility study. The focus of the results will be on the estimates of the treatments rather than statistical significance and as such no hypothesis testing will be undertaken. Differences between the two comparison groups will be presented in the form of an unadjusted mean difference for continuous outcomes, and an odds ratio for binary outcomes, with their associated 95% confidence intervals. These comparisons will be made on an intention to treat basis with consideration given to per protocol analysis as sensitivity.

5 Introduction

Obstructive Sleep Apnoea (OSA), a condition where airway collapse during sleep results in pauses in breathing, affects 24.5% of the UK population and results in daytime sleepiness, reduced quality of life and increased mortality rates. Over half of these patients will also have gastro-oesophageal reflux disease (GORD) where gastric contents escape back into the oesophagus causing pain, irritation and health complications. These conditions appear to be inter-related and Continual Positive Airway Pressure (CPAP) therapy, the gold standard treatment for OSA to prevent airway collapse, has been shown to reduce GORD. Mandibular Advancement Devices (MADs), a second line but increasingly used therapy for OSA where a gentle jaw thrust is maintained throughout the night, also limit airway collapse. However, whether MADs decrease GORD has not been tested. If they do, this may influence treatment decisions for the 45% of OSA patients who have GORD.

There is a growing body of evidence that Continuous Positive Airway Pressure (CPAP) therapy, the gold standard therapy for obstructive sleep apnoea, can reduce levels of gastro-oesophageal disease [1–4] by maintaining a patent airway, thus reducing intrathoracic pressure differentials. CPAP therapy increased the baseline lower oesophageal sphincter barrier pressure during sphincter relaxation and decreased the duration of sphincter relaxation [5]. Mandibular advancement devices, also maintain a patent airway which may also have a similar impact on intrathoracic pressure differentials and duration of lower oesophageal sphincter relaxation. In addition, the greater compliance observed with mandibular advancement devices may mean that reflux is suppressed for a greater proportion of the night. However, both of these theories remain untested to date.

The interdisciplinary methodology has not been tested before, therefore the aim of this study is to assess the feasibility of recruitment and the trial protocol. The objectives are to assess patient screening and recruitment rates, willingness to participate, acceptability of the multiple assessments needed to test for improvement in both conditions, and collection of information to inform sample size calculations for a definitive trial.

6 Trial objectives and purpose

The overall aim of this project is to conduct a feasibility study to address uncertainties with patient recruitment and patient tolerance of the trial.

A secondary aim is to calculate an estimate of the primary outcome effect to determine the sample size needed for the definitive trial if the progression criteria are met.

The objectives are to assess:

1. Patient screening to recruitment ratio

2. Patient willingness to be randomised and retention in the study

3. Acceptability of the trial and intervention. For instance, the burden placed on patients such as, two impedance monitoring tests, following the same diet on the day of the test and ability to wear the Watch-PAT device and the CPAP/MAD at the same time.

4. To determine an estimate of effect size of the clinical effectiveness of MADs and CPAP therapy at reducing nocturnal gastro-oesophageal reflux will be assessed. This will be done both while the device is in situ to determine the effect of the device and over the entire sleep duration to assess if the numbers of hours the therapy is used influences the overall clinical effectiveness.

7 Study design & Flowchart

7.1 Study Design

This will be a single-centre, tertiary care based, interdisciplinary parallel randomised controlled study.

