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1 June 2012

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Study Protocol

TOMADO: Crossover Randomised Controlled Trial (RCT) of Oral Mandibular Advancement Devices (MAD) for Obstructive Sleep Apnoea-Hypopnoea (OSAH).

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Protocol Identification Number: P01415

Date of Protocol: 16th May 2012

Protocol Version Number: 3.0

Trial Sponsor: Papworth Hospital NHS Foundation Trust

Funder: NIHR Health Technology Assessment (HTA) Programme

Funder Identification Number: 08/110/03

REC Reference: 10/H0308/4

NIHR CRN Study ID: 8532

ISRCTN No: ISRCTN02309506

'This project is funded by the NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series. Visit the HTA programme website for more details www.hta.ac.uk/link to project page. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health'

NIHR Health Technology Assessment programme funded project

MRC Biostatistics Unit

HERG Health Economics Research Group

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Approved by the following:

Name:

Signature:

Date:

Chief Investigator Name: Dr T Quinnell

Signature

Date:

Version History

	Version	Date	Amendment	Date approved
Current Version	3.0	16 May 2012	SA02	
Previous Version	2.0	30 November, 2010	SA01	20 December, 2010
Previous version	1.0	27 November, 2009		

STUDY SYNOPSIS

Title of Study	TOMADO: Crossover Randomised Controlled Trial (RCT) of Oral Mandibular Advancement Devices (MAD) for Obstructive Sleep Apnoea-Hypopnoea (OSAH)
Protocol Number	P01415
Number of Study Sites	1 (bMAD manufactured at another NHS site)
Number of Patients	90 – 96 (maximum)
Study Design	Crossover Randomized Controlled Trial (4-treatment, 4-period)
Patient Population	Patients with mild to moderate obstructive sleep apnoea syndrome (OSAH)
Objectives	1) Are MADs more effective than no treatment? 2) Does level of MAD sophistication – bespoke, semi-bespoke and over the counter, representing a spectrum of complexity and cost – influence treatment outcome?
Main Criteria for Inclusion	▪ Age ≥18 years. ▪ Obstructive sleep apnoea hypopnoea confirmed by respiratory or complete PSG with AHI 5 - < 30/hour ▪ Excessive daytime sleepiness: ESS ≥ 9
Outcomes	**Primary** ▪ Apnoea-Hypopnoea Index (AHI) **Secondary** ▪ Epworth Sleepiness Scale (ESS) ▪ 4% Oxygen Desaturation Index, mean, minimum and time <90% of nocturnal SpO2 ▪ Blood Pressure ▪ Functional status (FOSQ) and Generic (SF-36) ▪ Disease specific HRQoL (SAQLI) ▪ EuroQol EQ-5D ▪ Adherence, hours use and retention ▪ Snoring scale ▪ Health care usage and driving ▪ Side effects; withdrawals; and participant satisfaction and preference
Study Duration	Main study = 30 weeks per patient Follow up = 2 years per patient
Study Period	Main study = 2.5 years from September 2010, Recruitment beginning December 2010 Follow up = Approx. 2 years from last patient completing the main study. (Follow up expected to be completed by June 2015).

ABBREVIATIONS

AASM	American Academy of Sleep Medicine
AE	Adverse Event
AHI	Apnoea-hypopnea index
bMAD	Bespoke mandibular advancement device
BMI	Body mass index
CEAC	Corporate Environmental Advice Centre
CRA	Clinical Research Assistant
CRF	Case Report Form
CPAP	Continuous positive airway pressure
DI	Desaturation Index
DMEC	Data Monitoring and Ethics Committee
ESS	Epworth sleepiness scale
EQ-5D	EuroQol-5D
FOSQ	Functional outcomes of sleep questionnaire
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
MAD	Mandibular advancement device
NHS	National Health Service
NICE	National Institute for Clinical Excellence
OSAH	Obstructive sleep apnoea-hypopnea
OSAHS	Obstructive sleep apnoea-hypopnea syndrome
OTC	Over the counter
PI	Principal Investigator
PSG	Polysomnogram
PSS	Personal Social Services
QALY	Quality adjusted life years
R&D	Research & Development
RF	Research Fellow
RSSC	Respiratory Support & Sleep Centre
RTA	Road traffic accident
SAQLI	Sleep apnoea quality of life index
SAE	Serious Adverse Event
SF-36	Short Form- 36
SP1	SleepPro 1
SP2	SleepPro 2
SpO_2	Pulse oximeter oxygen saturation
TSC	Trial Steering Committee
VAS	Visual analogue scale

1. Introduction

OSAH is characterised by repetitive partial or complete upper airway obstruction during sleep, which leads to reduction (hypopnoea) or complete occlusion (apnoea) of airflow, typically causing nocturnal oxygen desaturation. These events are usually terminated by brief arousal from sleep, which leads to temporary restoration of airway patency. OSAH Syndrome (OSAHS) occurs when the resultant sleep fragmentation causes significant daytime sleepiness. Affecting around 4% of middle aged men and 2% of middle aged women [1], OSAHS has a major public health impact. It is associated with significantly increased risk of road traffic accidents [2], cognitive impairment, mood disturbance and decreased Health Related Quality of Life (HRQoL). OSAH is associated with hypertension [3]. Through this and other mechanisms it has an association with cardiovascular morbidity, although obesity and the metabolic syndrome confound this relationship.

Mild to moderate OSAH can be treated with a mandibular advancement device (MAD) worn intra-orally at night to hold the lower jaw and tongue forward making more space to breathe. MADs are considered an alternative treatment to continuous positive airway pressure (CPAP) delivered via a face or nasal mask. NICE Technology Appraisal No 139 [4] recommends CPAP as a treatment option for moderate or severe OSAH yet for mild OSAH this is only recommended if patients experience symptoms that affect their quality of life/daily activities and where other treatment options have been ineffective or are considered inappropriate. A Cochrane Review of MAD [5] concluded that MADs are an appropriate therapy for patients who are unwilling or unable to tolerate CPAP and also for patients with mild, symptomatic OSAH. See Appendix 1 for a summary of previous studies.

However, clinical equipoise persists regarding the role of MAD in OSAH. Research evidence suggests that while CPAP is superior to MAD in reducing the apnoea-hypopnea index (AHI – the frequency of apnoeas and hypopneas per hour of study), there is little difference in symptom control, such as daytime sleepiness. While studies generally support published treatment recommendations, there remain important limitations within the current evidence base. Interpretation of subgroup analyses is restricted by small numbers of studies, and few studies have actually investigated interventions for mild OSAH. The evidence base does not reflect the wide range of types of MADs currently available on the market and most individual trials have been small, of limited methodological quality and have not adequately addressed key outcomes like HRQoL.

There are two key issues which have yet to be explored. Firstly, there is a need for comparison of MAD with a no treatment control. Studies comparing MAD with sham MAD (involving discomfort and side-effects with no obvious therapeutic benefit), may give a biased estimate of the true effect of MAD. Secondly, there is a need to compare the different types of MADs available on the market. It is not clear whether the complexity of the device – whether over the counter (OTC), semi-bespoke or bespoke – determines the achievement of a therapeutically effective mandibular advancement or impacts on discomfort, side effects and therefore adherence, withdrawal and outcomes.

Published treatment guidelines recommend MAD as a potentially valuable therapy alongside other treatment strategies for OSAH. Despite this, the numbers of NHS patients currently prescribed a MAD are unknown and MAD therapy may in fact be under utilised. It is not known how many patients who decline CPAP are offered MAD as the next best alternative. In conducting this trial we hope to help inform NHS policy and clinician-patient decision making as regards the clinical utility of MADs in mild to moderate OSAH.

2. Study Objectives

Our main objectives are to determine:

1) Are MADs more effective than no treatment?

3) Does level of MAD sophistication – bespoke, semi-bespoke and over the counter (OTC), representing a spectrum of complexity and cost – influence treatment outcome?

3. Investigational Plan

3.1 STUDY DESIGN

The study will be a 4-treatment, 4-period crossover RCT comparing the clinical effectiveness and costs of three types of MAD (bespoke, semi-bespoke and OTC) and a no treatment control for participants with mild to moderate OSAH (AHI of 5 to 30/hour, [6] who refuse or do not require treatment with CPAP. Each 6 week period (4 week for no treatment arm) will comprise of a 2-week acclimatization phase, followed by a 4-week treatment phase. A 1 week washout period will follow active treatments.

Setting: The study will be conducted in the Respiratory Support & Sleep Centre (RSSC) at Papworth Hospital, a tertiary sleep disorders unit with a large national referral base and specialist expertise in the diagnosis and management of OSAH, including the capacity to undertake serial respiratory polysomnography (PSG).

