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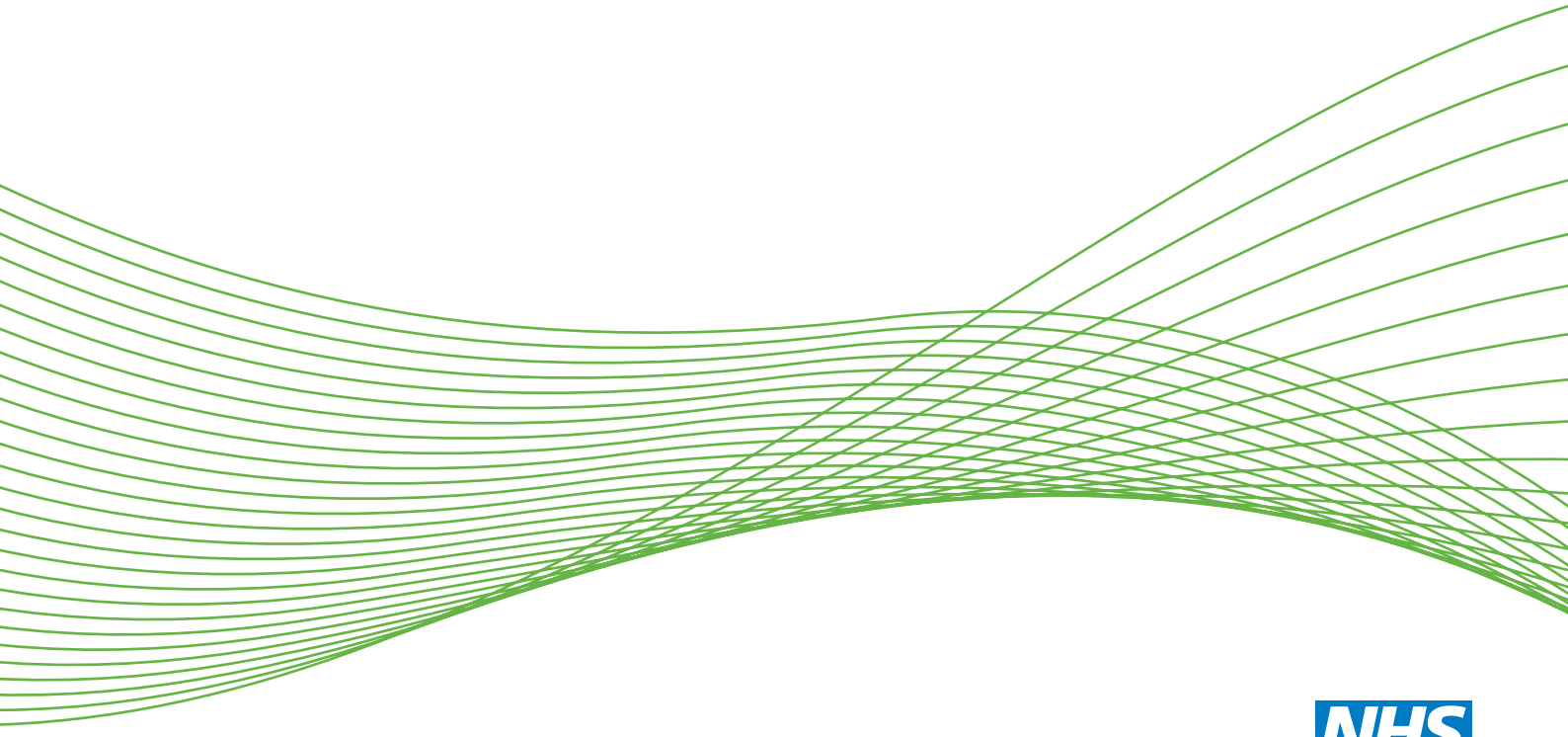

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Abstract

Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure

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Background: Obstructive sleep apnoea–hypopnoea (OSAH) causes excessive daytime sleepiness (EDS), impairs quality of life (QoL) and increases cardiovascular disease and road traffic accident risks. Continuous positive airway pressure (CPAP) treatment is clinically effective but undermined by intolerance, and its cost-effectiveness is borderline in milder cases. Mandibular advancement devices (MADs) are another option, but evidence is lacking regarding their clinical effectiveness and cost-effectiveness in milder disease.

Objectives: (1) Conduct a randomised controlled trial (RCT) examining the clinical effectiveness and cost-effectiveness of MADs against no treatment in mild to moderate OSAH. (2) Update systematic reviews and an existing health economic decision model with data from the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO) and newly published results to better inform long-term clinical effectiveness and cost-effectiveness of MADs and CPAP in mild to moderate OSAH.

TOMADO: A crossover RCT comparing clinical effectiveness and cost-effectiveness of three MADs: self-moulded [SleepPro 1™ (SP1); Meditas Ltd, Winchester, UK]; semibespoke [SleepPro 2™ (SP2); Meditas Ltd, Winchester, UK]; and fully bespoke [bespoke MAD (bMAD); NHS Oral-Maxillofacial Laboratory, Addenbrooke's Hospital, Cambridge, UK] against no treatment, in 90 adults with mild to moderate OSAH. All devices improved primary outcome [apnoea–hypopnoea index (AHI)] compared with no treatment: relative risk 0.74 [95% confidence interval (CI) 0.62 to 0.89] for SP1; relative risk 0.67 (95% CI 0.59 to 0.76) for SP2; and relative risk 0.64 (95% CI 0.55 to 0.76) for bMAD ($p < 0.001$). Differences between MADs were not significant. Sleepiness [as measured by the Epworth Sleepiness Scale (ESS)] was scored 1.51 [95% CI 0.73 to 2.29 (SP1)] to 2.37 [95% CI 1.53 to 3.22 (bMAD)] lower than no treatment ($p < 0.001$), with SP2 and bMAD significantly better than SP1. All MADs improved disease-specific QoL. Compliance was lower for SP1, which was unpopular at trial exit. At 4 weeks,

all devices were cost-effective at £20,000/quality-adjusted life-year (QALY), with SP2 the best value below £39,800/QALY.

Meta-analysis: A MEDLINE, EMBASE and Science Citation Index search updating two existing systematic reviews (one from November 2006 and the other from June 2008) to August 2013 identified 77 RCTs in adult OSAH patients comparing MAD with conservative management (CM), MADs with CPAP or CPAP with CM. MADs and CPAP significantly improved AHI [MAD −9.3/hour ($p < 0.001$); CPAP −25.4/hour ($p < 0.001$)]. Effect difference between CPAP and MADs was 7.0/hour ($p < 0.001$), favouring CPAP. No trials compared CPAP with MADs in mild OSAH. MAD and CPAP reduced the ESS score similarly [MAD 1.6 ($p < 0.001$); CPAP 1.6 ($p < 0.001$)].

Long-term cost-effectiveness: An existing model assessed lifetime cost–utility of MAD and CPAP in mild to moderate OSAH, using the revised meta-analysis to update input values. The TOMADO provided utility estimates, mapping ESS score to European Quality of Life-5 Dimensions three-level version for device cost–utility. Using SP2 as the standard device, MADs produced higher mean costs and mean QALYs than CM [incremental cost-effectiveness ratio (ICER) £6687/QALY]. From a willingness to pay (WTP) of £15,367/QALY, CPAP is cost-effective, although the likelihood of MADs ($p = 0.48$) and CPAP ($p = 0.49$) being cost-effective is very similar. Both were better than CM, but there was much uncertainty in the choice between CPAP and MAD (at a WTP £20,000/QALY, the probability of being the most cost-effective was 47% for MAD and 52% for CPAP). When SP2 lifespan increased to 18 months, the ICER for CPAP compared with MAD became £44,066. The ICER for SP1 compared with CM was £1552, and for bMAD compared with CM the ICER was £13,836. The ICER for CPAP compared with SP1 was £89,182, but CPAP produced lower mean costs and higher mean QALYs than bMAD. Differential compliance rates for CPAP reduces cost-effectiveness so MADs become less costly and more clinically effective with CPAP compliance 90% of SP2.

Conclusions: Mandibular advancement devices are clinically effective and cost-effective in mild to moderate OSAH. A semi-bespoke MAD is the appropriate first choice in most patients in the short term. Future work should explore whether or not adjustable MADs give additional clinical and cost benefits. Further data on longer-term cardiovascular risk and its risk factors would reduce uncertainty in the health economic model and improve precision of effectiveness estimates.

Trial registration: This trial is registered as ISRCTN02309506.

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List of abbreviations

A&E	accident and emergency
AASM	American Academy of Sleep Medicine
AE	adverse event
AHI	apnoea–hypopnoea index
aMAD	adjustable mandibular advancement device
APAP	auto-adjusting positive airway pressure
AR	adverse reaction
bMAD	bespoke mandibular advancement device
BMI	body mass index
BP	blood pressure
CEAC	cost-effectiveness acceptability curve
CEAF	cost-effectiveness acceptability frontier
CHD	coronary heart disease
CI	confidence interval
CM	conservative management
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
CVE	cardiovascular event
DBP	diastolic blood pressure
DI	desaturation index
DMEC	Data Monitoring and Ethics Committee
EDS	excessive daytime sleepiness
EEG	electroencephalography
EQ-5D-3L	European Quality of Life-5 Dimensions 3-level version
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
GP	general practitioner
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
IQR	interquartile range
MAD	mandibular advancement device
MCS	mental component scales
MeSH	medical subject heading
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
NICE	National Institute for Health and Care Excellence
ODI	oxygen desaturation index
OR	odds ratio
OSA	obstructive sleep apnoea
OSAH	obstructive sleep apnoea–hypopnoea
OSAHS	obstructive sleep apnoea–hypopnoea syndrome
PCS	physical component scales
PSG	polysomnography
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
R&D	research and development
RCT	randomised controlled trial
RDI	respiratory disturbance index
rPSG	respiratory polysomnography
RSSC	Respiratory Support & Sleep Centre
RTA	road traffic accident

SAE	serious adverse event
SAQLI	Short Calgary Sleep Apnoea Quality of Life Index
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36	Medical outcomes study 36-item short form
SF-6D	Short Form questionnaire-6 Dimensions
SP1	SleepPro 1
SP2	SleepPro 2
SpO_2	oxygen saturation
TOMADO	Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea
VAS	visual analogue scale
WTP	willingness to pay

Plain English summary

In obstructive sleep apnoea–hypopnoea (OSAH), the airways become blocked during sleep. Breathing becomes shallow or stops, waking the patient suddenly. OSAH causes daytime sleepiness which affects working, driving and other activities, as well as quality of life. It causes hypertension, which is associated with heart disease and strokes. In severe OSAH, the airways are kept open using continuous positive airway pressure (CPAP). This reduces breathing irregularity and daytime sleepiness but requires the patient to wear a mask overnight and is intrusive. An alternative is a mandibular advancement device (MAD) that fits in the mouth like a gum shield. This is less clinically effective at reducing breathing irregularity, but similarly clinically effective at controlling daytime sleepiness, and may be better for mild disease.

We conducted a randomised controlled trial [the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO)] comparing three MADs (bespoke, semibespoke and over the counter) with no treatment in patients with mild OSAH. All three MADs were significantly better than no treatment in reducing breathing disruption and daytime sleepiness, and the differences between MADs were small. The semi-bespoke MAD was most cost-effective in the short-term.

This trial was combined with relevant published trials of MADs and CPAP, and longer-term evidence on heart disease, stroke and road traffic accidents. This showed that:

- CPAP is the most effective treatment in moderate to severe OSAH based on reduction in apnoea–hypopnoea index.
- MADs and CPAP are equally effective treatment options for mild to moderate OSAH based on health outcomes and cost, but this is contingent on good compliance with treatment.
- Of the MADs investigated, the semi-bespoke device should be the first choice.

Scientific summary

Background

Obstructive sleep apnoea–hypopnoea (OSAH) involves repeated interruption of airflow during sleep because of episodic collapse of the pharyngeal airway. Typically this results in oxygen desaturations and microarousals from sleep. When there is significant sleep disruption, then excessive daytime sleepiness (EDS) can occur.

Obstructive sleep apnoea–hypopnoea affects 2–7% of the adult population. Men have approximately double the risk of developing the condition compared with women and it increases with age. Obesity is a major risk factor for OSAH, particularly when adiposity is distributed around the neck and upper body, which suggests that OSAH incidence will rise with the increasing prevalence of obesity.

Obstructive sleep apnoea–hypopnoea is associated with increased risk of cardiovascular disease (CVD), including stroke, via a causal link with hypertension. EDS increases road traffic accident (RTA) risk and health-related quality of life (HRQoL) is also decreased. Health-care usage is almost doubled in OSAH, primarily as a result of the increased cost of treating CVD.

Continuous positive airway pressure (CPAP) therapy is the cornerstone of OSAH treatment. There is evidence that CPAP reduces respiratory events and EDS and increases cognitive function and HRQoL. There is some evidence for beneficial effects on blood pressure (BP), from which improvement in cardiovascular end points may be inferred. CPAP has been shown to be cost-effective for moderate to severe OSAH at a willingness-to-pay (WTP) threshold of £20,000 per quality-adjusted life-year (QALY), and clinical guidelines recommend it as first-line treatment in these patients.