7.2 Flowchart

	Pre-Screening Visit	Visit 1: Screening visit		Visit 2 Intervention			Visit 3 or more	Final assessment visit	
				CPAP	MAD				
		Day 1	Day 2		App 1	App 2		Day 1	Day 2
Eligibility checked by research dentist or nurse	x								
Patient Information sheet given (10 minutes)	x								
Consent for additional screening procedures (5 minutes)	x								
RDQ brief dental questionnaires (2 minutes)	x								
Advice re reflux meds and recording diet prior to screening/final appointment given.	x						x		
Full written informed consent (10 minutes)		x							

Dental examination, manometry and placement of pH catheter (30-40 minutes)		x						x	
Receive Watch-PAT home sleep monitoring device (20-30 minutes)		x						x	
Medical history update, RSI, ESS, Leicester Cough Questionnaire, QoL questionnaires (15 mins)		x						x	
Return sleep monitoring device and remove pH catheter (40 minutes)			x						x
24h food intake recording while pH probe is placed		x	x					x	x
Eligibility criteria checked and confirmed			x						
Randomisation			x						
CPAP mask fitted and instructions given (30 mins)				x					
Digital oral impressions taken for MAD (20 mins)					x				
MAD delivered and instructions given (20 mins)						x			
Device titration appointments (20 mins)							x		
Questionnaire about participant views in taking part in the study									x

8 Subject selection

This will be a single-centre, tertiary care based, randomised controlled study. Participants will be recruited from King's Health Partners sleep services. Potential participants will be identified by the direct care team either by running a search text function to screen their referral letters or by their consultation in clinic. Patients referred for investigation of OSA, who also have a previously confirmed diagnosis of GORD with a 24hour pH study or highly symptomatic reflux, suggestive of GORD will then be informed by their direct care team that they may be eligible to be included in the study and asked if they would like to speak to a research dentist or nurse about participation.

A retrospective audit demonstrated that 5 patients per week undergoing a sleep study in the Lane Fox Unit have confirmed OSA and GORD. Our team have extensively discussed the stringent screening questionnaires we can employ to maximise the chances that the

screened participants will meet the inclusion and exclusion criteria, particularly the GORD criteria.

Of the 20+ patients eligible per month we are anticipating that 50% of these will not want to participate in screening. Of those screened we are anticipating that a further 50% will not meet inclusion criteria. We are costing for 88 participants to be screened and an overall recruitment rate of 3-4 per month so recruitment will take 12-14 months.

8.1 Subject inclusion criteria

1. Adult patients aged 18 or over
2. Confirmed OSA with Apnoea-Hypopnoea Index (AHI) score between 10 and 50
3. Confirmed gastro-oesophageal reflux disease with greater than 6 percent of acid exposure time <pH 4 over 24 hours
4. Patient will not have previously had CPAP or MAD therapy
5. Sufficient healthy teeth to support a mandibular advancement device (10 teeth in each jaw, no periodontal pockets >5, no frank cavitation or loose crowns/bridges)
6. Willing and able to provide informed consent to the study

8.2 Subject exclusion criteria

1. Pregnancy or breast feeding. Pregnancy may impact on gastro-oesophageal reflux. The protocol also dictates that they consume the exact same food/drinks that they had for the first investigation which may not be appropriate at this time. There is also a greater likelihood of interrupted sleep which may influence results.
2. Unable or unwilling to stop GORD medication 2 days prior to assessment or unable to undergo manometry and pH impedance testing. This will be decided by the gastroenterologist at Guy's hospital.
3. Known liver disease or oesophageal/gastric varices as this will impact on the severity of GORD independent of the mechanism of action of the sleep appliance.
4. Previous surgery or intervention for reflux such as fundoplication which may preclude pH impedance testing.
5. Any previous treatment for oesophageal neoplasia.
6. Unable/unwilling to tolerate either a CPAP mask or a mandibular advancement device
7. Medical history likely to impact on 24-hour impedance testing e.g bulimia nervosa
8. Participation in other research within previous 30 days.

9 Study procedures

9.1 Subject recruitment

Pre-screening Visit

Participants will be recruited from King's Health Partners sleep services. In a pre-screening assessment, potential participants will be identified by the direct care team either by by running a search text function to screen their referral letters or by their consultation in clinic. Patients referred for investigation of OSA, who also have either had a previously confirmed diagnosis of GORD with a 24hour pH study or have highly symptomatic reflux suggestive of GORD, will be informed by the direct care team that they may be eligible to be included in the study.