3.2 PARTICIPANTS

Eligible participants will be 18 years of age or older with mild to moderate OSAH confirmed by a respiratory PSG (AHI 5 - <30/hour), who do not require or have refused CPAP as defined in NICE Technology Appraisal 139 [7], and who experience symptomatic daytime sleepiness. Participants may be new referrals or existing patients. See section 3.3 for a detailed description of the inclusion/exclusion criteria.

Recruitment: Consecutive patients with a diagnosis of OSAH will be approached to participate in the study. There are two possible patient pathways in the recruitment of eligible patients:

1) Patients attending outpatient clinic or for inpatient (PSG) with a suspected diagnosis of OSAH will be sent a letter one week before their appointment which describes the trial and contains a participant information sheet. The clinician or research team member will outline the study following their appointment and will give the patient the opportunity to ask any questions. Written informed consent will be taken and baseline tests arranged. If the patient has not read the participant information sheet then the study will be explained to them and any questions answered. They will be given a participant information sheet and contacted 3-5 days later by telephone to ask if they would be interested in participating.

2) Patients without a known diagnosis prior to clinic appointment/inpatient PSG or patients attending the clinic who decline CPAP will also be invited to join the trial. Potential participants will be given a participant information sheet following their appointment and contacted 3-5 later days by telephone to ask whether they would be interested in participating. Those participants who give verbal consent will attend a research clinic, at which written informed consent will be taken and baseline tests carried out.

3.3 PLANNED INCLUSION/EXCLUSION CRITERIA

Pre-Screening
Diagnosis of OSAH will be made by a clinical sleep study involving either pulse oximetry, Embletta or PSG. All patients with (or suspected of having) mild to moderate OSAH will be screened for eligibility. Screening logs will be kept, documenting all reasons for non inclusion. Following consent and enrolment a respiratory PSG will be carried out (unless already performed for clinical reasons) to confirm the AHI (see Section 3.6) for the fulfillment of the eligibility criteria.

Inclusion Criteria:

- Age ≥18 years.
- Obstructive sleep apnoea hypopnoea confirmed by respiratory or complete PSG with AHI 5 - < 30/hour
- Excessive daytime sleepiness: ESS ≥ 9.

Exclusion Criteria:

- Central sleep apnoea as predominant form of sleep disordered breathing
- Coexistent sleep disorder, poor sleep hygiene or drug treatment considered likely to have significant impact on symptoms (especially sleepiness) or assessment of MAD effectiveness.
- Severe and/or unstable cardiovascular disease judged by clinician to warrant immediate CPAP.
- Other medical or psychiatric disorder judged likely to adversely interact with MAD or confound interpretation of its effectiveness.
- Significant periodontal disease or tooth decay; partial or complete edentulism; presence of fixed orthodontic devices.
- Temporomandibular joint pain or disease
- Clinical history suggestive of severe bruxism
- Restriction in mouth opening or advancement of mandible.
- Respiratory failure
- Inability to give informed consent or comply with the protocol
- Pregnancy
- Previous exposure to MAD treatment
- Disabling sleepiness leading to significant patient-specific safety concerns

3.4 STUDY PLAN

VISIT 1

Informed Consent: Participants will be given sufficient time to consider and discuss participation in the study. A member of the research team will explain the study to the patient and give them the opportunity to ask any questions. Participants will be advised that they are able to withdraw from the study at any point without any impact on their routine NHS care. A Research Fellow (RF), Clinical Research Assistant (CRA) or delegated research team member will confirm eligibility and obtain written informed consent before baseline tests are arranged.

Participants will be given a copy of the signed consent form to take away with them and a copy will be filed in the patient's notes and in the site file.

Screening/Baseline: A medical history and clinical examination will be undertaken to identify any contra-indications to participation. The clinical examination will include height, weight, neck circumference, waist-hip ratio, and blood pressure. Participants will complete a number of health status and HRQoL questionnaires including the generic SF-36, the disease specific Sleep Apnoea Quality of Life Index (SAQLI), and EuroQol-5D (EQ-5D). In addition they will complete Functional Outcome of Sleep Questionnaire (FOSQ) and a sleepiness scale (Epworth Sleepiness Scale; ESS). All eligible participants who satisfy the other inclusion/exclusion criteria will undergo a confirmatory respiratory PSG. The RF or CRA will set the equipment up (according to recommended guidelines, Section 3.5) and the patient will take the equipment home to wear that night. If participants have already received a respiratory PSG or inpatient PSG for clinical reasons then they will not need to repeat the sleep study and the AHI will be used as screening/baseline providing it is no more than four weeks prior to baseline (visit 1).

Participants will attend the following day to return the sleep study equipment and complete baseline assessment (Visit 2).

VISIT 2

The respiratory PSG data will be analysed to ensure that the participant meets the inclusion/exclusion criteria. Participants who do not meet the AHI inclusion/exclusion criterion will not progress any further in the trial.

Eligible Participants: Participants will be given and asked to complete a sleep diary each morning over the 6 weeks treatment period or 4 weeks no period treatment to assess sleep duration, snoring, compliance and retention. The participant will be asked to return the diary when they attend for the outcome measures at the end of each treatment.

Manufacture of MADs: An appointment will be made for participants to attend Addenbrooke's Hospital Oral-Maxillofacial department. Participants will first be assessed to confirm suitability for inclusion into the trial by Mr Malcolm Cameron, consultant maxillofacial surgeon, a consultant colleague or a trained and supervised delegate. If suitable then they will be measured and return for fitting of the bespoke MAD (see below).

In order to manufacture the semi-bespoke Sleep Pro 2 device participants will be given an impression kit to take home to mould and wear before sending it to the manufacturer in a pre-paid envelope (See Experimental Interventions below).

Experimental Interventions: Three broadly different types of MAD of varying sophistication, which represent devices currently available along a spectrum of complexity and cost, will be studied:

1) Sleep Pro 1 (SP1) (*Meditas Ltd., Winchester, UK*): A thermoplastic 'boil and bite' device which is fitted by the participant following the manufacturer's printed instructions. The participant softens the device in hot water then places it into their mouth and, having bitten down on it, advances the mandible to an individually-determined 'comfortable' position. The device is then manually moulded against the teeth and sets by subsequent immersion in cold water. Rewarming allows remoulding. (http://www.sleeppro.com).

2) Sleep Pro 2 (SP2) *(Meditas Ltd., Winchester, UK)*: A semi-bespoke device, formed from a dental impression mould used by the participant. An impression kit is posted to the participant. It consists of a SP1 with holes to allow the injection of dental putty, and the putty ingredients. The participant is instructed to mould the SP1 as above, then wear it for two nights to ensure optimum position and fit, remoulding if necessary. The participant then makes up the putty and injects it into the SP1, sending the resulting impression back to the manufacturer. The SP2 is produced from this mould. It is designed to grip the entire dentition. Thinner walls than the SP1 are intended to result in a more comfortable fit. Involvement of the participant's dentist in taking the impression is suggested, but it is not presented by the manufacturer as essential, nor key to achieving the best fit (http://www.sleeppro.com).

3) Bespoke Device (bMAD) *(Oral-Maxillofacial laboratory, Cambridge, UK)*: Custom made MAD, professionally fitted by specialist NHS Oral-Maxillofacial laboratory at Addenbrooke's Hospital. A 'wax bite' will be taken from the participant, which is when the degree of mandibular advancement is determined. Determining the degree of advancement is a balance between advancing the mandible sufficiently to bring the tongue base off the posterior pharyngeal wall and maintaining participant comfort. An impression is made from the wax bite which will ultimately be translated into an acrylic MAD. The participant returns for the fitting of the acrylic MAD which allows for optimal participant comfort.

Degree of Protrusion
As this is a pragmatic trial the SP1 and SP2 devices will both be advanced by the patient, according to manufacturer's instructions. The bMAD will be fitted by qualified dental experts, who will determine the degree of protrusion with the patient, aiming for maximal comfortable advancement. The aim is to advance the mandible by a minimum of 50% of maximal protrusion. The degree of protrusion of each device will be measured by the trial team (RF), although this may be less accurate with the SP1.

VISITS 3 and 4

Participants will attend Addenbrooke's Oral-Maxillofacial Laboratory for the measurement of the bespoke MAD approximately 1-2 weeks after their baseline visit with fitting 2 weeks later. Each appointment will take 20 minutes. In order to ensure devices are not used until the designated treatment period the bespoke MAD will be sent directly to the study team at Papworth Hospital.