The role of CPAP in the management of mild OSAH is less clear. CPAP requires a mask to be worn during sleep, which affects compliance and, therefore, effectiveness. There is a paucity of randomised trial evidence and the cost-effectiveness of CPAP appears more marginal in this group.

Mandibular advancement devices (MADs) are an alternative to CPAP in the treatment of OSAH. They are worn in the mouth during sleep, holding the mandible and tongue forward with the aim of maintaining upper airway patency. Available MADs represent a range of sophistication and cost. Reviews show that MADs are less efficacious than CPAP at reducing the apnoea–hypopnoea index (AHI), but are better than various placebos. Both CPAP and MADs improve EDS to a similar extent according to the Epworth Sleepiness Scale (ESS) score, and more than sham MADs and other placebos. Quality of life (QoL) has been understudied in MAD trials. A comprehensive economic analysis concluded that CPAP had a high probability of being more cost-effective than both MADs and conservative management (CM) in OSAH, at a £20,000 cost per QALY threshold. However, the evidence was from trials conducted in populations with moderate to severe OSAH. Recommendations from this study included the need to establish whether or not clinical effectiveness and cost-effectiveness vary between different types of MAD; the identification of patients likely to benefit from MAD treatment; and the assessment of HRQoL.

Objectives

1. To conduct a randomised controlled trial (RCT) [the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO)] to assess whether or not MADs are clinically effective and cost-effective compared with no treatment in patients with mild to moderate OSAH, and to identify which one of three increasingly sophisticated and costly MADs is most clinically effective and cost-effective.
2. To update systematic reviews of RCTs of the effectiveness of MADs and/or CPAP in order to inform a long-term decision model.
3. To update and adapt a previously developed health economic decision model, incorporating results from TOMADO and other recently published studies to inform long-term cost-effectiveness in mild to moderate OSAH.

Methods

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

TOMADO was an open-label, four-treatment, four-period, randomised crossover trial comparing the clinical effectiveness and cost-effectiveness of three types of MAD {[bespoke MAD (bMAD); NHS Oral-Maxillofacial Laboratory, Addenbrooke's Hospital, Cambridge, UK], semi-bespoke [SleepPro 2™ (SP2); Meditas Ltd, Winchester, UK] and over the counter [SleepPro 1™ (SP1); Meditas Ltd, Winchester, UK]} and a no-treatment control for patients with mild to moderate OSAH. Each 6-week period (4-week period for no-treatment arm) comprised a 2-week acclimatisation phase, followed by a 4-week treatment phase. A 1-week washout period followed active treatments. Eligible patients from the Respiratory Support and Sleep Centre at Papworth Hospital, Cambridge, UK, were $\geq$ 18 years of age with mild to moderate OSAH (AHI 5 events/hour to $<$ 30 events/hour) and symptomatic daytime sleepiness (ESS score of $\geq$ 9). Patients did not require or had refused CPAP. The main exclusion criteria were predominantly central sleep apnoea; requirement for immediate CPAP; significant periodontal disease or tooth decay; partial or complete edentulism; and presence of fixed orthodontic devices.

The primary outcome was the AHI. EDS measured using the ESS was an important secondary outcome. Other outcomes were daytime BP, condition-specific [Functional Outcomes of Sleep Questionnaire (FOSQ) and Calgary Sleep Apnoea Quality of Life Index (SAQLI)] and generic [Short Form questionnaire-36 items and European Quality of Life-5 Dimensions (EQ-5D-3L)] HRQoL, side effects, resource use and cost-effectiveness.

A sample size of 90 was required to detect an effect size of one-third (5% two-sided alpha, 80% power, 20% loss to follow-up).

Randomisation was performed by the independent research unit at Papworth Hospital and treatment sequence was based on Williams' Latin squares designs.

Statistical analysis used 'intention to treat' and included period effects. Analysis used mixed-effects models based on either Poisson or Normal distributions to estimate treatment effects.

Trial-based economic analysis estimated cost utility during the 4-week periods from the perspective of the NHS. MAD costs came from NHS supply prices (SP1), private supply prices (SP2) and from the cost of materials and staff time for manufacture of the bMAD. Other unit costs for outpatient care including labour, capital and overheads, were taken from national estimates.

The EQ-5D-3L provided the base-case health-utility score for calculation of QALYs. Both probabilistic and deterministic sensitivity analyses were conducted.

Meta-analysis of clinical studies

We updated systematic reviews of RCTs in adult OSAH patients who included at least one group allocated to CPAP or MAD. All MADs were viewed as a single treatment, as were all CPAP technologies. For the update of the two existing systematic reviews from 2006 and 2008, three databases (MEDLINE, EMBASE and the Science Citation Index) along with resulting reference lists were searched from November 2006 and June 2008 to August 2013. Primary outcomes were AHI and ESS score, but daytime BP and disease-specific HRQoL results were also extracted. Three comparisons were investigated: MADs compared with CM; MADs compared with CPAP; and CPAP compared with CM. Random-effects meta-analyses were used to estimate treatment effects, both overall and stratified for baseline severity of OSAH.

Long-term cost-effectiveness

A previously developed model was used to assess the lifetime cost–utility of MADs and CPAP in patients with mild to moderate OSAH, from a NHS perspective based on differences in symptoms associated with OSAH and long-term sequelae. Additional searches of the databases listed above were used to update and adapt cardiovascular, RTA and compliance input values for the model. The TOMADO was sourced for utility estimates based on mapping ESS scores to EQ-5D-3L utilities and for device costs. The base case included a hypothetical cohort of 10,000 men, aged 51 years, with systolic BP of 130 mmHg, total cholesterol of 224 mg/dl and an ESS score of 11.9, in line with the TOMADO population averages. Costs were based on the SP2 and an assumed device lifetime of 12 months. Sensitivity analysis explored assumptions around the lifetime of the devices and their costs, ESS treatment effects, compliance, time horizon and effects on cardiovascular and RTA risks.

Results

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

Sixteen patients of the 90 recruited withdrew from the study and did not provide any outcomes. TOMADO showed that, for patients with mild to moderate OSAH, the AHI for each of the three non-adjustable MADs studied was significantly lower than with no treatment {relative risk 0.74 [95% confidence interval (CI) 0.62 to 0.89] for SP1, relative risk 0.67 (95% CI 0.59 to 0.76) for SP2, relative risk 0.64 (95% CI 0.55 to 0.76) for bMAD; $p < 0.0.001$}. Differences between MADs were not statistically significant.

The effects of MADs on ESS score mirrored those for AHI, with reduction in ESS scores of 1.51 (95% CI 0.73 to 2.29) for SP1, 2.15 (95% CI 1.31 to 2.99) for SP2 and 2.37 (95% CI 1.53 to 3.22) for bMAD. SP2 and bMAD had significantly greater effects than SP1.

SleepPro 1 had shorter duration of use per night and greater likelihood of discontinuation during the treatment period. The SP1 was also less likely to be chosen as the preferred device by trial completers.

The relationship between MADs, sleepiness-related functioning and QoL (FOSQ and SAQLI) showed a similar pattern to that for AHI and ESS score, with significant effects for all MADs compared with no treatment, and SP1 performing less well than SP2 and bMAD. General HRQoL measures were largely insensitive to MAD treatment, with the exception that SP2 was associated with significantly higher Short Form questionnaire-6 Dimensions QALYs compared with control.

There were few serious adverse events (SAEs) during the study period and, of the four SAEs reported by four patients, three were short-term, cardiac-related events. Almost all patients reported at least one minor adverse event, with mouth discomfort and excess salivation being the main problems.

The trial-based cost-effectiveness analysis was limited by the short treatment period, but the improvements in HRQoL for all MADs compared with no treatment meant that all were cost-effective at a WTP of £20,000 per QALY. The SP2 was the most cost-effective MAD up to a WTP per QALY of £39,800.

Meta-analysis of clinical studies

The systematic review identified 12 studies including 629 patients comparing MAD with CM, 13 studies including 746 patients comparing MADs with CPAP and 52 studies including 5400 patients comparing CPAP with CM, with AHI or ESS score as one of the study end points. Study participants were predominantly middle-aged men (65–100% of participants were male; mean age range 44–59 years) who were overweight or obese. CPAP trials were generally conducted in patients with more severe OSAH according to AHI MAD trials. CM included sham devices, sham CPAP, placebo tablets, lifestyle advice and no treatment. Quality was variable, with many trials having < 50 patients and treatment periods generally short.

Heterogeneity between studies was variable and often unreliable because of the small number of studies available. Some heterogeneity could be explained by baseline severity, but unexplained heterogeneity remained.

Overall, compared with CM, both MADs and CPAP resulted in significant improvements in AHI [MAD −9.3 events/hour (95% CI −12.3 to −6.3 events/hour), $p < 0.001$; CPAP −25.4 events/hour (95% CI −30.7 to −20.1 events/hour), $p < 0.001$]. In direct comparisons of CPAP and MAD, the difference in effect between them was 7.0 events/hour (95% CI 5.4 to 8.7 events/hour; $p < 0.001$), in favour of CPAP. The reduction in AHI was strongly related to baseline severity. No trials compared CPAP with MAD trials in patients with mild OSAH according to AHI.

Excessive daytime sleepiness assessed by the ESS was less variable than AHI. Most trial populations were classed as having moderate baseline EDS. Overall, both MAD and CPAP resulted in a significant reduction in ESS score compared with CM [MAD 1.6, 95% CI 0.8 to 2.5 ($p < 0.001$); CPAP 1.6, 95% CI 0.65 to 2.53 ($p < 0.001$)]. The differences between the effects of MAD and CPAP were not significant in head-to-head comparisons (0.7, 95% CI −0.1 to 1.4; $p = 0.093$). Estimated effects on EDS were strongly related to baseline OSAH severity and, to a lesser extent, baseline AHI. When trials of similar baseline characteristics were compared, there was little difference between the effects of MADs and CPAP on post-treatment ESS score. The meta-analysis provided little insight into the effect of treatment on daytime BP above previous meta-analyses.

With the exception of TOMADO, few additional trials contributed to the literature on HRQoL.

Long-term cost-effectiveness

In the base case, using the SP2 as the standard device, MADs were found to be more costly and more effective than CM in patients with mild to moderate OSAH, with an estimated incremental cost-effectiveness ratio (ICER) of £6687 per QALY. From a WTP of £15,367/QALY, CPAP is cost-effective, although the likelihood of MADs ($p = 0.48$) and CPAP ($p = 0.49$) being cost-effective is very similar. Although it was clear that both of these treatments were better than CM, there was substantial uncertainty in the choice between the two treatment options, with probabilities of being the most cost-effective, at a WTP of £20,000 per QALY, of 47% for MADs and 52% for CPAP.

When the average lifespan of the SP2 was increased from 12 months to 18 months, the ICER for CPAP compared with MAD became £44,066. The ICER for the SP1 compared with CM was £1552 and for the bMAD was £13,836. The ICER for CPAP compared with the SP1 was high, at £89,182, but CPAP was both cheaper and more effective than the bMAD. Differential compliance rates for CPAP reduced its cost-effectiveness, so that MADs become both less costly and more effective if compliance with CPAP is 90% of SP2.

Discussion

TOMADO was an important addition to the evidence on the use of MADs in mild to moderate OSAH. While all MADs were effective compared with CM, the semi-bespoke SP2 provides most of the benefit of a bespoke device at a lower cost and was the most cost-effective device tested. Comparisons of treatments across published trials suggest that CPAP has a much greater effect than MADs on AHI, but the effects on EDS are similar. These trials focus on populations with moderate to severe OSAH and there is evidence that the extent of treatment effects is strongly related to baseline severity.

In cost-effectiveness modelling, it is clear that both MADs and CPAP are cost-effective compared with CM, at a WTP threshold of £20,000 per QALY. However, for mild to moderate OSAH there is little to choose between the two treatment modalities. There is significant uncertainty related to assumptions about device costs, lifetimes, compliance and longer-term cardiovascular and RTA rates.

Conclusions

Implications for service

- CPAP remains the most clinically effective and cost-effective treatment for patients with moderate to severe OSAH based on reduction in AHI. For patients who are intolerant of CPAP, treatment with a MAD is also effective compared with CM.
- Both MADs and CPAP are effective treatments for patients with mild to moderate OSAH, and there is little to choose between them in terms of clinical effectiveness and cost-effectiveness.
- Of the three MADs investigated, the semi-bespoke SP2 is the most cost-effective in the short term and should be the first-choice device, with the bMAD reserved for patients who have difficulty producing the SP2 mould or whose dental eligibility is more marginal.

Implications for research priorities

- Pragmatic clinical effectiveness and cost-effectiveness comparisons of adjustable and non-adjustable MADs across the entire range of OSAH severity are still required.
- Head-to-head comparisons of CPAP and MADs in milder OSAH would reduce the uncertainty surrounding the current guidance that CPAP should be reserved as second-line treatment in these patients.
- Similarity of effects for CPAP and MAD on EDS may be as a result of differential adherence to treatment. However, there is limited information on this beyond short-term trials. Medium- to long-term compliance with MADs and CPAP should be monitored and reported.
- Observational studies of HRQoL over time to supplement existing trial data would be useful to understand the treatment outcomes of greatest relevance to patients.
- Further data on longer-term risk of CVD and its risk factors would reduce model uncertainty and improve the precision of estimates of clinical effectiveness and cost-effectiveness.