Interested participants will then be asked additional questions on GORD and their dental status. The screening for GORD will be based on the Montreal definition of GORD which is typical heartburn and/ or regurgitation >3 times per week and Reflux Disease Questionnaire (RDQ) questionnaire score of >50%. The pre-screening questions for dental examination will include: do you have at least 10 teeth in each jaw, do you have any loose teeth, fillings or caps or do you have any obvious holes in your teeth.

Interested participants will be provided with a patient information sheet of the entire trial. It will be explained that participation in the trial will be dependent upon meeting the strict inclusion criteria but they will be reimbursed for the additional burden of the screening appointment. They will be given a minimum of 24 hours to make their decision.

9.2 Screening Procedures

Visit 1 (Screening Assessment Visit)

If participants agree to take part in the study, they will attend an afternoon appointment at the gastro-oesophageal centre at Guy's Hospital. When arranging an appointment for the screening visits, the nurse will call prior to the relevant days to advise that proton pump inhibitors will need to be stopped 7 days prior and H2-receptor antagonists or antacids 48 hours prior to this visit.

Full written informed consent will be obtained by the research nurse or dentist and, participants will undergo a brief dental screening by the research dentist to ensure that they have sufficiently healthy teeth to support a mandibular advancement device (10 teeth in each jaw, no periodontal pockets >5.5, no frank cavitation or loose crowns/bridges, (3 mins)). Following successfully meeting all of these inclusion criteria, they will then have a 24 hour impedance catheter placed. This relatively invasive procedure is necessary to diagnose gastro-oesophageal reflux disease and its use has been discussed with our PPI group. In order to guide placement of the pH impedance catheter, the patient will initially need to undergo high resolution manometry (HRM). Following local analgesia of the nares the catheter will be introduced trans-nasally and the patient instructed to drink water through a straw whilst the HRM catheter is advanced to the stomach. The HRM catheter depth will be adjusted to ensure manometric visual of the upper oesophageal sphincter (UOS), the gastro-oesophageal junction (GOJ) and gastric pressures. 10 single swallows of 5ml will performed

with each being 20 seconds apart. Each 5ml water swallow will be assessed in accordance to Chicago classification (version 3) using Manoview software (version 3) (Sierra Scientific Instruments). The HRM catheter will then be removed.

Patients will then undergo reflux monitoring using Sandhill Scientific multichannel impedance pH catheters (ZANBG-44) which are inserted trans-nasally after applying local anaesthesia (xylocaine). The dual pH sensors of the catheter will be positioned 5cm below and above the manometric LOS. The impedance sensors will be positioned above the LOS by 3cm, 5cm, 9cm, 15cm and 19cm. The data will be captured by ZepHrTM recording device.

For the 24 hours while the probe is inserted the participant will be asked to record everything that they have eaten or drank as this will impact on their reflux. Stopping reflux medication and the food diary are part of standard care for this procedure.

Following placement of the catheter, participants will be invited for their home sleep study.

Following the tests for GORD diagnosis and insertion of the 24 hour monitor, participants will attend the Lane Fox Unit in Guy's Hospital which are both disability accessible units, a short 5 minute walk from the gastroenterology department. Participants will be provided with a type 2 sleep study device, the WatchPAT 200 (WP200; Itamar Medical Ltd., Caesarea, Israel), and given comprehensive instructions on how to perform a home sleep study. A 24h number for technical support will be provided to the patient. After their overnight sleep study, they will return the following day to the gastroenterology department for removal of the probe and return of the WatchPAT.

The gastroenterology data will be captured by ZepHrTM recording device and data will be analysed using the BioVIEW Analysis software (5.7.1.0). The polysomnography data will be analysed by a qualified sleep technician.

Eligibility of all screened participants will be assessed according to the inclusion and exclusion criteria.