Randomisation
Eligible participants who have given informed consent and satisfy all inclusion/exclusion criteria will go forward to the randomised trial. All participants will have a 6 week period of treatment in each of the 3 treatment arms and 4 weeks in the no treatment control arm. Randomisation will take place once eligibility has been confirmed following measurement for the bMAD and Meditas have confirmed that the impression sent by the participant is adequate to make the SP2 device. The trial team will contact Papworth R&D Department on 01480 364143 to receive the randomisation sequence which will be generated by the trial statistician. Further details on the randomisation strategy is included in Section 7.

The first treatment period will begin within four weeks of randomisation.

Intervention schedule: Following the manufacture of the MADs, participants will start the first treatment arm. All participants will receive each MAD for a period of 6 weeks (or no treatment control for 4 weeks) in a randomised order. The MAD will be posted to the participant a few days before the start of the treatment period (or letter advising of no treatment according to participant's intervention schedule) and will be asked to start using the device immediately. Participants will also be asked to complete the daily sleep diary.

The first 2 weeks of each treatment period will act as an acclimatisation phase to give participants time to adjust to each device and will not be considered part of active treatment. The no treatment control period will last 4 weeks.

a) 2 week Acclimatisation Phase with Telephone Follow-up: The CRA will telephone participants at a pre-arranged time two weeks after treatment starts with each device to assess initial tolerability, adherence and to record any contact with the RF, maxillofacial laboratory or other clinical staff in the previous two weeks. A standardised written algorithm will be used to provide simple troubleshooting and non-specific behavioural prompts should a participant report non-tolerance/adherence. Clinical issues will be referred to the RF or a study Physician as required.

b) 4 week Treatment Period: All participants will receive 4 weeks treatment with each MAD and the no-treatment control, with outcome assessment at the end of each treatment period.

VISITS 5 and 6 (visit 6 is to return home sleep study equipment)

Participants will return at the end of each treatment phase for outcome assessment. This will involve a clinical examination, including weight, neck circumference, waist-hip ratio, and blood pressure and completion of the questionnaires as per Visit 1 (SF-36, SAQLI, EQ-5D, ESS and FOSQ). In addition they will be asked about any side effects, adherence, satisfaction with the MAD and withdrawals according to the CRF. Participants will return the daily sleep diary.

The CRA or RF will set up the sleep study equipment and they will be asked to return it the following day, along with the current device if on active treatment. A courier service can be arranged for participants who are unable to return the equipment themselves.

Data collection following the no treatment control period will be identical to the three active treatment arms.

1 week wash out period: A one-week washout period (no treatment) following each active treatment will ensure that the effects of the previous device have worn off. The next device will be given to the participant at the visit. Participants will wear the next MAD (or no treatment) according to the intervention schedule before returning for outcome assessment at the end of the treatment period.

VISITS 7, 9,11 and 12 (visits 8 and 10 are to return home sleep study equipment)

Visits 7, 9 and 11 will be identical to that of Visit 5 with the patient attending for the outcome assessment at the end of each treatment period. At Visit 12 participants will be asked to rank the three devices and no treatment in order of preference and will be allowed to keep their chosen MAD(s). Participant's future care will be discussed with follow up in existing clinics for OSAH participants. Participants who are intolerant of or refuse MAD and/or have persistent symptoms at the end of the study will be considered for CPAP.

Telephone Support: Participants will be given a contact telephone number for advice and support during the course of the study. Participants will be able to discuss any issues with the research team, who will document all calls to determine the level of support required in setting this service up to participants. The Oral-Maxillofacial Laboratory at Addenbrooke's Hospital will also provide a technical support line; again the number of calls will be documented.

3.5 PARTICIPANT WITHDRAWAL

Participants can withdraw from the trial at any time without having to give a reason and this will not affect their future care. A participant can be withdrawn from the trial under the guidance of the Principal Investigator (PI) if clinically necessary or if the participant is considered lost to follow-up. All details will be recorded on the relevant CRF.

3.6 PARTICIPANT TRIAL COMPLETION

A participant will complete the trial after their final visit, if they are withdrawn for any reason and if lost to follow-up or death. Any outstanding SAEs at trial completion will be followed up as thoroughly as possible.

3.7 END OF TRIAL

End of trial is defined as the last patient completing the final visit.

The TSC can end the trial acting on the recommendation of the DMEC. No specific stopping rules are defined and no interim analysis is planned.

3.8 LONGER-TERM FOLLOW-UP

Upon completion of the trial, participants will be allowed to keep the MAD(s) they prefer. All participants will then be followed up at one and two years (+/- 3 months) after completing the trial. Follow up will either be after a routine clinic appointment or by post. This follow-up is to assess long-term MAD use (or use of alternative treatment) including symptom control, tolerability, adherence, side effects and withdrawal, in addition to HRQoL.

Each follow up will involve the completion of questionnaires (SF-36, SAQLI, ESS and FOSQ) and questions about tolerability, adherence and side effects of MAD as was performed during the main trial. Participants who have continued using a MAD will also be asked if they have had any dental work performed and have their bite measured using a ruler. If attending a clinic appointment weight will also be recorded. The follow-up assessments are summarised in Table 5.

Participants will be informed about the follow-up study at trial completion and initial interest recorded. Approx. 1 month prior to the clinic appointment closest to one year after trial completion, participants will be posted the follow-up participant information sheet along with a covering letter asking if they would consider taking part. Participants will then be called approx. 1 week later to see if they are interested in taking part. If so, the participant will be seen following their routine clinic appointment. Written informed consent will be obtained. If participants are happy to take part in the trial but are unable to stay beyond their clinic appointment then participants will be asked to return the questionnaires in a stamped addressed envelope which will be provided.

Participants who do not have a clinic appointment booked within 3 months of the anniversary of trial completion will be posted the follow-up participant information sheet, consent form, questionnaires and covering letter. They will then be called approx. 1 week later to see if they are interested in taking part. If so, the participant will be asked to complete and return the consent form and questionnaires. Participants who do not initially respond will be contacted once by phone and once by letter to remind them to complete the questionnaires.

All participants who are followed up at year one will be contacted the following year to arrange follow up for year two. The year two follow up will be the same as year one, apart from consent will not be taken again.

If a participant declines follow up at year one this will be recorded and they will not be contacted the following year.

3.9 OUTCOME MEASURES

Schedule: Table 4 summarises outcome measures. Apart from patient preference, all outcomes will be assessed at baseline and at the end of each crossover phase (*i.e.* 5 times in total). See Section 3.7 for the schedule of events.

Primary Outcome:

i. Apnoea-Hypopnoea Index (AHI). AHI is the frequency of apnoeas and hypopneas per hour of study [6].

Respiratory PSG: All participants will undergo respiratory PSG monitoring in their own home using Embletta (Medcare) equipment to determine the AHI at baseline and following each treatment period. The Embletta system is fully compliant with British Thoracic Society and the Association for Respiratory Technology & Physiology recommendations [8] for portable monitoring in OSAH. Its diagnostic signals include body position, pulse oximetry, oronasal flow, nasal pressure, snoring and two respiratory effort signals through XactTrace Respiratory Inductive Plethysmograph (RIP) sensors.

All respiratory PSG studies will be scored manually by a NHS Polysomnographer according to the American Academy of Sleep Medicine (AASM) guidelines [6]. Throughout the study, 5% of studies will be scored in parallel by a second Polysomnographer to ensure inter-rater agreement and adherence to recommended guidelines.

Secondary Outcomes:

i. Epworth Sleepiness Scale (ESS). Subjective daytime sleepiness is a key feature of OSAH resulting from disrupted sleep. This measure has been included as an important secondary outcome as the effective control of sleepiness is a main aim of treatment.
ii. Physiological indices from the respiratory PSG – 4% Oxygen Desaturation Index, mean, minimum and time <90% of nocturnal SpO2
iii. Blood Pressure*
iv. Functional status (Functional Outcome of Sleep Questionnaire, FOSQ)* and Generic (SF-36)
v. Disease specific HRQoL (Calgary Sleep Apnoea Quality of Life Index, SAQLI)*
vi. EuroQol EQ-5D transformed to the utility scale*
vii. Adherence, hours use and retention (assessed by a daily sleep diary)
viii. Snoring scale* (Partner rated visual analogue scale)
ix. Health care usage and driving and RTA questionnaire (health economic modeling)
x. Side effects; withdrawals; and participant satisfaction* and preference*

*Outcome measured for research purposes

MAD Adherence

Adherence to treatment will be assessed using patient sleep diary. Participants will be asked to record the number of hours MAD was used each night and number of nights used each week. Adherence defined as use $\geq$ 4 hrs per night and $\geq$ 5 nights per week. If the participant has not completed the patient diary they will be asked to make their best estimate of their hours/nights use.