Trial registration

This trial is registered as ISRCTN02309506.

Funding

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Chapter 1 Introduction

Description of health problem

Definition of obstructive sleep apnoea–hypopnoea

Obstructive sleep apnoea–hypopnoea (OSAH) involves repeated interruption of airflow during sleep as a consequence of episodic collapse of the pharyngeal airway. Oxygen desaturations typically result and events terminate with respiratory effort-induced microarousals from sleep. When there is significant sleep disruption then daytime symptoms can result. Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) incorporates excessive daytime sleepiness (EDS).[1] For the purposes of consistency, the term OSAH will be used in this review instead of OSAHS.

Consequences of obstructive sleep apnoea–hypopnoea

Obstructive sleep apnoea–hypopnoea is causally linked with hypertension.[2] There is a 2.5-fold associated increase in cardiovascular risk,[3] with a reported 6% increase in stroke risk per unit increase in apnoea–hypopnoea index (AHI).[4] This association is supported by biologically plausible mechanisms and beneficial cardiovascular effects of OSAH treatment have been described.[5] However, difficult-to-exclude confounders mean that causation and the impact of OSAH treatment on cardiovascular disease (CVD) are still being explored. There are several other consequences of OSAH. Impaired vigilance is responsible for a two- to threefold increase in road traffic accident (RTA) risk,[6] and health-related quality of life (HRQoL) is also impaired.[7,8] Health-care usage is almost doubled in OSAH, with one of the main determinants of increased cost being CVD.[9]

Diagnosis and classification of obstructive sleep apnoea–hypopnoea

Obstructive sleep apnoea–hypopnoea is diagnosed and its severity determined on the basis of symptoms and respiratory monitoring during sleep. The simplest monitoring involves nocturnal oximetry, providing an hourly oxygen desaturation index (ODI) as a surrogate marker of respiratory events. Oximetry is relatively insensitive and so will miss some cases of OSAH.[10] The AHI is more sensitive and specific, combining oximetry with oronasal temperature and pressure monitors to measure airflow, and thoracic and abdominal movement gauges to distinguish obstructive from central events. To be scored, respiratory events must arbitrarily last at least 10 seconds. Apnoeas involve complete cessation of airflow. Hypopnoeas are variously defined by different classification systems.[11,12] Common is a degree of airflow amplitude reduction, which must be accompanied by either significant oxygen desaturation or, if measured, electroencephalography (EEG)-based evidence of microarousal from sleep. The multiple scoring systems introduce heterogeneity into what is otherwise a useful objective measure.[13] Nonetheless, the AHI provides an objective means of defining disease severity, monitoring disease course and measuring treatment response. The American Academy of Sleep Medicine (AASM), which is responsible for three hypopnoea definitions, arbitrarily defines mild OSAH as an AHI of $\geq 5 - \leq 15$ events per hour; moderate OSAH as an AHI of 15–30 events per hour; and severe OSAH as an AHI of > 30 events per hour.[11] These are widely applied criteria and are used in this report.

The extent of daytime sleepiness ranges greatly in OSAH and there is only moderate correlation with respiratory event frequency.[14] With the persistent uncertainty regarding the impact of treatment on cardiovascular end points, the main treatment indication remains EDS. Therefore, OSAH is alternatively classified according to severity of EDS and impacts of treatments are measured by symptom effects.

Daytime sleep propensity is most commonly assessed using the subjective, but extensively validated, Epworth Sleepiness Scale (ESS).[15] The likelihood of falling asleep in eight different situations is rated on a scale of 0 to 3 by the patient. The total score ranges from 0 to 24, with higher scores indicating greater sleepiness. A score of ≤ 10 is considered normal in the general population.[16] The ESS score has a roughly

Normal distribution in OSAH.[17] As a subjective measure, it is susceptible to significant placebo effects.[18] A recent meta-analysis estimated that 29% of ESS score improvement was attributable to placebo in high continuous positive airway pressure (CPAP) users.[19] However, the ESS has high internal consistency and has been found to be the best among a range of validated outcome measures in predicting real response to OSAH treatment.[17,18]

Daytime sleepiness can be objectively measured using validated EEG-based nap tests. The multiple sleep latency test (MSLT) involves measuring sleep onset latency in four or five 20-minute tests, at 2-hourly intervals over 1 day. Subjects are put back to bed after overnight polysomnography (PSG), which serves to validate results by confirming sufficient preceding nocturnal sleep. They are instructed to try to sleep in a darkened and sound-attenuated room. The maintenance of wakefulness test (MWT) is the related EEG vigilance assessment, involving four or five 40-minute tests.[20] The Osler test is similar to the MWT, but uses repeated behavioural tasks to monitor alertness.[21] Although all are useful objective tests, and the MSLT is particularly important for diagnosing narcolepsy, results show considerable overlap between healthy subjects and those with sleep disorders.[20] They are affected by multiple factors other than disease[20] and are time-consuming and resource expensive. As such, they have a limited role in the day-to-day diagnosis and management of OSAH and figure in only a few treatment trials.[22–25]

Epidemiology and risk factors

Obstructive sleep apnoea–hypopnoea syndrome affects 2–7% of the adult population[26] with the risk of developing the condition approximately twofold higher in men than in women.[27,28] It is common in middle age,[27] but prevalence may be higher in the elderly. One community-based study found 62% of older adults ($\geq$ 65 years) to have an AHI of $\geq$ 10.[29] Obesity is a major risk factor for OSAH, particularly when adiposity is distributed around the neck and upper body.[30,31] Another community study reported a quadrupling of disease prevalence associated with a one standard deviation (SD) increase in body mass index (BMI).[27] Causality is supported by longitudinal evidence of fluctuating disease severity in association with weight change.[28,32] Other lifestyle risk factors include smoking and alcohol use, while medical conditions with a possible causal association include hypothyroidism, polycystic ovary syndrome and acromegaly.[26,30]

Current service provision

Continuous positive airway pressure therapy

Continuous positive airway pressure therapy is the cornerstone of OSAH treatment. It works by providing a pneumatic splint to the upper airway, preventing pharyngeal collapse during sleep. Treatment is applied with a nasal mask or face mask, connected via a tube to a small electric air pump generating the pressure.

Continuous positive airway pressure greatly reduces obstructive respiratory events and daytime sleepiness and improves cognitive function and quality of life (QoL). There is evidence of beneficial effects on blood pressure (BP),[8,33,34] from which improvement in cardiovascular end points can be inferred, although direct evidence for this continues to be sought. CPAP improves impaired driving simulator performance and observational data have shown a reduction in excess RTA risk.[35,36] However, there is a lack of direct evidence for the latter.[8] CPAP has been shown to be clinically effective and cost-effective for moderate to severe OSAH at a willingness-to-pay (WTP) threshold of £20,000 per QALY and clinical guidelines recommend it as first-line treatment in these patients.[8,37,38]

The intrusive nature of CPAP means that intolerance can undermine its effectiveness. Not all patients accept treatment and reported usage ranges from 29% to 85%.[39–42] Efforts continue to explore ways of increasing CPAP acceptance and adherence. Pressure modification (e.g. with bilevel devices, autotitrating CPAP and expiratory pressure relief) and humidification are used, although current evidence suggests that compliance with positive airway pressure is similar regardless of the mode of delivery.[43] A variety of educational, supportive and behavioural interventions continue to be tried, but techniques are diverse and the overall quality of evidence is currently too low to guide patient selection or choice of intervention.[44]

The role of CPAP in the management of mild OSAH is less clear. There is a paucity of randomised trial evidence and cost-effectiveness of CPAP appears more marginal. McDaid *et al.*[8] calculated its cost to slightly exceed the National Institute for Health and Care Excellence (NICE) threshold for mild patients, with an incremental cost-effectiveness ratio (ICER) of £20,585 compared with conservative management (CM). Compliance with CPAP may also be worse in milder disease.[45] Clinical guidelines reflect the uncertainty, recommending that CPAP be tried when significant symptoms fail to respond to lifestyle measures and any other relevant treatment options.[37,38]

Non-continuous positive airway pressure therapy treatments

The existence of modifiable OSAH risk factors with plausible causative mechanisms encourages an approach to OSAH treatment which includes lifestyle measures. Clinical guidelines recommend that interventions such as weight loss, smoking cessation, reduction of alcohol intake and positional management (supine sleep avoidance) should be considered in the treatment of individual patients.[37,38] However, conclusive randomised trial evidence of effectiveness of lifestyle modification is still lacking.[46]

Various surgical techniques have been developed to try to treat OSAH. Their aim is to prevent pharyngeal occlusion by increasing upper airway dimensions, reducing collapsibility and/or bypassing obstruction. Several short-term studies have been reported. However, diverse techniques, inconsistent effects and a lack of longer-term data mean that conclusive evidence of effectiveness is lacking.[47]

Pharmacotherapy continues to be explored in OSAH. Several drugs have been investigated, attempting to exploit various hypothetical pharmacological mechanisms to reduce respiratory events and/or improve symptoms. Despite some positive results from individual trials, effectiveness has not been proven.[48]

Description of the technology being assessed

Mandibular advancement devices (MADs) are recommended in various clinical guidelines as an alternative to CPAP in the treatment of OSAH.[38] They are worn in the mouth during sleep, holding the mandible and tongue forward with the aim of maintaining upper airway patency. Improvement in respiratory event frequency has been associated with MAD-mediated increases in upper airway dimensions[49] and reduced pharyngeal collapsibility.[50] There are numerous types of MADs available, representing a range of sophistication and cost, both in terms of the devices themselves and the processes involved in their provision.

Three meta-analyses have examined the evidence for the use of MADs in OSAH and have produced consistent results in areas of overlap.[8,33,51] Their findings will be reviewed in more detail in *Chapters 3* and *4*. Broadly, the evidence shows that MADs are less efficacious than CPAP at reducing the frequency of obstructive respiratory events, but are better than various placebos, including sham MADs which hold the mandible in a neutral position rather than protrude it. However, both CPAP and MADs improve EDS, according to the ESS score, to a similar extent, and more than sham MADs and other placebos. Data regarding the impacts of CPAP and MADs on objective tests of sleepiness or alertness are minimal. Two studies found no effect of CPAP or MADs on MWT,[22,23] while another reported similar improvements in Osler test results for CPAP and MADs.[24] QoL has also been understudied in MAD trials. Those that have reported generic and disease-specific measures have not found consistent differences between CPAP and MADs.[8,33] The repeated discrepancies demonstrated between efficacy and effectiveness may reflect differences in treatment tolerances. Limited trial data suggest that patients who respond to both CPAP and MADs may prefer MADs.[33] A recent randomised trial comparing MADs with CPAP in moderate to severe OSAH revealed no differences in several important health outcomes, including BP and driving simulator performance, despite CPAP being more efficacious in reducing AHI. Superior MAD compliance was postulated as an explanation for these findings.[52]

Meanwhile, in terms of cost-effectiveness, a systematic review and economic analysis funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme concluded from a base-case analysis that CPAP had a high probability of being more cost-effective than both dental devices and CM in OSAH, at a £20,000 cost per quality-adjusted life-year (QALY) threshold.[8] However, these trials were largely conducted in patient populations with moderate to severe OSAH and all trials involving MADs were in populations with moderate disease on average.

The lack of evidence regarding the clinical effectiveness and cost-effectiveness of MADs in OSAH was a key finding of the meta-analyses and leaves residual uncertainty about their exact role. Inconsistent treatment effects of CPAP compared with MADs in moderate disease may in part be a function of device heterogeneity and direct comparisons of effectiveness of MADs against CPAP in mild and severe disease were not available.[8] It has also been argued that sham MADs may exaggerate the benefits of active devices by undermining sleep quality without reducing respiratory events.[51] Resulting recommendations for further research include establishing whether or not clinical effectiveness and cost-effectiveness varies between different types of MAD;[8] identifying which patients are likely to benefit from MAD treatment[8,51] and the exploration of carryover and period effects in crossover trials using standardised and validated subjective measures.[51]

Aims and objectives

The aims of this study were as follows:

1. To conduct a randomised, controlled, crossover trial to assess whether or not MADs are clinically effective and cost-effective compared with no treatment in patients with mild to moderate OSAH [the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea (TOMADO)].
2. To determine, within TOMADO, which one of three increasingly sophisticated and costly MADs is most effective in the treatment of mild to moderate OSAH.
3. To update systematic reviews of randomised, controlled trials of the effectiveness of MADs and/or CPAP in order to inform a long-term decision model.
4. To update the health economic decision model developed by the York group, and presented in McDaid *et al.*,[8] incorporating results from TOMADO and other recently published studies.

Chapter 2 The randomised, controlled, crossover Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

Introduction

After 2008 there was clear guidance to support the use of CPAP for moderate or severe OSAH, but CPAP was not recommended for mild OSAH unless patients experienced symptoms that affected QoL/daily activities and other treatment options had failed.[37] A Cochrane review of MADs concluded that they are an appropriate therapy for patients who are unable or unwilling to tolerate CPAP.[51] Research suggested that CPAP is superior to MADs in reducing AHI, but that control of daytime sleepiness is similar. However, the evidence base was limited as most individual studies were small, of limited methodological quality or did not address key outcomes such as HRQoL, and few focused on mild OSAH. Therefore, clinical equipoise existed regarding the role of MADs in OSAH and this prompted the TOMADO study.