9.3 Randomisation Procedures

Participants who meet the inclusion/exclusion criteria will be randomly allocated in a 1:1 ratio by the clinical trials unit in King's College London to either the CPAP (22) or the MAD (22) arm by the clinical trials unit. The intervention will consist of either a mandibular advancement device (n=22, Somnomed Avant) with the dental sleep medicine department or continuous positive airway therapy (n=22) with the sleep medicine department.

9.4 Masking & other measures taken to avoid bias

9.4.1 Masking

The patient and clinician cannot be blinded to the group allocation. However, all data analysis and statistical analysis will be performed blinded to the group allocation. The proposed clinical primary outcome assessment in the later definitive trial is an objective, computer-generated clinical measurement outcome and is less likely to be subject to bias.

9.4.2 Other measures taken to minimise / avoid bias

N/A

9.5 Schedule of Treatment for each visit

Visit 2 Intervention

Mandibular Advancement Device

Medical history will be updated, and a full intraoral soft tissue and hard tissue examination will be completed. Participants will complete a reflux symptom index questionnaire, Epworth Sleepiness Scale questionnaire, Leicester Cough Questionnaire and a QoL questionnaire. Intraoral digital impressions and a digital protrusive record will be taken using 3M true definition intraoral scanner (3M ESPE, UK). A mandibular advancement device (SomnoMed Avant, Somnomed UK) with a compliance chip for objective compliance monitoring will be constructed and fitted 3 weeks later.

Following checks for fit, retention and comfort, the appliance will be titrated over the following two weeks using subjective patient improvements in sleep and quality of life to gauge successful titration. The patient will be given a period of three weeks to become accustomed to the device.

CPAP Therapy

Medical history will be updated, and a full intraoral soft tissue and hard tissue examination will be completed. Participants will complete a reflux symptom index questionnaire, Epworth Sleepiness Scale questionnaire and a QoL questionnaire. A CPAP mask will be fitted and patients will be issued with an autoset CPAP device (APAP, S8/S9, ResMed Ltd, Sydney, Australia) for home use. The patients will be instructed upon use. The patient will be allowed a period of three weeks to become accustomed to the device.

Visit 3 Titration of devices

Some adjustment of the devices may be needed to ensure comfort and efficacy of the device. This will be done as routine care and scheduled as needed.

Visit 4 (Repeat pH impedance testing and questionnaires)

Following successful titration for each device and a three-week accustomisation period the 24 hour impedance monitoring and home sleep study will be repeated. As at visit 1, participants will be asked to cease their proton pump inhibitors, H2-receptor antagonists or antacids. A dental examination will be carried out to ensure there have been no changes in the oral cavity by the research dentist. Participants will be asked to review their diet diary from the day they first did the test and repeat what they ate or drank as closely as possible for the day. That afternoon the participant will attend the oesophageal physiology laboratory. Participants will repeat the reflux symptom index questionnaire, Epworth Sleepiness Scale questionnaire, Leicester Cough Questionnaire and a QoL questionnaire. The pH impedance testing and Watch-PAT testing will be repeated as described above. Compliance levels for the MAD and CPAP therapy on the same night will be obtained.

Upon returning the next day to have their pH probe removed and to return the Watch-PAT, participants will be asked to complete a questionnaire about their views in taking part in the study.

9.6 Qualitative Interviews

To enhance our understanding of acceptability of recruitment processes, screening procedures, and of taking part in the trial we will conduct telephone interviews with participants (approx. n=16) over the course of the project. We will use a sampling matrix to include eligible patients who were screened but did not take part in the trial, patients who could not tolerate the device or discontinued the trial for other reasons and those who completed the trial.

Using the Theoretical Framework of Acceptability to underpin the interview guide, participants will be asked about different domains of acceptability (e.g. affective attitude, burden, coherence, perceived effectiveness) for each element of the trial, including recruitment, randomisation, appointments and procedures, use of devices.