Stage of trial	**Data to be collected**
Screening	Confirmation of eligibility and application of inclusion/exclusion criteria
Baseline	Basic participant characteristics (age, sex, body mass index (BMI), neck circumference, waist-hip ratio, cardiovascular disease risk factors, blood pressure) Respiratory PSG ESS, FOSQ HRQoL measures – SF-36, EQ-5D and SAQLI Health care usage and driving questionnaire (RTAs)
Crossover Treatment Periods 1-4	**Two week acclimatisation phase** Adherence/Retention Tolerability Participant contact with research staff/maxillofacial laboratory

	Four week treatment phase BMI, neck circumference, waist-hip ratio, blood pressure Respiratory PSG ESS, FOSQ HRQoL measures – SF-36, EQ-5D and SAQLI Daily sleep diary (including Partner VAS snoring score) VAS satisfaction with MAD Health care usage and driving questionnaire (RTAs) Side effects, withdrawals and adherence.
Treatment Period 4	Participant MAD / no treatment order of preference
Follow up Years 1 - 2	ESS, FOSQ HRQoL measures – SF-36 and SAQLI Tolerability Side effects, withdrawals and adherence BMI Bite measurement

Table 4. Outcome Measures Collection

3.10 VISIT SCHEDULE AND ASSESSMENTS

Visits should be scheduled and performed according to Table 5.

Study Phase	**Screening/ Baseline**			**Phase 1**	**Phase 2**	**Phase 3**	**Phase 4**	**Follow Up**	
Visit No	V1	V2	V3/4	V5/6	V7/8	V9/10	V11/12		
Weeks	W1	W1		W9	W17	W25	W33	Year 1	Year 2
Inclusion/exclusion criteria	×								
Written informed consent	×							×	
Basic demographics	×[1]								
Medical history	×[1]								
Clinical examination	×[1]	×		×	×	×	×	(weight)	(weight)
Respiratory PSG	×[1]			×	×	×	×		
Randomisation			×						
MAD measurement			×						
MAD fitting			×						
Blood Pressure		×		×	×	×	×		
ESS	×			×	×	×	×	×	×
FOSQ	×			×	×	×	×	×	×
SF-36	×			×	×	×	×	×	×
SAQLI	×			×	×	×	×	×	×
EQ-5D	×			×	×	×	×		
Partner VAS snoring scale				×	×	×	×		
Health care usage and driving	×			×	×	×	×		
Side effects				×	×	×	×	×	×
Daily sleep diary				×	×	×	×		
Withdrawals				×	×	×	×	×	×
Adherence				×	×	×	×	×	×
Patient satisfaction				×	×	×	×	×	×
Patient preference							×		
Bite measurement								×	×

[1] assessed at screening but also acts as a baseline measure

Table 5. Assessment Schedule

4. ECONOMIC EVALUATION

4.1 Economic Evaluation of the Crossover RCT: McDaid et al [9] concluded that MAD/dental devices may be a treatment option for moderate disease but it remains unclear precisely what type of device may be effective. This was a result of a lack of high quality evidence on their effectiveness. The economic evaluation element of the cross-over trial will provide descriptive data on the resource use, unit costs and health state utilities observed during the 4-week period. The parameter data obtained in the cross-over trial will allow the key uncertainty about the MAD devices to be addressed in a reanalysis of the long term cost-effectiveness model of McDaid et al [9].

Efficacy Parameter Estimates: Health state utilities will be elicited from participants in the cross-over trial using the EQ-5D with the UK social tariff [10]. Systolic blood pressure results will also be collected.

Resource Use and Unit Costs: Resource use and unit costs are being primarily collected to be incorporated into the long term cost-utility. However, mean costs by intervention will be reported for the four week cross-over trial. The perspective for collecting the costs of resource use will be that of the NHS and Personal Social Services (PSS), as advocated in the NICE reference case [11]. Trial protocol driven costs which do not affect participant care outcomes such as administering research questionnaires will be omitted and only health service cost will be included.

Resource use: Resource use data will be collected for the duration of the trial. The type of MAD unit (SP1, SP2 or bMAD) will be recorded as will the frequency of clinic contact (face–to-face clinical contact and telephone consultation) and primary care visits relating to OSAH.

Unit costs: MAD unit costs will be obtained from the finance department of Papworth Hospital. Unit costs for clinician time including labour, capital and overheads will be taken from national estimates [12]. Any medication costs will be taken from the NHS electronics drug tariff [13] or the British National Formulary [14]. The unit costs of any hospital procedures will be taken from the NHS reference costs [15]. In the absence of national estimates, unit costs will be taken from published sources and centre specific costs for Papworth Hospital. Unit costs will be applied to the resource use identified for each participant to obtain mean costs for the entire period of the trial. Costs will be reported in 2007/2008 pounds.

Within-Trial Economic Analysis: Health state utility data will be converted to quality adjusted life years (QALYs) for the four week time horizon of the trial using the area under the curve method. To avoid bias and increase precision in estimates regression adjustment will be applied to costs [16, 17]. Independent variables in the regression adjustment will include MAD group and the potential confounding variable of participants' weight. In addition to regression adjusted results, raw scores will be reported for completeness. Results will be expressed as means accompanied by their 95% confidence intervals. In the event that descriptive statistics suggest skewness of the cost data distribution bootstrap replications will be performed to establish the robustness of results.

4.2 Long-term Economic Model: The aim of the long term economic model is to determine the cost effectiveness of MAD devices for the treatment of OSAH. The objectives are to:

1) Determine the cost effectiveness of MADs compared to a no-treatment control

2) Determine the cost effectiveness of MADs compared to all relevant NHS comparators (no treatment, CPAP, conservative care)

Methods: A cost-utility analysis will be conducted to establish the cost-effectiveness of alternative treatments for OSAH. This will be done by populating a probabilistic Markov cohort process model with the best available data on efficacy, QALYs, resource use and costs.

Economic Model: A new decision analytic model will not need to be developed for this project as McDaid et al [9] developed a model to economically evaluate CPAP for their recently published HTA monograph. The economists that developed the peer reviewed 'York economic model' have agreed to collaborate with the project team, granting us access to the economic model and literature review strategies.

The model characterises the participants' lifetime prognosis using the health states; OSAH, OSAH following coronary heart disease, OSAH following a stroke and death. As OSAH interventions are designed to affect sleepiness and can subsequently affect the risk of road traffic accidents (RTAs), RTAs are also included in the model.

The health effects of OSAH interventions will be expressed in QALYs. The cost of the resource use associated with each intervention will be estimated in accordance with the NICE reference case [11]. An NHS and PSS perspective will be adopted and costs and benefits will be discounted at 3.5%. Costs will be presented in 2007/2008 pounds. Resources that will be costed include the cost of OSAH devices, outpatient appointments, sleep studies, cardiovascular events and RTAs. All cost will include labour, capital and overhead costs, and will be annualised in the case of capital costs.

Transition Probabilities and Resource-Use Data: For MAD arms and the no-treatment arm health state utilities (from EQ-5D), systolic blood pressure (used in conjunction with hypothetical participant characteristics [9]) to predict cardiovascular events using the Framingham risk equations), resource use and unit cost data will be taken from the results of the cross-over trial. All remaining parameter estimates will be obtained by updating the systematic literature review conducted by McDaid et al [9]. The search strategy employed in 2006 will be re-run to identify any relevant data that has emerged in the intervening period. New data will be utilised with previously identified data using conventional meta-analysis techniques based on random effects models.

Analysis: Cost-effectiveness will be summarised as the mean incremental cost per QALY (mean incremental net monetary benefit). Uncertainty surrounding the most cost-effective intervention will be summarised using cost-effectiveness acceptability curves. Parameter uncertainty will be propagated through the model using probabilistic methods/sensitivity analysis. A single stage approach to estimation will be adopted to simultaneously estimate model parameters and cost-effectiveness outcomes of interest, such as mean incremental benefit, CEACs etc. In common with McDaid et al [9] Excel software will be used to synthesize different sources of evidence and implement the model i.e. estimation will be based on Markov Chain Monte Carlo simulation techniques. Uncertainty in fixed parameters and scenarios will be assessed using one-way and multi-way sensitivity analysis.

5. Data Collection

5.1 Source Documentation

Data will be collected by a Clinical Research Assistant (CRA) who is not involved in the routine care of the participants and who will record the data on electronic case report forms (CRFs). All data will be anonymised with participants assigned a participation number at randomisation into the trial.