Methods

Primary objectives of Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

The primary objective was to determine whether or not MADs are more effective than no treatment and whether or not the level of MAD sophistication (bespoke, semi-bespoke and over the counter) influences outcomes for patients with mild to moderate OSAH.

Secondary objectives of the Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

The secondary objectives were to produce a trial-based cost-effectiveness analysis to determine, from a NHS perspective, whether or not MADs are cost-effective compared with no treatment in mild to moderate OSAH, and whether or not the degree of MAD sophistication influences cost-effectiveness. It was also intended that the results would contribute to a comprehensive long-term cost–utility analysis (see *Chapter 4*).

Study design

The study was an open-label, four-treatment, four-period, randomised crossover trial comparing the clinical effectiveness and cost-effectiveness of three types of MAD {bespoke MAD (bMAD; NHS Oral-Maxillofacial Laboratory, Addenbrooke's Hospital, Cambridge, UK), semi-bespoke [SleepPro 2™ (SP2); Meditas Ltd, Winchester, UK] and over the counter [SleepPro 1™ (SP1); Meditas Ltd, Winchester, UK]} and a no-treatment control for patients with mild to moderate OSAH (AHI of 5 events/hour to < 30 events/hour). Each 6-week period (4 weeks for no-treatment arm) comprised a 2-week acclimatisation phase, followed by a 4-week treatment phase. A 1-week washout period followed active treatments.

The study was reviewed and approved by the National Research Ethics Service Research Ethics Committee East of England – Cambridge Central (reference 10/H0308/4) and local (research consortia and primary care trust), ethical and research governance committees, and was registered as an International Standard Randomised Controlled Trial, number (ISRCTN) 02309506. The trial protocol can be accessed at www.thelancet.com/protocol-reviews/10PRT-4998.

Public and patient involvement

There was involvement from a patient in the study design and conduct, with input into production of patient information and other trial documentation, and membership of both the trial management group and the trial steering group. Although patient involvement in the Data Monitoring and Ethics Committee (DMEC) was arranged, the patient representative was not able to contribute to the meetings.

Participants

All newly referred or existing patients attending the Respiratory Support and Sleep Centre (RSSC), a tertiary care, specialist sleep centre, at Papworth Hospital (Cambridge, UK), were invited to be screened for eligibility in the trial if they were ≥ 18 years of age and had, or were suspected of having, mild to moderate OSAH (AHI 5 events/hour to < 30 events/hour), confirmed by either respiratory PSG (rPSG) (Embletta™; Embla Systems, Kanata, ON, Canada) or complete PSG, and who had symptomatic daytime sleepiness defined by an ESS score of ≥ 9. Potential patients did not require CPAP, as defined in NICE Technology Appraisal number 139,[37] or they had refused CPAP or chose inclusion in TOMADO instead. Patients were excluded if they were pregnant or had any of the following:

- central sleep apnoea as the predominant form of sleep-disordered breathing
- coexistent sleep disorder, poor sleep hygiene or drug treatment considered likely to have a significant impact on symptoms (especially sleepiness) or assessment of MAD effectiveness
- severe and/or unstable CVD judged by clinician to warrant immediate CPAP
- other medical or psychiatric disorders judged likely to adversely interact with MADs 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
- previous exposure to MAD treatment
- disabling sleepiness leading to significant patient-specific safety concerns.

Screening/baseline visit

Following signed consent and enrolment, a medical history and clinical examination were undertaken to establish eligibility. The clinical examination included height, weight, neck circumference, waist-to-hip ratio and BP. Patients completed the generic HRQoL questionnaire, medical outcomes Short Form questionnaire-36 items (SF-36),[53] the disease-specific Calgary Sleep Apnoea Quality of Life Index (SAQLI)[54] and the European Quality of Life-5 dimensions three-level version (EQ-5D-3L) for use as a utility measurement.[55] In addition, they completed a Functional Outcome of Sleep Questionnaire (FOSQ)[56] and the ESS questionnaire.[15] All patients who satisfied the other inclusion/exclusion criteria underwent confirmatory rPSG, unless they had already undergone rPSG or inpatient PSG within the previous 4 weeks for clinical reasons. In that case, the clinical PSG output was used as a baseline value.

Interventions

Three different non-adjustable MADs representing currently available devices along a spectrum of complexity and cost were studied:

1. **SleepPro 1™:** a thermoplastic 'boil and bite' device fitted by the patient following the manufacturer's printed instructions. The patient softened the device in hot water, placed it into his or her mouth and, having bitten down on it, advanced the mandible to an individually determined 'comfortable' position. The device was then manually moulded against the teeth and set by subsequent immersion in cold water. Rewarming allowed remoulding.

2. **SleepPro 2™:** a semi-bespoke device, formed from a dental impression mould used by the patient. At the screening/baseline visit patients were given an impression kit to mould at home and then send to the manufacturer in order for the SP2 to be made. The impression kit consisted of a SP1 with holes to allow the injection of dental putty. The patient was instructed to mould the SP1 (as for the SP1 device), then wear it for two nights to ensure optimum position and fit, remoulding if necessary. The patient then made up the putty and injected it into the SP1, before sending the resulting impression back to the manufacturer. The SP2 was produced from this mould. It was designed to grip the entire dentition. Thinner walls than the SP1 were intended to result in a more comfortable fit. Involvement of the patient's dentist in taking the impression was suggested, but not considered to be essential or key to achieving the best fit by the manufacturer.
3. **Bespoke device:** a custom-made MAD professionally fitted by a specialist NHS oral–maxillofacial laboratory at Addenbrooke's Hospital, Cambridge, UK. A positional 'wax bite' was taken from the patient and the degree of mandibular advancement (50–70% of the maximal protrusive distance from centric occlusion, i.e. the 'normal' bite where the teeth all interdigitate maximally) was determined. Upper and lower full dental impressions were taken in alginate by a suitably qualified dental professional and cast in dental stone. The casts were trimmed and articulated using the positional wax bite. A blow-down splint in soft acrylic was created on each cast and then fused with a further acrylic blow-down to ensure the upper and lower dentition were positioned in the predetermined optimal position to hold the mandible forward. The patient returned roughly 2 weeks later for the fitting. The fitting allowed for optimal balance between advancing the mandible sufficiently to bring the tongue base off the posterior pharyngeal wall and patient comfort.

Degree of protrusion

As this was a pragmatic trial, the SP1 and SP2 devices were both advanced by the patient, according to manufacturer's instructions. The bMAD was fitted by qualified dental experts, who determined the degree of protrusion with the patient, aiming for maximal comfortable advancement. The aim was to advance the mandible by a minimum of 50% of maximal protrusion. The degree of protrusion of each device was measured by the trial team, where possible, at the end of the patient's involvement in the study.

Patients started the first treatment arm following the manufacture of all of the MADs. The first 2 weeks of each treatment period were an acclimatisation phase to allow patients to adjust to each device and not considered part of active treatment. After 2 weeks, patients were telephoned to assess initial tolerability and adherence, and to record any contact with the research team, maxillofacial laboratory or other clinical staff in the previous 2 weeks. All patients received 4 weeks of treatment with each MAD and the no-treatment control, with outcome assessment at the end of each treatment period.

A 1-week no-treatment washout period followed each active treatment to avoid carryover effects. All MADs were kept at Papworth outside the treatment period and patients were asked to return each device at the end of the treatment assessment, and before starting the next treatment.

Outcome measures

Primary outcome measure

The primary outcome measure was the AHI, defined as the number of apnoea or hypopnoea events per hour of sleep. It was assessed by home rPSG using Embletta™ equipment following each treatment period. Airflow was measured using both a nasal air pressure transducer and an oronasal thermal sensor. All rPSG studies were scored manually in anonymised batches by a NHS polysomnographer, blinded to treatment allocation, in accordance with the AASM guidelines.[12] Throughout the trial, 16% of sleep studies were scored in parallel by a second polysomnographer to ensure inter-rater agreement and adherence to recommended guidelines.

Secondary outcome measures

- Subjective sleepiness (ESS): daytime sleepiness is a key feature of OSAH, resulting from disrupted sleep, and its effective control is a major aim of treatment. Patients are required to assess, on a 4-point scale (0, 1, 2 and 3), the likelihood of falling asleep during eight different daily activities (see *Appendix 1*). Item scores are summed giving a range for the overall score of 0–24, with 0–9 classified as normal daytime sleepiness, 10–15 as mild daytime sleepiness and 16–24 as moderate/severe daytime sleepiness.
- Physiological indices from rPSG: 4% ODI, mean, minimum and time spent < 90% of nocturnal oxygen saturation (SpO_2).
- Systolic BP (SBP) and diastolic BP (DBP).
- Functional status (FOSQ): the FOSQ is a condition-specific functional status measure designed to evaluate the impact of disorders of excessive sleepiness on activities of daily living (see *Appendix 2*). In total, there are 30 questions and five subscales: general productivity, social outcome, activity level, vigilance and intimate relationships and sexual activity. The total score can range from 5 to 20, with a lower score representing greater dysfunction. The potential range of scores for each subscale is 1–4, with a lower score representing greater dysfunction. The FOSQ was administered at baseline and after each of the four treatment periods.
- Disease-specific HRQoL (SAQLI): the SAQLI is a condition-specific questionnaire to assess obstructive sleep apnoea-related QoL (see *Appendix 3*). There are 14 questions and four domains. The total score can range from 1 to 7, with a lower score representing greater dysfunction. The potential range of scores for each subscale is also 1–7, with a lower score representing greater dysfunction.
- Generic HRQoL using both the SF-36 and the EQ-5D-3L: the SF-36 has eight dimensions of HRQoL on a scale of 0 (minimum function) to 100 (maximum function), named: physical functioning; role limitations because of physical problems; pain; energy/vitality; social functioning; mental health; role limitations because of emotional problems; and general health (see *Appendix 4*). These scales can be combined into two composite scales named the physical component score (PCS) and the mental component score (MCS).[57] We have adopted the commonly used standardisation method so that for a general population the PCS and MCS have mean 50 and SD 10. The EQ-5D-3L (see *Appendix 5*) has five dimensions (morbidity, self-care, usual activities, pain or discomfort and anxiety or depression), each with three levels (no problems, a moderate problem or a severe problem).
- Treatment adherence, hours of use and device retention as well as patient sleep duration (assessed by a daily sleep diary).
- Snoring scale: partner-rated visual analogue scale (VAS).
- Driving and RTA questionnaire (for economic modelling).
- Side effects, withdrawals, patient satisfaction and device preference at trial exit.
- Resource use: data on individual health-care resource use were collected on a study-specific case report form (see *Appendix 6*). This included type of device, number of home/surgery visits [general practitioner (GPs), nurses] number of visits [dentists, accident and emergency (A&E), outpatients, additional visits to Addenbrooke's Hospital for bMADs], hospital admissions (overnight, emergency), telephone calls (NHS Direct, RSSC helpline, ambulance), use of 'other' services (free listing), length of stay in hospital if applicable, diagnostic tests and cause of admission [heart attack, RTA, stroke, 'other (free listing)'].

At their final visit, patients were asked to rank the three devices and no treatment in order of preference and were allowed to keep their preferred MAD(s). Patients who were intolerant of, or refused, MADs and/or had persistent symptoms at the end of the study were considered for CPAP.

Safety monitoring

Adverse events (AEs) and adverse reactions (ARs) were monitored throughout the trial and recorded at each end of treatment visit. An AE was defined as any untoward occurrence in a clinical investigation subject who was receiving a trial intervention which did not necessarily have a causal relationship with the intervention. An AR was defined as an AE for which a causal relationship with the intervention was at least a reasonable possibility, i.e. the relationship could not be ruled out.

The main expected ARs of MAD therapy were temporomandibular joint/jaw discomfort, mouth discomfort, dry mouth, excessive salivation, gum discomfort, tooth discomfort, loose teeth, malocclusion and mouth ulcers. It was left to the investigator's clinical judgement whether or not an AE was of sufficient severity to necessitate the patient's removal from the trial treatment. A patient could voluntarily withdraw from treatment at any time if he or she found an AE to be intolerable.

The severity of AEs was graded as mild, moderate or severe. The relationship between the trial treatment and the AE (the causality) was graded as either unrelated, possibly related, probably related or definitely related by an independent respiratory and sleep medicine consultant physician who sat on the Trial Steering Committee.

All AEs were followed up until resolution or to the end of the AE reporting period.

Serious adverse events (SAEs) were reported to the sponsor within 24 hours of a member of the trial team becoming aware of the event. All SAEs were followed up until resolution or the event was considered stable.

Patient withdrawal

Patients could withdraw from the trial at any time without giving a reason. All patients who withdrew from the study continued to receive normal clinical care if necessary from their GP or consultant in the RSSC.

Sample size and power calculation

Based on the pre-trial systematic review of published studies, the minimum clinically important effect size was considered to be of the order of one-third. An effect size of one-third would be detected with 80% power in a sample size of 72 patients (two-sided significance of 5%). Allowing for 20% loss to follow-up, we aimed to recruit a sample of 90 patients.