Participants will be asked about prospective acceptability (prior to participating), concurrent acceptability (whilst participating) and retrospective acceptability (after participating) as they move through the trial. Participants will also be asked about barriers to trial participation, potential improvements, and how to create advocacy for the trial amongst stakeholders.

The interviews will be audio-recorded and professionally transcribed verbatim, in preparation for Framework Analysis whereby a thematic framework is developed and applied to the transcripts, allowing systematic analysis and interpretation of the qualitative data. Participants will receive an additional £25 if they take part in this 25-minute interview.

9.7 Embedded Study Within a Trial Assessing Potential Participant Identification through Referral Letters

Potential participants will either be identified by the direct care team on clinic through the consultation or before the clinic bu running a search text function of referral letters to identify trial participants.

The first phase (Months 2-5) will involve running the search text function concurrently with the standard recruitment approach without informing the clinical staff of potential participants identified with the search. A member of the research team, not involved in recruitment, will perform the text search and document the number of participants identified. At the same time, we will document the number of participants identified and recruited by the clinical staff and compare discrepancies.

The second phase (months 6-9) will involve the clinical staff having access, in advance of the clinic, to the participants identified by the referral text search. We will document the number of participants identified and recruited by the clinical research staff. The clinician consulting the patient on their initial appointment will be informed that there is a potential study participant before the clinic starts and a member of the research team will be present to pre-screen and provide patient information if the patient gives verbal consent to be approached by a member of the research team.

9.8 Health Economics as Part of the Feasibility Study

During the feasibility phase, the best way of collecting relevant service costs, and patient borne costs, from both a NHS and a wider societal perspective. We will, during this feasibility phase, explore, identify, measure and value costs of service contacts in a future full trial context. We will pilot the Eq-5D(5L) and other measures which could be used in a full RCT to calculate Quality Adjusted Life Years (QALYs) in a cost-effectiveness ratio. We will determine the if these are sufficiently sensitive to measure change in the patient group. We will also determine the appropriate sensitivity analysis in a full economic analysis in this patient group.

9.9 End of Study Definition

The end of study is defined as when all recruited participants have undergone the second sleep study/gastro-oesophageal reflux assessments and the results and participant feedback on the trial has been assessed. This will mean that the research team have all the information necessary to decide whether it is feasible to proceed with a full trial.

10 Assessment of Safety

All adverse events (AEs) will be recorded from the time of randomisation. AEs will be classified according to severity and whether related to the study intervention. The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

- Serious adverse Event (SAE): Any adverse event that:
  - results in death;
  - is life-threatening;
  - required hospitalisation or prolongation of existing hospitalisation;
  - results in persistent or significant disability or incapacity;
  - consists of a congenital anomaly or birth defect.

- Important Medical Events (IME) & Pregnancy: Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

All SAEs will be reported immediately by the Chief Investigator (and no later than 24hrs) to the GSTT R&D office (Sponsor).

10.1 Ethics Reporting

Reports of related and unexpected SAEs will be submitted to the Main REC within 15 days of the chief investigator becoming aware of the event, using the NRES template. The form will be completed in typescript and signed by the chief investigator. The main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt will be sent to the R&D Directorate.

10.2 Trial Steering Committee

There is an inter-disciplinary research team of clinical academics consisting of dentists, a sleep clinician and a gastro-enterologist. If any safety concerns become apparent there will be an emergency meeting set up for optimal care or changes to the protocol.

10.3 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents (PIS, ICF and GP letter) will be submitted for review to Research Ethics Committee (REC) under the HRA.

11 Compliance and withdrawal

11.1 Subject compliance

Compliance with the treatment will be assessed objectively through the devices which is part of standard of care. Compliance chips are inserted into the Mandibular Advancement Devices. These thermosensors report on the time and duration of nocturnal use. CPAP therapy automatically reports on the time and duration of nocturnal use.
If the patient is unable to comply with the device, data will be analysed per protocol.