The investigator/clinical research assistant will maintain source documents (patient's hospital case notes) for each patient in the study, consisting of all demographic and medical information, including respiratory sleep study results. A copy of the consent form and patient information sheet will also be filed in the patient's case notes. All information in the CRFs, apart from the questionnaires, will be traceable to and consistent with the source documents in the patient's hospital case notes (Ref. ICH/GCP 4.9.2).

The questionnaires will be scanned by the Papworth R&D department and entered onto a database which will be password protected. The R&D Unit will undertake periodic audit and monitoring.

5.2 Labeling of Source Documentation

The patients' hospital case notes are to be labelled in the following way to indicate that the patient is randomised into a clinical trial:

- An alert sticker to be stuck on the inside front cover of the patient's notes:

Patient consented to research trial: TOMADO Date of consent: :…… Do not destroy notes before 15 years from this date

- To be stuck on the communication/history sheet page:

Patient randomised into
The TOMADO Trial: Crossover Randomised Controlled **T**rial (RCT) of **O**ral **M**andibular **A**dvancement **D**evices (MAD) for **O**bstructive Sleep Apnoea-Hypopnoea (OSAH).
CI: Dr T Quinnell
Research Team Ext 4944
Or R&D 4448

When a patient completes or if they are withdrawn from the study a red strike through line will be drawn through the second label.

5.3 Data Collection

Data will be recorded on a Formic database produced by Papworth R&D department. Formic is a PC software that allows pre-designed questionnaires to be scanned for data-capture and subsequent analysis. The five questionnaires completed by the participants (SF-36, SAQLI, EQ-5D, ESS and FOSQ) will be scanned into Formic whereas all other data will be entered manually from the source data. The following instructions should be followed for the participant questionnaires:

Originals/photocopies

- Do **not** photocopy the forms. Further supplies can be supplied from the Formic office in the R&D department (01480 364147).
- The forms should be completed in black or blue ink.

Initials/Characters

- Patient initials must be written in upper case letters.
- If there are only two initials, complete the first and third boxes and put a dash in the second box.
- The initials for a patient must be in the same format on all the forms throughout the study.

Errors

- If an error is made when answering yes/no boxes, fill the box in completely and place an **X** in the correct box.
- If an incorrect entry is made in a box which needs to be amended e.g. a date box, cross out the incorrect entry and enter the correct response in the box or write the answer as close to the outside of the box as possible.
- If there are multiple errors on the same page it is advisable to complete a new form.
- All corrections made by trial staff should be initialed and dated and explained, if necessary (Ref. ICH/GCP 4.9.3).

Free Text

Free text cannot be scanned but is analysed separately

Incomplete Data

Ensure that all sections of the forms are completed or that an explanatory comment is added

6. Outcome Measure Analysis

Primary outcome measure

A NHS Polysomnographer independent of the research team and thus who is blinded to treatment allocation will analyse respiratory PSG studies in order to calculate AHI.

Secondary outcome measures

Secondary outcomes will be administered by the CRA on pre-prepared CRFs. Participants cannot be blinded as they are likely to be aware or will be able to divulge which device they are using.

7. Statistical Analysis

Randomisation: Eligible participants who have given informed consent and satisfy all inclusion/exclusion criteria will go forward to the randomised trial. All participants will have a 6 week period of treatment in each of the 3 treatment arms and 4 weeks in the no treatment control arm. The order in which the treatments are used will be decided according to a computer-generated random number sequence. A common randomisation strategy for crossover trials of this kind is based on Latin Squares designs in which participants are randomised in blocks of 4, with each treatment being represented in each period. These designs are both efficient and well balanced for period. Williams' Latin Squares are particular types of Latin Squares that are efficient and have attractive properties if some of the participants fail to complete all 4 periods (providing most participants do complete all periods). For this reason the randomisation will be based on 2 related Williams' Latin Squares designs, with participants randomised in blocks of 8 to ensure good treatment by period balance. Sequences for each block of 8 participants will be as follows.

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	C	D	B
2	B	D	C	A
3	C	B	A	D
4	D	A	B	C
5	A	D	C	B
6	B	C	D	A
7	C	A	B	D
8	D	B	A	C

Although randomisation in blocks of 8 will mean that for every eighth participant the sequence will be predictable this is considered to be less important in a crossover trial.

Sample size calculation

We have based sample size estimation on hypothesis testing rather than precision. In the published reviews considered in Section 3.2, the difference in AHI between MAD and sham MAD was of the order of 10-15 units, with a standard deviation of the difference of approximately 20, and effect size between 1/2 and 3/4. Differences between active MAD are likely to be smaller, with minimum clinically important effect sizes of the order of 1/3. An effect size of 1/3 suggests a sample size of 72 participants for 80% power to detect the effect with 2-sided significance of 5%. Allowing for 20% loss to follow up we plan to recruit a sample of 90 participants, each having all 4 treatments.

ADDENDUM: To ensure the randomisation target of 90 is reached and avoid stop-start recruitment we will screen an extra 6 patients. If all of the extra 6 patients are eligible the maximum number randomised will be 96.

Statistical Analysis

All statistical analyses and reporting will comply with the CONSORT guidelines where possible [18, 19]. In particular, we intend to follow up all participants irrespective of their level of compliance with the MAD and include all periods in the analysis using '*intention to treat*'.

There are 3 main features to consider in the analysis of crossover trials, treatment comparisons, period effects and carryover. Given the nature of the treatments (external devices designed to control symptoms) and the inclusion of a 1 week washout between MAD periods, carryover effects can be ignored. In theory, period effects are unlikely but with all participants required to assess all 4 treatments and stay in the trial for approximately 7-8 months it would be unwise to ignore their possibility. In addition, if compliance is related to time in the study, a period effect may be induced. Thus, in addition to a design that retains some balance even if there is some participant attrition (see section 3.3.9), we will include period effects in the analysis.

Analyses: Exploratory analysis will look at mean differences between treatments by period pair. Treatment effects will also be plotted over time to further explore period effects. The main inferential analysis will

employ linear mixed models with participants included as a random effect and treatment and period as fixed effects. Treatment x period interactions will also be explored although power to detect these second order effects is likely to be limited. There is discussion among statisticians about the relative merits of random and fixed effects for participants and this will be the subject of sensitivity analysis.

The initial analysis will include all participants who complete at least 2 treatment periods. If there are substantial missing data sensitivity analysis surrounding assumptions of 'missing at random' will be undertaken. Similar analyses will be undertaken on a logistic scale for binary outcomes such as the probability of a complete response to treatment (AHI reduced to fewer than 5/hour).

Regression analyses will be conducted to assess the effects of baseline AHI, ESS, age, sex, BMI, neck circumference and waist-hip ratio on subsequent AHI and ESS scores. These analyses will also explore interactions between these variables and treatment effects although we accept that there will be limited power, so results will be considered as hypothesis generating. In addition, one subgroup analysis is planned, concentrating on participants who decline CPAP vs. those with mild-moderate OSAH for whom CPAP is not indicated.

8. Strengths and Limitations

This pragmatic trial was designed to allow the comparison of the clinical and cost effectiveness of three types of MAD in the treatment of mild to moderate OSAH. The study design has been carefully balanced in order to optimise the detection of any treatment effects whilst minimising participant inconvenience.

The treatment periods are relatively short (6 weeks) but benefits of both MAD and CPAP in terms of subjective sleepiness and measures of cardiovascular risk have previously been demonstrated within this time frame[20, 21]. An acclimatisation period (2 weeks) is incorporated into each treatment to allow the participant time to get used to each device. The telephone call at the end of this period will allow the assessment of device tolerability and retention, and provide an opportunity for the trial team to encourage continued participation in the trial even if the current treatment is proving intolerable or ineffective. A wash-out period of one week will follow each active treatment period to ensure no carryover effects from the previous device. Existing evidence suggests that this is sufficient for physiological measurements (AHI) and symptoms to return to baseline [22-24].

We recognise that the study schedule places a high burden on participants with the number of visits required. The cross-over design will allow patients to trial a different device within a relatively short period of time if they find one device problematic. Participants will benefit from close surveillance of their condition throughout the trial through regular contact with the research team and will be supported through a telephone support line. All patient travel expenses will be reimbursed.

Adherence was a consideration in the statistical analysis of the study. The randomisation strategy ensures that patients who have completed at least two treatment periods can be included in the analysis. The data will be analysed on an intention to treat basis.

9. Monitoring and audit

The study will be monitored and audited by a representative from our Research & Development Department and/or local West Anglian Comprehensive Local Research Network (CLRN) who are independent of the trial.