Randomisation

Randomisation took place once eligibility was confirmed following measurement for the bMAD and once impression suitability for the SP2 device had been confirmed by the manufacturer. A computer-generated random number sequence produced by the trial statistician determined treatment order. Randomisation was based on two related Williams' Latin squares designs, with patients randomised in permuted blocks of eight with sequences shown in *Table 1*. Although randomisation in blocks of eight meant that for every eighth patient the sequence was predictable, this was considered to be less important in a crossover trial. Randomisation sequences were held in the research and development (R&D) unit and restricted to research

TABLE 1 Randomisation sequences according to two Williams' Latin squares designs

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

administration staff. The trial team were informed of the randomisation sequence to be given to a patient via telephone contact with the R&D research administrators.

Blinding

Treatment blinding was not possible in this trial. However, the primary outcome, AHI, was ascertained from anonymised PSG traces, which were analysed in batches of 10 by an independent NHS polysomnographer who was not aware of treatment allocations.

Statistical analysis

All patients were followed up irrespective of their level of compliance with the MADs, and all periods for which there was a measurement were included in the analysis using 'intention to treat'.

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 in this crossover trial were considered negligible. In exploratory analysis no treatment by period interactions were identified, which supports this view. Period effects were included in the analysis to account for the long trial period (7–8 months) and in case compliance was related to time in the study.

Initially, the distribution of the outcome measures was assessed by comparing histograms against standard parametric distributions starting with the Gaussian distribution and, if necessary, exploring other plausible families. This was completed for all observations and by treatment group and period. Based on these analyses the primary outcome, AHI, was found to be distributed as a Poisson random variable, which is consistent with a measurement of an event rate per hour. The 4% ODI was also well modelled by a Poisson distribution. All other continuous outcomes were well modelled by Normal distributions. Treatment effects were also plotted over time to further explore period effects.

Given that there were repeated measurements for each patient the main inferential analysis employed a range of mixed models. Initially a full model was fitted that included the main effects of treatment and time period, the interaction between these two and random-effects terms for patient. However, likelihood ratio tests comparing models with and without time by treatment showed that these interaction terms were negligible, and so they were not included in subsequent models. Both treatment and time period in all models were included for consistency and because there was evidence of changes over time in some of the outcome measures based on the likelihood ratio test comparing models with and without the time period effects. The main inferential models were formulated as follows.

For patient i ($i = 1, \ldots, 90$) with response y_{ijk} for treatment j, $j = 1,2,3,4$ in time period k, $k = 1,2,3,4$ we fitted the generalised mixed model,

$$E[y_{ijk}] = \eta_{ijk} = h(\mu_{ijk}), \tag{1}$$

and

$$\mu_{ijk} = \beta_o + \beta_j + \tau_k + \mu_i \tag{2}$$

where β_o is the intercept fixed at the control treatment in period 1, β_j, $j = 2,3,4$ is the vector of length 3 representing treatment fixed effect, τ_k, $k = 2,3,4$ is the vector of length 3 representing the time period fixed effects and μ_i is the random-effect term for patient i nested in period 1.

For AHI, a Poisson mixed-effects regression was used, with a $h(\ )$ log-link function and the random-effects $\exp(u_i)$ having Gamma(1,α) distribution. A similar Poisson-Gamma model was fitted to the 4% ODI. For both of these models an additional term was included in the regression equation for the times each person was asleep during the test in which the response was recorded. Response to treatment was classified as complete if the AHI was < 5 events/hour, and partial if the AHI was reduced by 50% but was > 5 events/hour; otherwise, patients were classed as non-responders. Mixed-effects logistic regression, using the logit link function, was used to assess treatment effect on complete/partial response, with patient random effects, u_i, having a Normal $(0,\sigma^2)$ distribution on the logit scale. All other outcomes were analysed using normal mixed-effects models, with $h(\ )$ the identity link function and the u_i having a Normal $(0,\sigma^2)$ distribution.

In all analyses estimation of treatment effects was of primary interest, but hypothesis testing was also performed. Nested models were compared using likelihood ratio tests. Model fit was assessed informally by examination of standardised residuals. The approach to multiple testing was as follows. For each of the general(ised) linear mixed models, treatment effects were described as 'statistically significant' if the likelihood ratio test comparing the models with and without treatment effects was < 0.05. The TOMADO protocol states that comparison of each MAD against no treatment was important so that, for models that were 'significant' overall, we present the significance level is presented based on the Wald test $[(\beta_j/se(\beta_j))\sim N(0,1)]$ without adjustment for multiple comparisons. For comparisons between MADs, the (conservative) Bonferroni correction should be applied, that is, standard *p*-values for these comparisons should be multiplied by 3. Corrections have not been routinely applied, so that readers may make their preferred corrections and where the results are uncorrected has been indicated.

The initial analysis included all patients who completed any treatment period and supplied an outcome measurement. A second analysis included patients who had completed all four periods and provided measurements (complete cases analysis). Both these analyses assumed missing at random for incomplete data and gave almost identical results, so that complete cases results for the AHI and ESS score are omitted from this report. All other results in this report relate to patients who provided any follow-up information. The majority of the missing data arose from patients who did not complete any treatment periods or from sporadic technical failures of the PSG study. These considerations, coupled with (i) the consistency of complete cases and any follow-up analyses, (ii) the consistency of inferences regarding each MAD's effectiveness across all outcomes and (iii) the clear nature of the results, meant that further sensitivity analysis to account for missing data was considered unnecessary.

Regression analyses were conducted to assess the effects on subsequent AHI and ESS scores of baseline AHI, ESS score, degree of protrusion of the device, age, sex, BMI and compliance, and contemporaneous BMI. These analyses also explored interactions between these variables and treatment effects, although there was limited power. Before the trial, one subgroup analysis of patients who declined CPAP compared with those with mild to moderate OSAH for whom CPAP was not considered necessary. As there were only four patients in the former group, no subgroup analyses were undertaken.

All analyses were performed using Stata (StataCorp LP, College Station, TX, USA) version 12.0 and version 13.0 for Microsoft Windows (64-bit).

Adherence to treatment protocols, treatment preferences, partner scoring assessment, RTAs and AEs were summarised and compared informally. Treatment preference results were available for patients who had completed all four treatment periods and are summarised.

Trial-based economic analysis

The economic evaluation of the crossover trial provided descriptive data on the resource use, unit costs and health state utilities observed during the 4-week periods from the perspective of the NHS.

Resource use

Patient-reported resource use was collected on the case report form (see *Appendix 6*) for the duration of the trial. Resources used as part of the research protocol that do not affect participant care outcomes (e.g. administering research questionnaires) were omitted. Clinician time required for administering each device was included separately to the reported resource use and priced using the *NHS Reference Costs (2011/12)*[58] for the type of outpatient visit required. Information on medication use during the trial was limited; it was not possible to track start/end date or dosage accurately or to identify which medication usage was associated with which intervention period, therefore they are omitted from the total cost of each intervention. However, medication costs during the trial were negligible.

Unit costs

A NHS supply price was available for SP1 (£18), to which was added the cost of postage (£3) giving a total cost of £21. Instructions were provided with the device for moulding and fitting of the device by the patient and, therefore, no additional clinician time was needed for fitting. As no NHS supply price was available for SP2, the private supply price of £125 was used and, with postage costs of £3, the total cost for SP2 was £128. As the SP1 device can be fitted and managed entirely by the patient, the mould used to manufacture the SP2 is created by the patient using a supplied dental mould kit and, in some cases, patients seek support from a dentist to help with this process. However, in practice, no trial participants required time from dentists to create the SP2 mould.

The bMAD custom device has two significant elements of cost: the manufacture of the custom device itself and two visits to a maxillofacial consultant (for mould creation and fitting). The manufacturer of the custom bMAD provided estimates of the time taken to produce the MAD from the patient's dental mould (7 hours by a grade 6–8 technician in a NHS maxillofacial laboratory). Using an hourly rate of £50/hour (taken from band 8d of the NHS Agenda for Change pay scales 2011/12) for the technician gave a total cost of manufacture of £350. Materials for production of the bMAD were negligible and, therefore, are considered to be subsumed in the figure of £350. The consultant visits for measurement and fitting of the bMAD were assumed to take a similar amount of time as an average first attendance and follow-up appointment with a consultant at a maxillofacial unit; *NHS Reference Costs (2011/12)*[58] were therefore taken directly. This equated to a cost of £110.36 and £91.95 for the first and second visits, respectively. The total cost of a bMAD was therefore £552.31 (£350.00 + £110.36 + £91.95). If any additional visits to Addenbrooke's Hospital were required for fitting or measurement, this was recorded on the case report form. The additional visits were priced at the same rate and costs applied in addition to the standard two visits.

As health-care resources and health outcomes were required for a 4-week intervention period, the costs of the MADs were spread over their expected lifetime. For example, as the SP1 and SP2 devices had an expected lifetime of 12 months, the manufacturing costs were multiplied by 4/52 (weeks). Similarly, the bMAD had an expected lifetime of 18 months, so that the costs were multiplied by 4/78 (weeks) for the 4-week intervention period. Point estimates of the life expectancy of devices were provided by the manufacturer but without confidence intervals (CIs). Discussion with the manufacturers indicates that lifetimes may vary around these estimates and this is investigated in the sensitivity analyses. No discount rates are used as a result of the short time horizon of the study.

Unit costs for outpatient care, including labour, capital and overheads, were taken from national estimates.[59] The unit costs of any hospital procedures such as outpatient visits or admissions were sourced from the *NHS Reference Costs (2011/12)*.[58] In the absence of national estimates, unit costs were taken from published sources[60] and centre-specific costs for Papworth Hospital. *Appendix 7* shows the unit costs used with sources of data.

In order to inform probabilistic sensitivity analysis, information on the variation of each unit cost (e.g. upper and lower quartiles) was collected and, where no information was available, the standard error (SE) was assumed to be 10% of the mean. For all unit costs, the estimated mean and SEs are

assumed to have been generated from a Gamma distribution. All unit costs are valued in 2011/12 British pounds sterling (see *Appendix 7*).

Unit costs, multiplied by the frequency of resource use, provided a total cost for each item. This was summed by treatment and divided by the number of participants in each intervention group for an average cost per participant by intervention group. The 'per participant' resource use costs in *Appendix 8* are the raw group means, unadjusted for differences at baseline.

Health state utilities and quality-adjusted life-years

Health state utility weights were taken from two sources: EQ-5D-3L weights were valued using the UK social tariff reflecting the values from a representative sample of the UK population;[61] and SF-36 health state responses were converted to the Short Form questionnaire 6-Dimensions (SF-6D) utility scale[62] using values from a random sample of the general population in England/UK.[63] The utilities are scaled so that full health = 1, death = 0, with the EQ-5D-3L allowing for health states worse than death valued lower than 0 at a minimum of −0.59.

Base-case QALYs use the EQ-5D-3L scores. As the treatment period was a fixed 4-week duration for each intervention and EQ-5D-3L was only collected at one time point for each, the 4-week QALY is calculated as a 4-week proportion of the 52-week year, i.e. QALY = (4 × utility score)/52. The difference in QALYs is not annualised for the within-trial analysis given the short time period.

Methods of cost-effectiveness analysis

The within-trial analysis was a pairwise comparison of mean costs between each treatment and the 'no-treatment' control. For each individual and each treatment, total costs were calculated by summing the multiplication of resources used by their unit costs. The ICER was estimated for each MAD against no treatment as the mean of within-patient difference in total 4-week costs, divided by the within-patient difference in 4-week QALYs. A mixed-effects model was used to estimate within-patient differences in total costs and QALYs. Differences in costs and differences in QALYs were estimated in separate models. Baseline EQ-5D-3L scores, patient weight and the time period, were included as covariates. In addition, for comparisons between each treatment, the incremental net monetary benefit (INMB) over 4 weeks was estimated assuming that decision-makers are willing to pay £20,000 per QALY.

Probabilistic sensitivity analysis was conducted to incorporate the uncertainty in estimates cost and effects. Samples (with replacement) of patients were generated and for each sample the mixed-effect model was rerun and unit costs were resampled from the estimated Gamma distributions. Two thousand bootstrap samples produced a set of possible costs and effects for each intervention, each of which were used to estimate an incremental cost (difference in total cost) and incremental effect (difference in QALYs). These were used to construct a series of cost-effectiveness acceptability curves (CEACs) which plot the probability that each MAD is cost-effective against the maximum WTP for one QALY. In addition, a cost-effectiveness acceptability frontier (CEAF) was constructed to plot the most cost-effective device against the maximum WTP.

Deterministic sensitivity analyses were conducted to assess the impact on the INMB of changes in the purchase price of each MAD and varying the expected lifespan of devices from 6 to 60 months. Assumptions regarding rare events and complications, such as RTA, were investigated in the sensitivity analyses in the long-term model of cost-effectiveness (see *Chapter 4*).

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea results

Patient recruitment

Between December 2010 and July 2012, 440 patients were screened for the trial. Two hundred and eighty-one patients were excluded at screening, 51 of whom were excluded for dental ineligibility by a sleep physician. A total of 159 patients gave written informed consent. Sixty-nine patients either refused or were ineligible following the baseline sleep study or the hospital visit for the bMAD fitting. Only two patients who were considered dentally suitable for the trial by a sleep physician were subsequently excluded by the hospital maxillofacial team for poor oral hygiene and tooth decay. The remaining 90 patients were recruited to the trial and received a randomised treatment allocation sequence (*Figure 1*).