11.2 Withdrawal / dropout of subjects

Methods to prevent attrition have been discussed extensively with our PPI group and have been successful in the past with our previous study having a 5% attrition rate (22). Participants will be remunerated per visit at a level of £50 per visit outside of standard care for their time and inconvenience. After the trial, participants who would prefer to try the alternative therapy, either CPAP or an MAD will receive the additional treatment. The main analysis conducted will be an intention to treat analysis. A per protocol analysis will also be undertaken as a sensitivity analysis. Participants who fail to attend visit 2 will be excluded from any analysis.

11.3 Protocol Compliance

All non-compliances with the protocol will be documented. As this is a feasibility study any deviations from the protocol will be discussed with our PPI group and research team and will inform the definitive trial. Alternatively, if deviations to the protocol are found to frequently recur, this may require immediate action and the definitive trial is unlikely to progress without major changes in the study design.

12 Data

12.1 Data to be collected

Data Collection Table					
Variable	Source of data	Collection time point(s)	Who will collect data	Validity of tool	Form data will take
Feasibility Primary Outcomes					
Percentage of approached patients who were screened for the trial	Documenting numbers of those approached by a research nurse versus those screened	At patient's initial visit to the sleep centre (approached) and at patient's attendance at the	The research nurse	Simple demographics	Numeric

		gastroenterology lab (screened)			
Percentage of eligible patients who were randomised	Documenting numbers of those meeting the elligibily criteria versus those who were randomised in the trial	After screening has taken place	The research dentist and research nurse	Simple demographics	Numeric
Percentage of patients who completed the trial	Documenting numbers of those who were randomised and those who completed	After the patients who were recruited to the trial complete the second gastroenterology assessment appointment	The research dentist and research nurse	Simple demographics	Numeric
Clinical Outcome to Signal Efficacy					
Change in percentage acid contact time pH < 4 with the device in situ	Data from 24-hour pH monitoring	Initial gastroenterology screening visit and follow up gastroenterology assessment post therapy	The gastroenterology department will collect data which will be reviewed by the PI	Gold standard assessment criteria	Numeric
Secondary Outcomes					
Patient acceptability of the trial (as determined by qualitative interviews throughout the trial)	Participant Interviews	Eligible participants that did not take part, drop out patients	Research Nurse overseen by Dr. Suzanne Scott	N/A	Qualitative
Hours that device is worn during sleep	Output from therapeutic device	Throughout device use	The research dentist and PI	Gold standard assessment	Numeric
Health Related Quality of Life using the EQ-5D-5L questionnaire at baseline	Participant Questionnaire	At the screening appointment and after trial completion	The research nurse and dentist	Standardised assessment tool	Numeric

and post intervention					
VAS rating of both therapies	Participant Questionnaire	At the screening appointment and after trial completion	The research nurse and dentist	Standardised assessment tool	Numeric
Documentation of Health resource use including intervention costs	Documentation of resources used to include average appointment times and attending health care practitioners	Throughout trial	Research nurse	N/A	N/A
Number of potential participants identified by care team with and without screening of referral letters	Participants identified on clinics	Before the pre-screening clinic and after the pre-screening	The research nurse	Simple descriptives	Numeric

Additional measures that will inform the definitive trial					
Change in total percentage acid contact time <pH 4 over sleeping period.	Data from 24-hour pH monitoring	Initial gastroenterology screening visit and follow up gastroenterology assessment post therapy	The gastroenterology department will collect data which will be reviewed by the PI	Gold standard assessment criteria	Numeric
Change in Reflux Symptom Index (RSI)	Participant Questionnaire	At the screening appointment and after trial completion	The research nurse and dentist	Standardised assessment tool	Numeric
Change in Epworth Sleepiness Scale (ESS)	Participant Questionnaire	At the screening appointment and after trial completion	The research nurse and dentist	Standardised assessment tool	Numeric
Change in Cough	Participant Questionnaire	At the screening appointment and after trial completion	The research nurse and dentist	Standardised assessment tool	Numeric