A Trial Steering Committee (TSC) will be convened to monitor the progress of the trial, ensure all objectives are met, review all relevant information or amendments, and investigate any recommendations to the protocol. The TSC will consist of at least two external OSAH experts and a patient representative.

A Data Monitoring and Ethics Committee will meet twice a year (or as required) to ensure the safety, rights and well-being of participants are safe-guarding. An independent chair and clinician will attend the meetings.

10. Adverse and Serious Adverse Event Reporting

10.1 Adverse Event Reporting

MAD treatment for mild to moderate OSAH has been used extensively in clinical trials and in patient populations. Thus its adverse event profile is generally well known. Description of the tolerability and adverse event profile is an important aim of this trial. It is unlikely that novel (unexpected) adverse events will occur and the adverse event profile is anticipated to be modest.

An adverse event (AE) is defined as 'any untoward occurrence in a participant or clinical investigation subject receiving a trial intervention and which does not necessarily have a causal relationship with this intervention'. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study intervention, whether or not considered related to the intervention.

Adverse Reactions (AR)

An **AR** is an AE where a causal relationship with the intervention is at least a reasonable possibility i.e., the relationship cannot be ruled out.

Expected Adverse Reactions

MAD therapy is generally very well tolerated. The main expected ARs of MAD therapy are:

Temporomandibular joint / Jaw Discomfort
Mouth Discomfort
Dry Mouth
Excessive Salivation
Gum Discomfort
Tooth Discomfort
Loose Teeth
Malocclusion
Mouth ulcers

These ARs can be minimised by careful MAD fitting. The frequency of these ARs will be recorded on the case report forms (CRFs).

Unexpected Adverse Reactions

An Unexpected AR is one which is of a nature or severity that is not consistent with the expected AR profile of the trial intervention. Unexpected ARs will be recorded on the CRFs. The probability of Unexpected ARs is low.

Recording of Adverse Events

For this trial, the AE reporting period is from randomisation to the patient's last trial visit (after the 4th treatment), or until the point of patient withdrawal from the trial. AE recording will be limited to any ARs, any other AE considered by the Principal Investigator to be of medical interest/importance to the trial and all Serious AEs (SAEs – see Section 10.2). AEs will be recorded on the routine CRFs.

It will be left to the investigator's clinical judgement whether or not an AE is of sufficient severity to require the patient's removal from the trial treatment. A patient may also voluntarily withdraw from treatment if they find an AE to be intolerable.

The secondary adverse consequences of sleepiness (the correction of which is the primary reason for considering MAD therapy in OSAHS) are recorded as trial outcomes.

Severity of Adverse Events

The severity of AEs will be graded as mild, moderate or severe.

Relationship to trial treatment

The relationship between the trial treatment and the AE (the causality) will be graded as: Unrelated, Possibly related, Definitely related.

Follow-up after Adverse Events
All AEs will be followed up until resolution or to the end of the AE reporting period.

10.2 Serious Adverse Event Reporting

A Serious Adverse Event (SAE) is an AE which meets at least one of the following criteria:

1. Results in death
2. Is life-threatening (i.e. with an immediate risk of death at the time of the event)
3. Requires hospitalisation or prolongs existing hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included)
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is considered to be an important medical event. This, though not included in the above, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed. Medical and scientific judgement should be exercised in deciding whether an AE is serious in other situations.

Serious Adverse Event Reporting
All SAEs should be reported to the sponsor within the specified timeline of a member of the trial team becoming aware of the event. SAEs which are Related and Unexpected (ie SUSARS – Suspected Unexpected Serious Adverse Reactions) will also be reported to the REC, within the appropriate time period. SUSARs will also be reported to Meditas or the PI at Addenbrooke's Maxillofacial Lab depending on the device in question.

All AEs should be reported to Meditas and the PI at Addenbrooke's Maxillofacial Lab (as relevant) within 3 months of the end of study.

Follow-up after Serious Adverse Events
All SAEs will be followed up until resolution or the event is considered stable.

11. Financial and Insurance

This study is being funding by the NIHR Health Technology Assessment (HTA) Programme. Any negligent harm to study participants will be covered by the NHS indemnity insurance.

12. Publication Policy

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and the NIHR HTA Programme. Authorship will be determined by mutual agreement. All publications will acknowledge the funding body of the study. The data will be analysed, as stipulated in the protocol, by the Trust statisticians.

13. Amendments

All amendments will be discussed and approved by the Trial Steering Committee (TSC) before submission to the HTA, REC and R&D. No changes will be implemented before approval is given.

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APPENDIX 1: SUMMARY OF PREVIOUS STUDIES

The evidence supporting the treatment recommendations for mild to moderate OSAH were carefully reviewed in the preparation of the study.

CPAP vs. Control: As shown in Table 1, meta-analysis of up to 23 studies indicates a statistically significant benefit of CPAP compared to control[1] in terms of both AHI [1] and ESS [1,2] although there was considerable statistical heterogeneity (I^2= 70.6%). Treatment effects were generally higher in severe baseline AHI and ESS subgroups and were smaller and more likely to be statistically non-significant in lower baseline AHI and ESS subgroups.

Study and Outcome/Subgroup Outcome	No. Studies	Mean Difference	95% Confidence Interval
Giles et al [1]			
AHI [PG/1st arm X studies] – Overall	7	-17.02	-19.25, -14.80
AHI [X studies] – Overall	1	-9.20	-18.26, -0.14
ESS [PG/1st arm X studies] – Overall	10	-3.83	-4.57, -3.09
ESS [PG/1st arm X studies] – Mild (</=10) baseline ESS	2	-1.21	-2.98, 0.55
ESS [PG/1st arm X studies] – Mod (12-13.9) baseline ESS	2	-3.39	-4.81, -1.96
ESS [PG/1st arm X studies] – Mod/Severe (14-15.9) baseline ESS	3	-5.36	-5.00, -3.71
ESS [PG/1st arm X studies] – Severe (>/=16) baseline ESS	3	-4.61	-5.86, -3.35
ESS [PG/1st arm X studies] – Mod† (15.1-29.9) baseline AHI	2	-2.45	-4.01, -0.90
ESS [PG/1st arm X studies] – Severe† (>30) baseline AHI	7	-4.07	-5.03, -3.11
ESS [PG/1st arm X studies] – Unclear baseline AHI	1	-4.80	-6.56, -3.04
ESS [X studies] – Overall	7	-1.92	-2.59, -1.25
ESS [X studies] – Mild (</=10) baseline ESS	1	0.02	-3.51, 3.71
ESS [X studies] – Mild/Mod (10-11.9) baseline ESS	3	-1.34	-2.25, -0.42
ESS [X studies] – Mod (12-13.9) baseline ESS	3	-2.83	-3.86, -1.79
ESS [X studies] – Mild† (5-15) baseline AHI	3	-1.69	-3.18, -0.21
ESS [X studies] – Mod† (15.1-29.9) baseline AHI	3	-1.71	-2.49, -0.92
ESS [X studies] – Severe† (>30) baseline AHI	1	-6.01	-7.00, -3.00
McDaid et al [2]			
ESS [X studies] – Overall	23	-2.70	-3.45, -1.96
ESS [X studies] – Mild (0-9) baseline ESS	2	-1.07	-1.82, -0.31
ESS [X studies] – Mod (10-15) baseline ESS	16	-2.33	-3.04, -1.62
ESS [X studies] – Severe (16-24) baseline ESS	5	-4.99	-6.51, -3.47
ESS [X studies] – Mild (5-14) baseline AHI	3	-1.50	-3.43, 0.42
ESS [X studies] – Mod (15-30) baseline AHI	7	-2.04	-2.99, -1.09
ESS [X studies] – Severe (>30) baseline AHI	13	-3.41	-4.56, -2.26

Control= Sham (placebo) CPAP, placebo medication or best supportive care (including lifestyle modification);
[PG/1st arm X studies] = Parallel group studies/First arm crossover studies; [X studies] = Crossover studies; †= AASM [3].

Table 1. CPAP versus Control: Apnoea Hypopnoea Index and Epworth Sleepiness Score

CPAP vs. MAD: Table 2 illustrates that these reviews found that CPAP significantly improved AHI compared to MAD [1] although in terms of ESS CPAP was not significantly different to MAD [1,2]. Subgroup/sensitivity analyses were consistent with this finding and the difference in ESS was greater in the severe than in the moderate baseline AHI subgroup. All studies were judged as moderate baseline sleepiness (ESS).

[1] Giles et al [1]) define control as sham CPAP, or other controls such as tablets, weight reduction or other preventative measures. McDaid et al [2] define control as placebo (including placebo pill or sham CPAP), or best supportive/usual care (including conservative intervention such as lifestyle advice regarding weight loss, alcohol consumption and sleep hygiene in addition to sleep posture advice or treatment).