Baseline characteristics

Baseline measurements are recorded in *Table 2*. Mean (SD) age was 50.9 (11.6) years and ranged from 26 years to 79 years. Eighty per cent were men (72/90). Mean (SD) AHI at baseline was 13.8 (6.2) events per hour, with three patients who were accepted on the basis of desaturation index (DI) having a baseline AHI of < 5 events per hour, rendering them ineligible for the trial on confirmatory PSG. These patients were retained in the trial according to 'intention to treat'. Mean (SD) ESS score was 11.9 (3.5) and, although 12 patients had a baseline ESS score below the acceptance threshold of 9, they were eligible based on an ESS score of ≥ 9 at screening. Again these patients remained in the trial.

Risk factors for heart disease were common in this group. Median [interquartile range (IQR)] BMI was 30.6 kg/m^2 (27.9–35.1 kg/m^2) and mean BP pressure was normal at 130/80 mmHg, but varied widely from 98/57 to 177/116 mmHg. Diabetes was present in eight (9%) patients, 23 (26%) were being treated for hypertension and 21 (23%) for hypercholesterolaemia. Five (6%) patients had been diagnosed with ischaemic heart disease and three (3%) had previous cardiovascular events (CVEs).

Of the 90 patients entered into the trial, 86 were new patients (who had not refused CPAP) and four were patients who had tried CPAP but could not tolerate it.

Withdrawals

Figure 1 shows patient progress through the trial. During the trial, 16 (18%) patients withdrew and the reasons for withdrawal are described in the *Table 3*.

Of the 16 patients who withdrew from the trial, seven (8%) did not complete any treatment periods, three were using the bMAD, two were using the SP1, one was using the SP2 and one patient was in the no-treatment arm. A further two (2%) patients who withdrew between the first and second treatments provided no primary outcome data as a result of technical failure of the sleep study after the first treatment period. These nine patients ($7 + 2$) provided no information after baseline and are excluded from all analyses. The main reasons for withdrawal in patients who did not complete any treatment period were intolerance of a device or were related to an AE. It is likely that these patients would not tolerate any of the devices and all wanted to try alternative treatments (CPAP or CM including weight loss).

Seven (8%) further patients withdrew during the trial: four were using the bMAD, one was using SP1 and two were using the SP2. Only one of these withdrawals (SP2) was as a result of intolerance to the device. These cases were included in the main analysis. Seven other sleep studies failed, leaving 305 studies (85% of 360) in 81 patients [of 90 (90%)] for AHI analysis. For all other outcomes, 314 (87%) measurements and 83 (92%) patients were available for analyses.

One patient who was randomised early in the trial was unable to remould another SP2 to replace their damaged SP2 and subsequently withdrew. Thereafter successful SP2 moulding was made a prerequisite for randomisation. Four patients were subsequently not randomised because they could not mould the SP2.

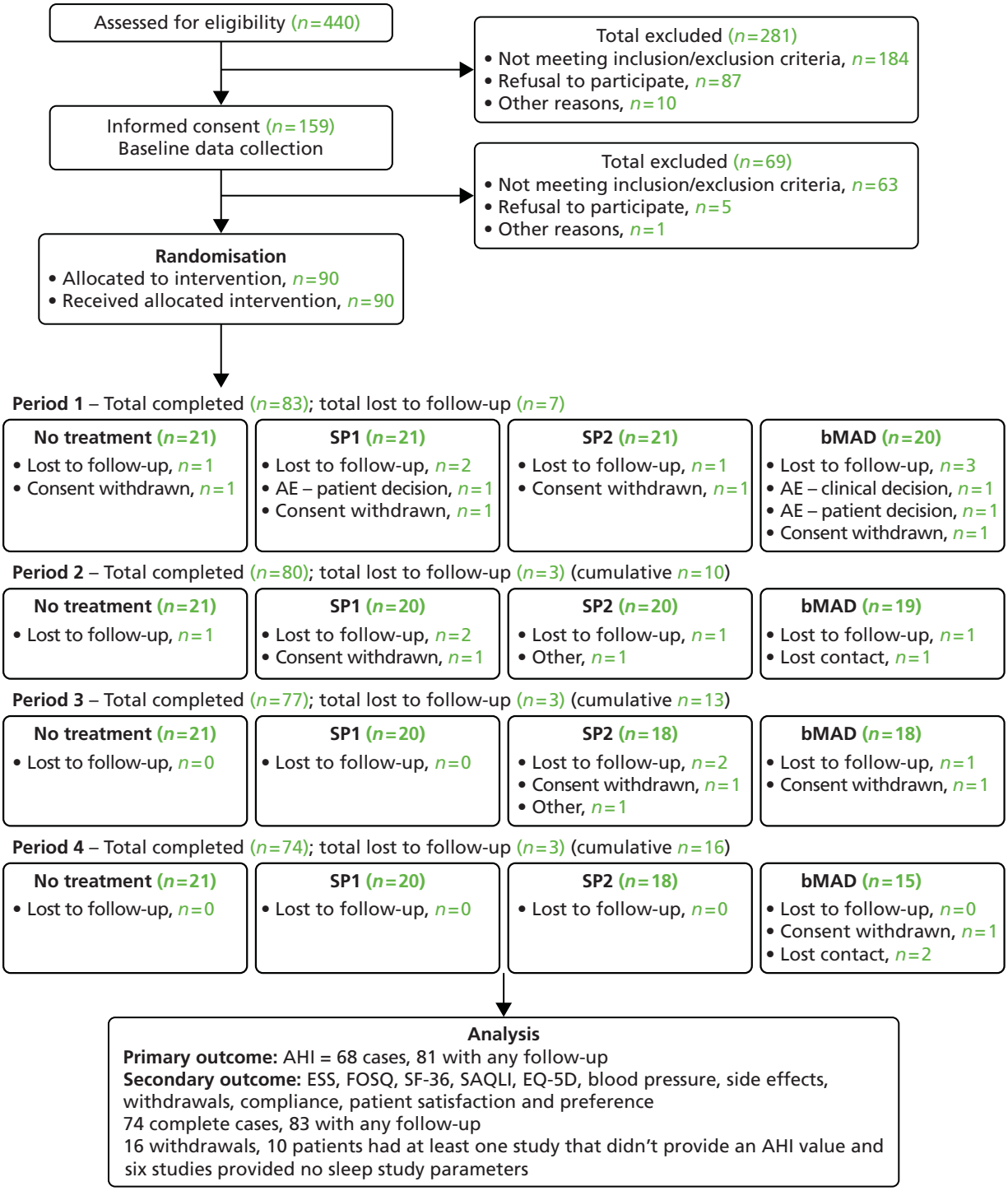

FIGURE 1 Patient flow through the trial.

TABLE 2 Baseline characteristics of trial patients

	Unit/category	Total ($n = 90$)	Min.	Max.
Demographic information				
Gender	Male	72 (80%)		
	Female	18 (20%)		
Age at randomisation	Years	50.9 (11.6)	26.1	79.6
Height	m	1.74 (0.74)	1.6	1.9
Smoking history	Non-smoker	44 (49%)		
	Ex-smoker	39 (43%)		
	Smoker	7 (8%)		
Cardiovascular history				
Diabetes	Type I	1 (1%)		
	Type II	7 (8%)		
Hypertension		23 (26%)		
Hypercholesterolaemia		21 (23%)		
Ischaemic heart disease		5 (6%)		
Previous stroke		2 (2%)		
Previous transient ischaemic attack		1 (1%)		
Clinical measurements				
Weight	kg	93.9 (82.4–103.6)	65.6	168.8
BMI	kg/m^2	30.6 (27.9–35.1)	23.9	54.5
Waist circumference	cm	105.5 (98.5–115.5)	83.0	147.0
Neck circumference	cm	41.2 (3.4)	32.5	49.5
Hip circumference	cm	108.3 (102.5–116.5)	93.0	156.0
Waist-to-hip ratio		0.97 (0.06)	0.8	1.1
SBP	mmHg	130.0 (15.3)	98.7	177.7
DBP	mmHg	80.4 (10.0)	57.7	116.0
Sleep study				
Type of study	Embletta™	70 (78%)		
	PSG	20 (22%)		
Analysed time	Minutes	493.3 (66.1)	310	617
AHI	Events per hour	13.8 (6.2)	2.9	27.7
	Missing[a]	1		
4% ODI	Events per hour	9.8 (5.2)	0.6	22.0
Minimum SpO_2%		83.7 (4.7)	71.0	91.0
	Missing[a]	2		
Mean SpO_2%		94.2 (1.3)	89.8	97.7
	Missing[a]	1		
Time < 90% of nocturnal SpO_2%	Minutes	8.3 (2.9–24.8)	0.0	315.4
	Missing[a]	1		

TABLE 2 Baseline characteristics of trial patients (*continued*)

	Unit/category	Total ($n = 90$)	Min.	Max.
ESS score				
At screening	Unit score	13.0 (3.1)	8	21
At baseline	Unit score	11.9 (3.5)	3	20
Other baseline information				
Regular bed partner	Yes	78 (87%)		
	No	12 (13%)		

Max., maximum; min., minimum.
a Missing data for sleep study results is as a result of technical problems.
Categorical variables show frequency (%) and continuous variables show either mean (SD) or median (interquartile range).

TABLE 3 Characteristics of patients who withdrew during the study

Patient ID	Period	Reason	Explanation	Future care
005	1 (bMAD)	AE – clinical decision	Bleeding gums because of poor oral hygiene	Discharged with CM only
012	4 (bMAD)	Consent withdrawn	No time for final visit because of work commitments	Use SP1 as performed best of treatments tested
013	Between 1 (SP1) and 2 (bMAD)	Lost to follow-up	Could not contact patient	Discharged back to GP
014	3 (SP2)	Consent withdrawn	Time constraints – did not get around to moulding SP2 and did not think they ever would	Continue with current device
017	Between 1 (SP1) and 2 (SP2)	Other	Withdrawn because of unreliability and unable to comply with protocol	Continue with current device
024	1 (no treatment)	Consent withdrawn	Patient could not tolerate SP2 moulding	No further treatment
039	3 (SP2)	Other	Patient unable to attend visits despite rescheduling, so trial team withdrew patient	Weight loss
040	1 (bMAD)	Consent withdrawn	Patient too unwell to complete trial visits because of comorbidities	Start CPAP
042	1 (bMAD)	AE – patient decision	Patient worried about crowns and bridges moving/breaking	Start CPAP
043	4 (bMAD)	Lost to follow-up	Could not contact patient	Recommend use SP2
047	1 (SP1)	Consent withdrawn	Patient did not like device and did not want to try any others	Weight loss
049	1 (SP1)	AE – patient decision	Broke tooth crown whilst wearing device	Start CPAP
050	2 (SP1)	Consent withdrawn	Did not like the bMAD and did not want to try any others	Start CPAP
066	3 (bMAD)	Consent withdrawn	Marital problems	Start CPAP
086	4 (bMAD)	Lost to follow-up	Could not contact patient	Recommend use SP2
089	1 (SP2)	Consent withdrawn	Did not like device and did not think it worked	Start CPAP

This was in part because of intolerance that would probably have applied to all three devices, but technical difficulty was a factor in some cases.

Baseline characteristics for the patients who withdrew from the study were similar to those who completed follow-up (data available on request).

Primary outcome: apnoea–hypopnoea index

Table 4 shows the mean AHI (SD) for each treatment, alongside the results of the Poisson-gamma regression analysis. Mean AHI for each treatment is plotted in *Figure 2*. This shows that that the rate of apnoea/hypopnoea events per hour for each MAD, relative to no treatment, is reduced significantly, with estimated relative rates of 0.74, 0.69 and 0.64 for SP1, SP2 and bMAD, respectively. The reductions for the SP1, SP2 and bMAD represent effect sizes of approximately 0.36, 0.47 and 0.49 SDs, respectively, all of which exceed the minimum clinically important difference of one-third proposed during study planning. In post-hoc pairwise comparisons there were no significant differences in AHI between the different MADs (*Table 5*).

Examination of the standardised residuals for AHI showed that this model was a good fit to the data, with no systematic effects observed.

TABLE 4 Summary of results from mixed-effects model for AHI ($n = 81$)

AHI ($n = 81$)	Mean (SD)	Coefficient	95% CI	*p*-value	Global *p*-value
Constant		14.22	11.66 to 17.34	< 0.001	
AHI relative to no treatment					
No treatment	14.6 (10.5)	–	–	–	< 0.001
SP1	10.8 (9.5)	0.74	0.62 to 0.89	0.001	
SP2	9.7 (8.9)	0.67	0.59 to 0.76	< 0.001	
bMAD	9.5 (8.4)	0.64	0.55 to 0.76	< 0.001	

Note
Period effects not shown.