Data collection forms included in appendices

1. *Qualitative Interview Guide*
2. *Epworth Sleepiness Score* [6]
3. *Reflux Symptom Index* [7]
4. *Reflux Disease Questionnaire* [8]
5. *Leicester Cough Questionnaire* [9]
6. *EQ-5D-5L* [10]
7. *VAS index of device acceptability*

12.2 Data handling and record keeping

All data will be entered by a clinical research nurse/dentist. All clinical data will be handled securely on an eCRF (MACRO, Infermed) maintained by the King's Clinical Trials Unit (King's College London, London, UK). All data storage will be anonymised with restricted access and data stored on a secure RAID server. SSL-encrypted data transmission over NHS e-mail when communicating with NHS practices will be employed. De-identified data will published and then the clinical trials data will be stored for 5 years by the King's Health Partners Clinical Trials Office and all data will be protected in adherence to the Data Protection Act 1998. The chief investigator and trial team will ensure the quality of the data. This research was financed through the National Institute for Health Research and was subject to rigorous peer review.

13 Statistical considerations

The statistician and co-investigator in this trial is Dr. Zoe Hoare, Chief Statistician at the NWORTH clinical trials unit.

13.1 Sample size calculation (some pilot/feasibility studies may not require a formal sample size calculation)

This is a feasibility study as the research question of MAD vs CPAP when attempting to treat nocturnal GORD has not been investigated. There are several studies investigating change in % acid exposure from baseline while wearing the CPAP device. Samples sizes suggested from current data based on change in total acid were between 86 to 168 (Tawk et al.) per group (excluding any attrition). Thus, the worst case scenario has been considered throughout to try in an effort to be as conservative as possible. An approach taken by Cocks and Torgerson requires a feasibility sample equivalent to approximately 9% of the proposed definitive sample. If we were to assume a one sided non-inferiority design with a margin of 4.15 (% total acid) together with a SD of 10.8 (Tawk et al.) with a power of 90% and alpha of 2.5% for a definitive study this requires a sample of 288 (without attrition).

Considering the likelihood of the main study finding this an effect of this size within an 80% confidence interval, then an approach taken by Cocks and Torgerson requires a feasibility sample equivalent to approximately 9% of the proposed definitive sample. Meaning that if the observed difference between the arms in the feasibility study is zero, then the upper 80% confidence interval would exclude the proposed estimated effect). Therefore, if a definitive trial requires 288 participants then approximately 9% of this is 26.

Accommodating an overall attrition rate, including tolerance to the devices, of 40% requires a sample of 44 to be randomised. A sample of 44 will also give us a 95% confidence interval of +/- 14% around the attrition rate.

13.2 Statistical analysis

Baseline characteristics will be summarized for all participants within the trial arms. Participants' uptake of and adherence to both CPAP and MAD, as well as follow-up rates, will be summarized and presented as percentages.

Although determining differences in clinical outcomes between the arms is not the primary purpose of this feasibility study, comparisons will be undertaken to investigate the feasibility of studying these outcomes and to calculate potential estimates and 95% confidence intervals. As recommended in guidelines for good practice for the analysis of pilot studies [11], the focus of the results will be on the estimates of the treatments rather than statistical significance and as such no hypothesis testing will be undertaken. Differences between the two comparison groups will be presented in the form of an unadjusted mean difference for continuous outcomes, and an odds ratio for binary outcomes, with their associated 95% confidence intervals. These comparisons will be made on an intention to treat basis with consideration given to per protocol analysis as sensitivity. While every effort will be made to minimise missing data, assessment of the levels of missing data will indicate suitability of measures to be continued into the definitive trial.

For the qualitative research, anonymised, transcribed-verbatim, audio-recordings of the qualitative interviews will be analysed using the Theoretical Domains Framework (TDF) and a deductive approach with an agreed TDF-based coding guide with scope for additional codes. Data will be managed in NVivo.