Study and Outcome/Subgroup Outcome	No. Studies	Mean Difference	95% Confidence Interval
Giles et al [1]			
AHI [PG/1st arm X studies] – Overall	2	-13.02	-18.37, -7.67
AHI [X studies] – Overall	7	-7.97	-9.56, -6.38
ESS [PG/1st arm X studies] – Overall	1	0.20	-1.60, 2.00
ESS [X studies] – Overall	4	-0.54	-1.38, 0.29
McDaid et al [2]			
ESS [X studies] – Overall { Mod (10- 15) baseline ESS}	6	-0.85	-2.11, 0.41
ESS [PG/1st arm X studies] – Overall	2	-0.60	-2.70, 1.50
ESS [X studies] – Overall	4	-1.00	-1.10, 0.70
ESS [X studies] – Mod (15-30) baseline AHI	4	-0.20	-1.10, 0.70
ESS [X studies] – Severe (>30) baseline AHI	2	-1.80	-6.00, 2.30

[PG/1st arm X studies] = Parallel group studies/First arm crossover studies; [X studies] = Crossover studies.

Table 2. CPAP versus MAD: Apnoea Hypopnoea Index and Epworth Sleepiness Score

Our notion that the level of MAD sophistication might influence treatment outcome was partially supported. Censoring trials involving one-piece MADs (ESS [3 trials] 0.13, 95% CI: -0.71 to 0.97) and considering only two-piece MADs allowing incremental mandibular advancement (ESS [2 trials] 0.11, 95% CI: -0.84 to 1.06) in post-hoc sensitivity analyses [1] moved the effect in favour of MADs. In addition, compared to MAD CPAP significantly improved minimum saturation, arousals and sleep efficiency although there were no significant differences in objective sleepiness (Maintenance of Wakefulness Test) and generic or disease-specific HRQoL. Furthermore, although participants were significantly more likely to dropout on MAD than CPAP, despite mostly similar side effects, those who responded to both treatments preferred MAD [4,5].

MAD vs. sham-MAD: Lim et al [6] concluded that relative to a sham appliance, using a MAD resulted in significant benefits in AHI, ESS, arousals and minimum oxygen saturation (Table 3) but not in withdrawals or blood pressure. Although beneficial effects were found for HRQoL (Functional Outcomes of Sleep Questionnaire: weighted mean difference 17.00, 95% CI: 2.66 to 31.34), this was from a single small study.

Study and Outcome/Subgroup Outcome	No. Studies	Mean Difference	95% Confidence Interval
Lim et al (6)			
AHI [PG/1st arm X studies]	5	-10.78	-15.53, -6.03
AHI [X studies]	4	-15.15	-19.40, -10.89
ESS [PG/1st arm X studies]	4	-2.09	-3.80, -0.37
ESS [X studies]	4	-1.81	-2.72, -0.90

[PG/1st arm X studies] = Parallel group studies/First arm crossover studies; [X studies] = Crossover studies.

Table 3. MAD versus Sham MAD: Apnoea Hypopnoea Index and Epworth Sleepiness Score

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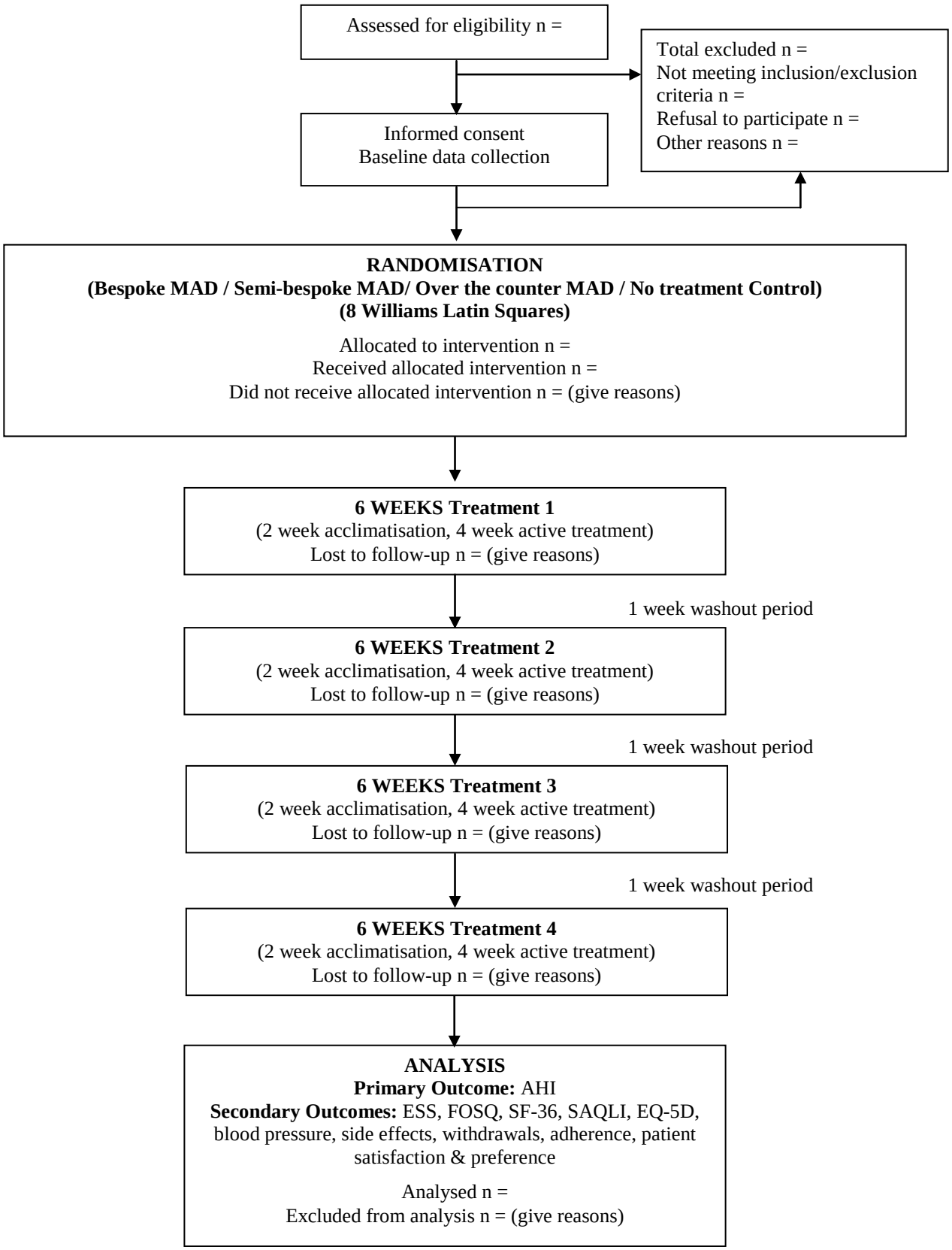
APPENDIX 2. FLOW DIAGRAM

CONSORT Diagram

TOMADO: Crossover Randomised Controlled Trial (RCT) of Oral Mandibular Advancement Devices (MAD) for Obstructive Sleep Apnoea-Hypopnoea (OSAH)



APPENDIX 3: RECRUITMENT SCHEDULE

Month	Baseline Ass	Phase 1	Phase 2	Phase 3	Phase 4	Total – new pt	Total – follow-ups	Total episodes
Month 1 Month 2 Month 3	STUDY SET UP Recruitment and staff training, obtain ethics approval, agree protocols, and initiate trial.							
Month 4	10					10	0	10
Month 5	9					9	0	9
Month 6	10	9				10	9	19
Month 7	9	8				9	8	17
Month 8	8	10	8			8	18	26
Month 9	10	9	8			10	17	27
Month 10	7	8	10	8		7	26	33
Month 11	8	9	8	8		8	25	33
Month 12	10	7	8	9	7	10	31	41
Month 13	9	7	9	7	8	9	31	40
Month 14		9	6	8	9		32	32
Month 15		9	7	8	7		31	31
Month 16			9	6	6		21	21
Month 17			8	6	8		22	22
Month 18				9	5		14	14
Month 19				8	6		14	14
Month 20					8		8	8
Month 21					8		8	8
Month 22 Month 23 Month 24	ANALYSIS & REPORTING Final report to HTA, dissemination of research findings							
Month 25 Month 26 Month 27 Month 28 Month 29 Month 30	UPDATED LITERATURE SEARCH & COMPLETION OF HEALTH ECONOMIC MODEL							
	90	85	81	77	72	90	315	405

APPENDIX 4: QUESTIONNAIRES

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in the last 4 weeks. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0	Would never doze
1	Slight chance of dozing
2	Moderate chance of dozing
3	High chance of dozing

Situation	**0**	**1**	**2**	**3**
Sitting and reading				
Watching TV				
Sitting inactive in a public place (e.g. a theatre or a meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest when circumstances allow				
Sitting and talking to someone				
Sitting quietly after lunch without alcohol				
In a car, while stopped for a few minutes in traffic				

Functional Outcomes of Sleep Questionnaire

Note: In this questionnaire, when the words "sleep" or "tired are used, it describes the feeling that you can't keep your eyes open, your head is droopy, that you want to nod off or that you feel the urge to nap. These words do not refer to the tired or fatigued feeling you may have after you exercised.