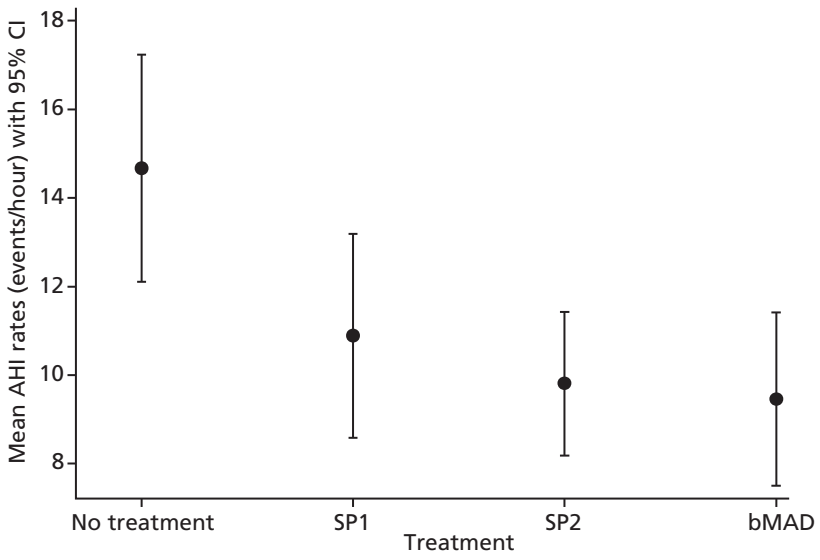

FIGURE 2 Estimated mean AHI and 95% CI for the four treatments from the Poisson-Gamma model.

TABLE 5 Comparison of AHI between different MAD

Comparison	Observed contrast	95% CI	*p*-value
SP2 with SP1	0.90	0.77 to 1.05	0.193
bMAD with SP1	0.87	0.73 to 1.04	0.119
bMAD with SP2	0.96	0.83 to 1.12	0.639

Note
These comparisons are *not* adjusted for multiple comparisons. Differences are significant at 5% level according to the Bonferroni method if the *p*-value is < 0.017.

Apnoea–hypopnoea index: responders to treatment

Of the patients who had an AHI value for at least one treatment, complete or partial AHI response during MAD use was observed in 29 (38%) patients for the SP1, 38 (49%) patients for the SP2 and 33 (45%) patients for bMAD, compared with 17 (22%) patients during the no-treatment period (*Table 6* and *Figure 3*). Patients who responded to one MAD were more likely to respond to others, but this was not completely predictable. Four of the 74 completers (5%) had a complete response to all treatments, nine (12%) had a partial or complete response to all treatments and 20 (27%) did not have a response to any treatment. The four patients who completely responded to all treatments also had low AHI during the no-treatment period (AHI at baseline 3.1, 5.4, 7.6 and 8.9).

TABLE 6 Response of patients by treatment

Treatment	Complete response	Partial response	Failure
No treatment ($n = 76$)	10 (13%)	7 (9%)	59 (78%)
SP1 ($n = 77$)	14 (18%)	15 (19%)	48 (62%)
SP2 ($n = 78$)	29 (37%)	9 (12%)	40 (51%)
bMAD ($n = 74$)	27 (36%)	6 (8%)	41 (55%)

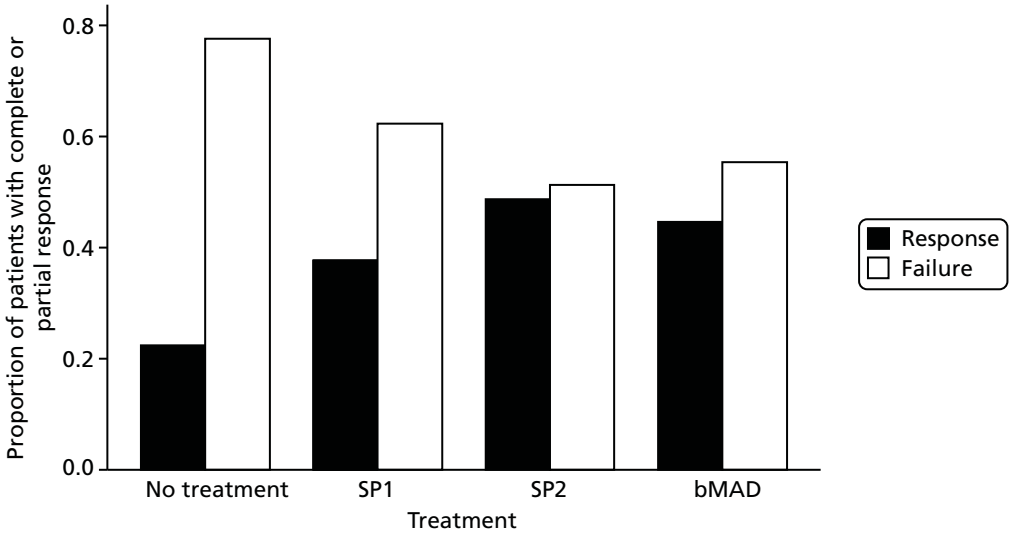

FIGURE 3 Complete or partial response of patients by treatment.

Predictors of apnoea–hypopnoea index response

Using mixed-effects logistic models for complete/partial response, all MADs had significantly greater response rates than during the no-treatment period (*Table 7*). Response was significantly associated with baseline BMI [odds ratio (OR) 0.89, 95% CI 0.81 to 0.98; $p = 0.014$] and with contemporaneous BMI (OR per kg/m^2 0.88, 95% CI 0.80 to 0.98; $p = 0.007$). It was also weakly associated with protrusion (OR 1.03 per % protrusion, 95% CI 1.00 to 1.05 per % protrusion; $p = 0.034$). Baseline AHI, ESS score, sex and age (years), as well as measures of compliance, were not significantly associated with response.

Secondary outcomes

Epworth Sleepiness Scale

Table 8 shows summary statistics for the four treatment periods as well as the results of the mixed-effects linear regression. *Figure 4* plots estimated ESS score by treatment. There was a clear, statistically significant, reduction (improvement) in ESS score for all MADs compared with no treatment, with effect sizes of approximately 0.35, 0.50 and 0.55 SDs compared with no treatment. In addition, there was a weakly significant difference between the SP1 and the bMAD in post-hoc pairwise comparisons (*Table 9*).

TABLE 7 Summary of results from mixed-effects logistic regression for complete or partial response to treatment ($n = 81$)

Response to treatment ($n = 81$)	OR (SE)	95% CI	*p*-value	Global *p*-value
Constant	0.12	0.04 to 0.32	< 0.001	
No treatment	–	–		0.0006
SP1	2.90	1.16 to 7.25	0.022	
SP2	5.75	2.48 to 13.33	< 0.001	
bMAD	4.64	1.79 to 12.02	0.002	

Note
Period effects not shown.

TABLE 8 Summary of results from mixed-effects model for ESS score ($n = 83$)

ESS score ($n = 83$)	Mean (SD)	Coefficient	95% CI	*p*-value	Global *p*-value
Constant		10.65	9.64 to 11.66	< 0.001	
Difference in ESS score compared with no treatment					
No treatment	10.1 (4.3)	–	–	–	< 0.001
SP1	8.5 (4.0)	−1.51	−2.29 to −0.73	< 0.001	
SP2	8.0 (4.1)	−2.15	−2.99 to −1.31	< 0.001	
bMAD	7.7 (3.8)	−2.37	−3.22 to −1.53	< 0.001	

Note
Period effects not shown.

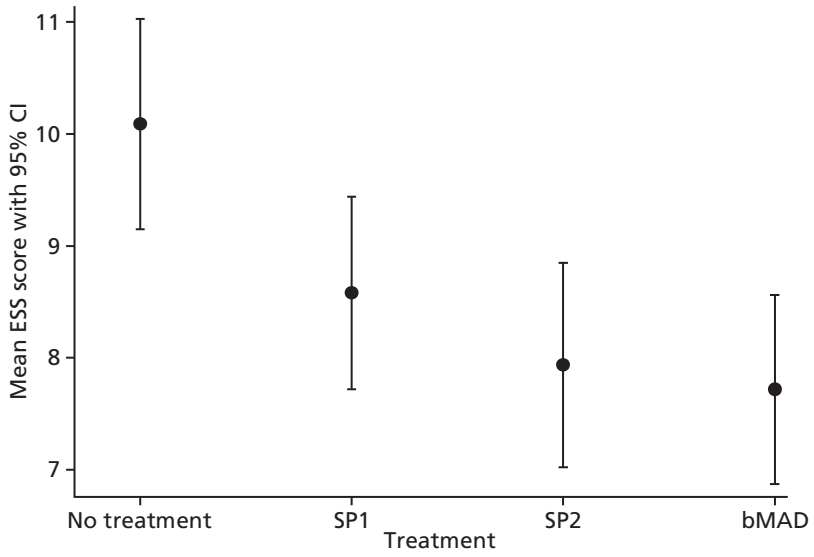

FIGURE 4 Estimated mean ESS score and 95% CI for the different treatments from the mixed-effects model.

TABLE 9 Comparison of ESS score between different MADs

Comparison	Observed contrast	95% CI	*p*-value
SP2 with SP1	−0.64	−1.44 to 0.15	0.112
bMAD with SP1	−0.86	−1.63 to −0.09	0.029
bMAD with SP2	−0.22	−0.97 to 0.53	0.568

Note
These comparisons are *not* adjusted for multiple comparisons. Differences are significant at 5% level according to the Bonferroni method if the *p*-value is < 0.017.

Four per cent oxygen desaturation index

The findings for 4% ODI mirrored those for AHI, as can be seen in *Table 10*. Although all MADs used resulted in significantly lower desaturation index relative to no treatment, there were no significant differences between MADs. In general, similar patterns were observed for minimum and mean SpO_2 and time with $< 90\%$ SpO_2 (data available on request).

Daytime blood pressure

Blood pressure was taken three times at each visit and the average of the three measurements recorded. There was very little evidence of an effect of any of the MADs on either SBP or DBP during the trial. Mean (SD) SBP and DBP at the end of the no-treatment period was 127.4 mmHg (12.2) and 79.2 mmHg (8.3), respectively. For SBP, the mean (SD) at the end of treatment with the SP1, SP2 and bMAD was 127.0 mmHg (13.5), 128.8 mmHg (14.7) and 127.2 mmHg (12.6), respectively. Corresponding results for DBP were 79.0 mmHg (9.4), 79.9 mmHg (9.2) and 79.5 mmHg (10.0), respectively.

Treatment compliance

Of the 314 sleep diaries expected from the 81 patients who completed at least one period, 14 were not returned and three were not completed satisfactorily. Compliance was slightly worse in terms of the number of nights used, and significantly worse for duration of use per night, for the SP1 than for the SP2 or the bMAD (*Table 11*; $p < 0.001$), but there were no significant differences in compliance between the SP2 and the bMAD. Patients were also more likely to discontinue use of the SP1 than the other two devices (*Table 12*).

TABLE 10 Summary of results from mixed-effects model for 4% ODI ($n = 81$)

4% ODI ($n = 81$)	Mean (SD)	Coefficient	95% CI	*p*-value	Global *p*-value
Constant		11.03	9.00 to 13.52	< 0.001	
4% ODI rate relative to no treatment					
No treatment	11.0 (8.4)	–	–	–	< 0.001
SP1	8.4 (8.5)	0.75 (0.08)	0.60 to 0.92	0.007	
SP2	7.3 (7.4)	0.65 (0.06)	0.55 to 0.77	< 0.001	
bMAD	6.8 (6.8)	0.60 (0.06)	0.50 to 0.72	< 0.001	

Note
Period effects not shown.

TABLE 11 Compliance with treatment

Treatment usage category	Treatment	Median (IQR)	Min., max.
Number of nights used (out of 28)	SP1 ($n = 81$)	25 (17–28)	0.0, 28.0
	SP2 ($n = 78$)	27 (23–28)	0.0, 28.0
	bMAD ($n = 76$)	26 (23–28)	0.0, 28.0
Number of hours used per night	SP1 ($n = 80$)	5.1 (2.5–6.4)	0.0, 8.3
	SP2 ($n = 78$)	6.3 (4.9–7.1)	0.0, 8.3
	bMAD ($n = 76$)	6.3 (5.1–7.0)	0.0, 8.0

Max., maximum; min., minimum.

TABLE 12 Treatment interruption or discontinuation for patients who used the device for < 28 days

Treatment	Number used for < 28 days	Interrupted	Discontinued	Interrupted then discontinued
SP1 ($n = 81$)	50 (62%)	36 (72%)	11 (22%)	3 (6%)
SP2 ($n = 78$)	46 (59%)	42 (91%)	4 (9%)	0 (0%)
bMAD ($n = 76$)	55 (72%)	49 (89%)	4 (7%)	2 (4%)

Patient evaluation of treatments

On average, patients considered the SP2 and the bMAD to be as comfortable as no treatment, but the SP1 was significantly less comfortable than all other treatments (VAS for comfort, *Table 13*). This resulted in greater satisfaction for the SP2 and the bMAD than for no treatment or the SP1 (VAS for satisfaction, *Table 13*). *Table 14* shows that patients reported that the SP1 was more likely to fall out during sleep than the SP2, and that the SP2 was more likely to fall out than the bMAD. In addition, patients reported that they were more likely to remove the SP1 during sleep than either the SP2 or the bMAD (*Table 15*).