Dr. Hoare and Dr Scott will oversee the quantitative analysis and qualitative analysis respectively.

13.3 Interim analysis and data monitoring

13.3.1 Stopping / discontinuation rules and breaking of randomisation code

As this is a feasibility trial we will be recording feasibility outcomes. These include

1. Percentage of screened patients who were eligible for the trial
2. Percentage of eligible patients who agreed to participate
3. Percentage of patients who completed the trial

We will then assess one clinical outcome to assess signal of efficacy which is the change in percentage acid contact time pH < 4 with the device in situ.

As this is a feasibility study, there will be a natural break at the end of the study if patient recruitment and trial acceptability is not satisfactory.

This will be assessed via a red/amber/green criteria as outlined in the outcome measures.

13.3.2 Monitoring, quality control and assurance

The trial manager will be in charge of trial governance, data management and monitoring in addition to a trial administrator who will contact participants, book appointments, file trial documentation. There will be a quarterly trial steering group with all investigators, the trial manager and PPI members. All data will be collected according to Good Clinical Practice and will adhere to research governance guidance. This will be overseen by the King's Clinical Trials Unit.

14 Ethical considerations

Ethical approval will be obtained from the HRA. It is highly likely, given that we are investigating the efficacy of commonly used approaches, that this will be approved. The participant will be informed that the decision to participate or not participate in the study will not influence any clinical decision or subsequent care. They may withdraw from the study at any stage without affecting care. If a patient requires dental and or medical care during the study period, it will be administered by their treating clinician. Adverse event monitoring will comply with our Clinical Trial Unit procedures.

15 Financing and Insurance

This research is funded by NIHR Research for Patient Benefit programme.

The study is co-sponsored by Guys and St Thomas' NHS Foundation Trust (GSTT) and King's College London (KCL). The sponsors will, at all times, maintain adequate insurance in relation to the study. KCL through its' own professional indemnity (Clinical Trials) & no fault compensation and the GSTT having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

16 Reporting and dissemination

Results will be presented at national and international conferences in addition to publishing in high impact inter-disciplinary journals. We plan to engage sleep clinicians, GP's, dentists, patients and the public using established social media platforms, association bodies and our PPI group. However, until a definitive trial is conducted we will remain cautious and results will not influence how we teach, diagnose and treatment plan in clinical care. We will however share our findings via the Hope2Sleep Charity, British Sleep Society, the British Society of Gastroenterology and the British Dental Association. We aim to attend three conferences as this is an inter-disciplinary project to receive feedback on the project. If the trial progresses, we alongside our PPI group, will approach policy and patient group stakeholders to maximise the impact of the definitive trial.

Tables, Figures, References
Appendices
Including (where relevant):
Patient information sheet
Patient consent form
Data collection forms and validation information
Ethics form
Summary of product characteristics
Investigators brochure

Useful reading/websites

Integrated Research Application System (IRAS)
https://www.myresearchproject.org.uk/

Health Research Authority (HRA)
www.hra.nhs.uk

HRA Guidance for Patient Information Sheet and Informed Consent
http://www.hra.nhs.uk/research-community/before-you-apply/participant-information-sheets-and-informed-consent/

CONSORT statement
A set of recommendations for improving the quality of reports of parallel group randomised trials
http://www.consort-statement.org/

ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Martin Bland et al, Statistical guide for research grant applications
http://www-users.york.ac.uk/~mb55/guide/guide.htm
Includes detailed information and definitions of many aspects required for a research protocol as well as information about randomisation software and services

Martin Bland, Directory of randomisation software and services
http://www-users.york.ac.uk/~mb55/guide/randsery.htm

Declaration of Helsinki
(http://www.wma.net/en/30publications/10policies/b3/index.html)

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC 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	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
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 NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	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	Main REC with a copy to be sent to the sponsor

			participants	

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