FOSQ questions are answered using numbers from 0 to 4 (see answer key below):

0= I don't do this activity for other reasons
1= Yes, extreme
2= Yes, moderate
3= Yes, a little,
4= No

Please fill out this form completely and select only one answer for each question.

	0	**1**	**2**	**3**	**4**
Q1) Do you generally have difficulty concentrating on things you do because you are sleepy or tired?					
Q2) Do you generally have difficulty remembering things because you are sleepy or tired?					
Q3) Dou you have difficulty finishing a meal because you become sleepy or tired?					
Q4) Do you have difficulty working on a hobby (for example: sewing, collecting, gardening) because you are sleepy or tired?					
Q5) Do you have difficulty doing work around the house (for example: cleaning house, doing laundry, taking out the trash, repair work) because you are sleep or tired?					
Q6) Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?					
Q7) Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?					
Q8) Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?					
Q9) Do you have difficulty take care of financial affairs and doing paperwork (for example: writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?					
Q10) Do you have difficulty performing employed or volunteer work because you are sleepy or tired?					
Q11) Do you have difficulty maintaining a telephone conversation because you become sleepy or tired?					
Q12) Do you have difficulty visiting with you family or friends in your home because you become sleepy or tired?					
Q13) Do you have difficulty visiting with your family or friends in their homes because you become sleepy or tired?					

Q14) Do you have difficulty doing things for your family or friends because you become sleepy or tired? Q15) Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?					
Q16) Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?					
Q17) Do you have difficulty watching a movie or videotape because you become sleepy or tired?					
Q18) Do you have difficulty enjoying the theater or a lecture because you become sleepy or tired?					
Q19) Do you have difficulty enjoying a concert because you become sleepy or tired?					
Q20) Do you have difficulty watching television because you are sleepy or tired?					
Q21) Do you have difficulty participating in religious services, meeting or a group club because you are sleepy or tired?					
Q22) Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?					
Q23) Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?					
Q24) Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?					
Q25) Do you have difficulty keeping a pace with others your own age because you are sleepy or tired?					
Q26) How would you rate yourself in your general level of activity?					
Q27) Has your intimate or sexual relationship been affected because you are sleepy or tired?					
Q28) Has your desire for intimacy or sex been affected because you are sleepy or tired?					
Q29) Has your ability to become sexually aroused been affected because you are sleepy or tired?					
Q30) Has your ability to have an orgasm been affected because you are sleep or tired?					

EuroQol - 5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

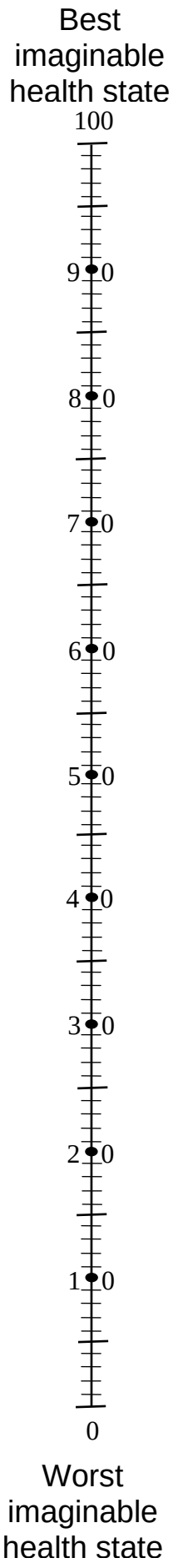
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

e would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



SF-36 Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

1. In general, would you say your health is:

Excellent	☐
Very good	☐
Good	☐
Fair	☐
Poor	☐

2. Compared to one year ago, how would you rate your health in general now?

Much better now than a year ago	☐
Somewhat better now than a year ago	☐
About the same as one year ago	☐
Somewhat worse now than one year ago	☐
Much worse now than one year ago	☐

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

Lifting or carrying groceries.

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

Climbing several flights of stairs.

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

Climbing one flight of stairs.

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

.

Bending, kneeling or stooping.

Yes, limited a lot.	☐
Yes, limited a little.	☐
No, not limited at all.	☐

Walking more than one mile.

Yes, limited a lot.	☐
Yes, limited a little.	☐

No, not limited at all. ☐

Walking several blocks.
Yes, limited a lot. ☐
Yes, limited a little. ☐
No, not limited at all. ☐

Walking one block.
Yes, limited a lot. ☐
Yes, limited a little. ☐
No, not limited at all. ☐

Bathing or dressing yourself.
Yes, limited a lot. ☐
Yes, limited a little. ☐
No, not limited at all. ☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
a. Cut down the amount of time you spent on work or other activities?
Yes ☐ No ☐

b. Accomplished less than you would like?
Yes ☐ No ☐

c. Were limited in the kind of work or other activities
Yes ☐ No ☐

d. Had difficulty performing the work or other activities (for example, it took extra time)
Yes ☐ No ☐

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?
Yes ☐ No ☐

b. Accomplished less than you would like
Yes ☐ No ☐

c. Didn't do work or other activities as carefully as usual
Yes ☐ No ☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?
Not at all ☐
Slightly ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

7. How much bodily pain have you had during the past 4 weeks?
None ☐
Very mild ☐
Mild ☐
Moderate ☐
Severe ☐
Very severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

b. have you been a very nervous person?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

c. have you felt so down in the dumps nothing could cheer you up?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

d. have you felt calm and peaceful?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

e. did you have a lot of energy?

- All of the time
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

f. have you felt downhearted and blue?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

g. did you feel worn out?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

h.. have you been a happy person?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

i. did you feel tired?

- All of the time ☐
- Most of the time ☐
- A good bit of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

a. I seem to get sick a little easier than other people

- Definitely true ☐
- Mostly true ☐
- Don't know ☐
- Mostly false ☐
- Definitely false ☐

b. I am as healthy as anybody I know

- Definitely true ☐
- Mostly true ☐
- Don't know ☐
- Mostly false ☐
- Definitely false ☐

c. I expect my health to get worse

- Definitely true ☐
- Mostly true ☐
- Don't know ☐
- Mostly false ☐
- Definitely false ☐

d. My health is excellent

- Definitely true ☐
- Mostly true ☐
- Don't know ☐
- Mostly false ☐
- Definitely false ☐

Short Calgary Sleep Apnoea Quality of Life Index (SAQLI)

Instructions for completing this questionnaire: Please circle your answer.

We would like to understand whether **your sleep apnoea and/or snoring** have had an impact on your daily activities, emotions, social interactions, and about symptoms that may have resulted.

OVER THE PAST 4 WEEKS:	Not at all	A little	small to moderate	moderate amount	moderate to large	Large amount	Very large amount
How much have you had to push yourself to remain alert during a typical day (e.g. work, school, childcare, housework)?	7	6	5	4	3	2	1
How often have you had to use all your energy to accomplish your most important activity (e.g. work, school, childcare, housework)?	7	6	5	4	3	2	1
How much difficulty have you had finding the energy to do other activities (e.g. exercise, relaxing activities)?	7	6	5	4	3	2	1
How much difficulty have you had fighting to stay awake?	7	6	5	4	3	2	1
How much of a problem has it been to be told that your snoring is irritating?	7	6	5	4	3	2	1
How much of a problem have frequent conflicts or arguments been?	7	6	5	4	3	2	1
How often have you looked for excuses for being tired?	7	6	5	4	3	2	1
How often have you not wanted to do things with your family and/or friends?	7	6	5	4	3	2	1
How often have you felt depressed, down, or hopeless?	7	6	5	4	3	2	1
How often have you been impatient?	7	6	5	4	3	2	1
How much of a problem has it been to cope with everyday issues?	7	6	5	4	3	2	1
How much of a problem have you had with decreased energy?	7	6	5	4	3	2	1
How much of a problem have you had with fatigue?	7	6	5	4	3	2	1
How much of a problem have you had waking up feeling unrefreshed?	7	6	5	4	3	2	1