The 74 patients who completed all treatments were asked to state their preferred treatment. Of these, 30 (41%) ranked the bMAD highest and 23 (31%) ranked it second. The SP2 was ranked highest by 22 (30%) patients and second by 34 (46%) (*Figure 5*). Only 10 (14%) patients ranked no treatment highest.

Most patients (56/90, 62%) continued with their preferred device after the study ended, with five (6%) others retaining the MAD that gave the best results for them. Other treatments undertaken by patients after the trial are listed in *Table 16*.

TABLE 13 Summaries of the visual analogue valuations of treatment comfort and satisfaction

Treatment	*n*	Median treatment comfort (IQR)	Min.	Max.
No treatment	78	50 (50–97)	1	100
SP1	81	34 (16–50)	0	91
SP2	78	52 (36–82)	0	100
bMAD	77	50 (25–76)	0	97
Treatment	***n***	**Median treatment satisfaction (IQR)**	**Min.**	**Max.**
No treatment	78	50 (25–50)	0	100
SP1	81	43 (14–65)	0	99
SP2	78	67 (41–87)	0	100
bMAD	77	71 (38–87)	0	100

Max., maximum; min., minimum.

TABLE 14 Patient report of frequency that device fell out

On average, how often the device fell out	Frequency (%) for SP1 ($n = 81$)	Frequency (%) for SP2[a] ($n = 78$)	Frequency (%) for bMAD ($n = 77$)
Never fell out	27 (33%)	43 (56%)	51 (66%)
Fell out occasionally, but not every night	35 (43%)	26 (34%)	22 (29%)
Fell out once or twice every night	11 (14%)	5 (6%)	4 (5%)
Fell out > 2 times every night	8 (10%)	3 (4%)	0 (0%)

a One missing value for the SP2, as the patient did not wear the device for longer than 1 minute.

TABLE 15 Patient report of frequency that device was removed

On average, how often the device was removed	Frequency (%) for SP1 ($n = 81$)	Frequency (%) for SP2[a] ($n = 78$)	Frequency (%) for bMAD ($n = 77$)
Never removed	25 (31%)	40 (52%)	34 (44%)
Removed 1–3 nights/week	33 (41%)	23 (30%)	28 (36%)
Removed 4–6 nights/week	10 (12%)	9 (12%)	8 (10%)
Removed every night	13 (16%)	5 (6%)	7 (9%)

a One missing value for the SP2, as the patient did not wear the device for longer than 1 minute.

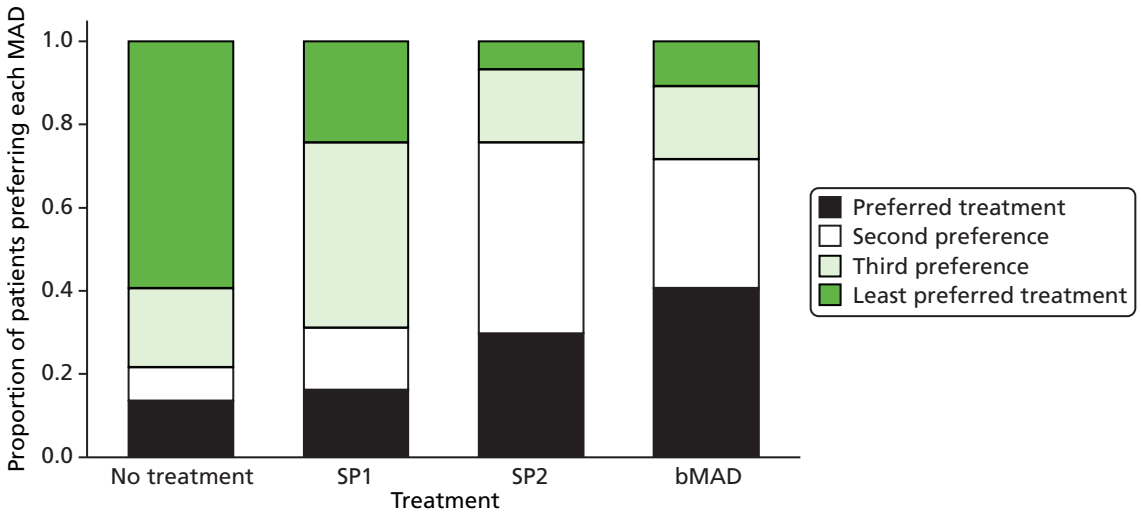

FIGURE 5 Bar chart of patient preference.

TABLE 16 Patient management after completing TOMADO

Number of patients ($n = 90$)	Future care
16	Start CPAP
56	Use preferred MAD
5	Continued with the MAD that provided the best results
2	Withdrew – continued with current MAD
3	No further treatment
3	Advised weight loss
2	CM only
2	Lost to follow-up – recommended to use SP2
1	Ropinirole for restless legs syndrome

Functional Outcomes of Sleep Questionnaire

Eighty-three (92%) patients had at least one FOSQ result (*Table 17*). *Figure 6* summarises the results for the five subscales. The overall FOSQ scores showed a weak period effect ($p = 0.021$), suggesting that there may be some adjustment of questionnaire responses over time. After including period effects in the model, there were significant improvements for all the MADs compared with the no-treatment period. In addition, there were small but significant differences between the SP1 and SP2 and between the SP1 and bMAD but not between the SP2 and bMAD (*Table 18*). The plot of individual FOSQ scales (*Figure 7*) suggests that this improvement is because of small increases in all dimensions but particularly for activity level and general productivity.

Short Calgary Sleep Apnoea Quality of Life Index

The summaries and model results for the overall score are shown in *Table 19* and *Figure 8*. In common with the FOSQ overall score, there was a significant effect of all MADs compared with no treatment and a small but significant difference between the SP1 and SP2 and between the SP1 and bMAD, but not between the SP2 and bMAD (*Table 20*). *Figure 9* shows results for each subscale of the SAQLI and, again, shows a small improvement across all dimensions, particularly daily activities and symptoms.

TABLE 17 Summary of results from mixed-effects model for the FOSQ ($n = 83$)

FOSQ ($n = 83$)	Mean (SD)	Coefficient	95% CI	*p*-value	Global *p*-value
Constant		16.21	15.65 to 16.78	< 0.001	
Difference in FOSQ compared with no treatment					
No treatment	16.62 (2.55)	–	–	–	< 0.001
SP1	17.13 (2.42)	0.50	0.08 to 0.92	0.018	
SP2	17.70 (2.14)	1.10	0.65 to 1.55	< 0.001	
bMAD	17.90 (1.92)	1.31	0.84 to 1.78	< 0.001	

Note
Period effects not shown.

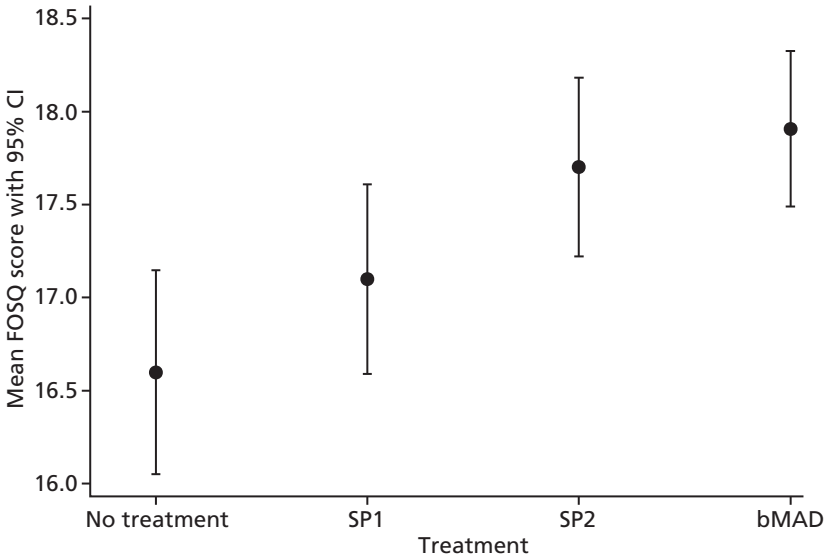

FIGURE 6 Estimated mean FOSQ and 95% CI for the different treatments from the linear mixed-effects model.

TABLE 18 Comparison of total FOSQ score between different MADs

Comparison	Observed contrast	95% CI	*p*-value
SP2 to SP1	0.60	0.18 to 1.03	0.005
bMAD to SP1	0.81	0.41 to 1.20	< 0.001
bMAD to SP2	0.21	–0.19 to 0.60	0.304

Note
These comparisons are *not* adjusted for multiple comparisons. Differences are significant at 5% level according to the Bonferroni method if the *p*-value is < 0.017.

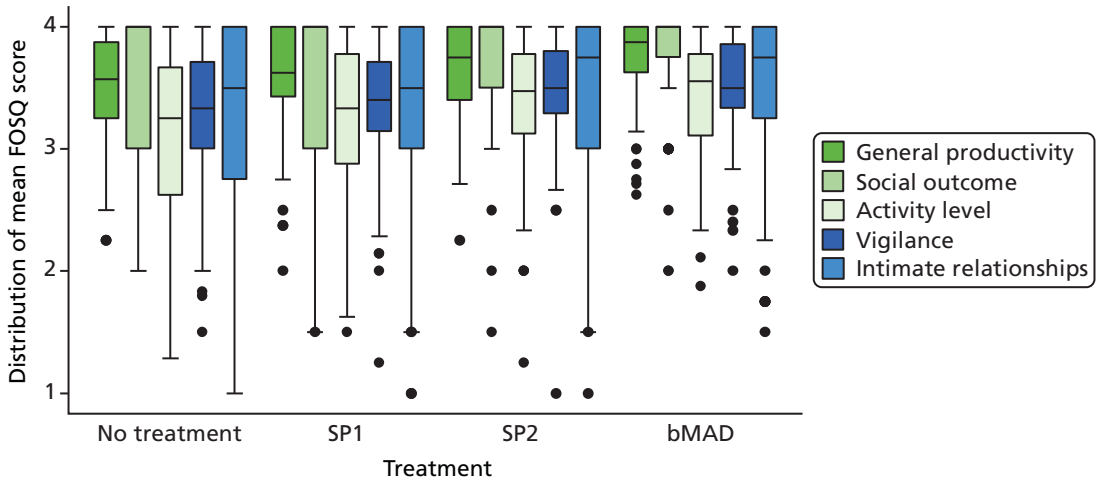

FIGURE 7 Box plots of the mean score for each domain of the FOSQ.

TABLE 19 Summary of results from mixed-effects model for the SAQLI ($n = 83$)

SAQLI ($n = 83$)	Mean (SD)	Coefficient	95% CI	p-value	Global p-value
Constant		4.79 (0.15)	4.50 to 5.09	< 0.001	
Difference in SAQLI compared with no treatment					
No treatment	5.01 (1.24)	–	–	–	< 0.001
SP1	5.25 (1.20)	0.27 (0.10)	0.07 to 0.48	0.008	
SP2	5.60 (1.12)	0.62 (0.12)	0.38 to 0.86	< 0.001	
bMAD	5.64 (1.06)	0.65 (0.13)	0.41 to 0.90	< 0.001	

Note
Period effects not shown.

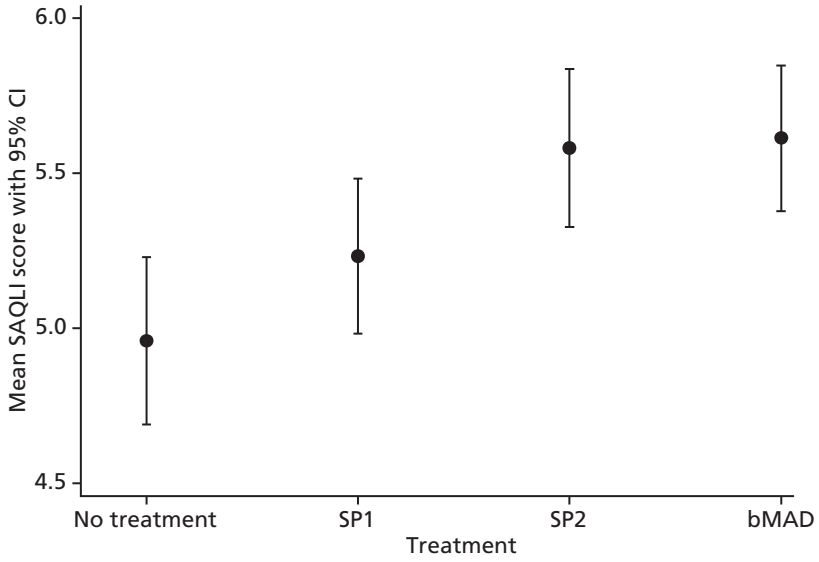

FIGURE 8 Estimated mean SAQLI score and 95% CI for the different treatments from the linear mixed-effects model.

TABLE 20 Comparison of total SAQLI score between different MADs

Comparison	Observed contrast	95% CI	*p*-value
SP2 to SP1	0.35	0.13 to 0.57	0.002
bMAD to SP1	0.38	0.17 to 0.59	< 0.001
bMAD to SP2	0.03	–0.20 to 0.26	0.785

Note
These comparisons are *not* adjusted for multiple comparisons. Differences are significant at 5% level according to the Bonferroni method if the *p*-value is < 0.017.

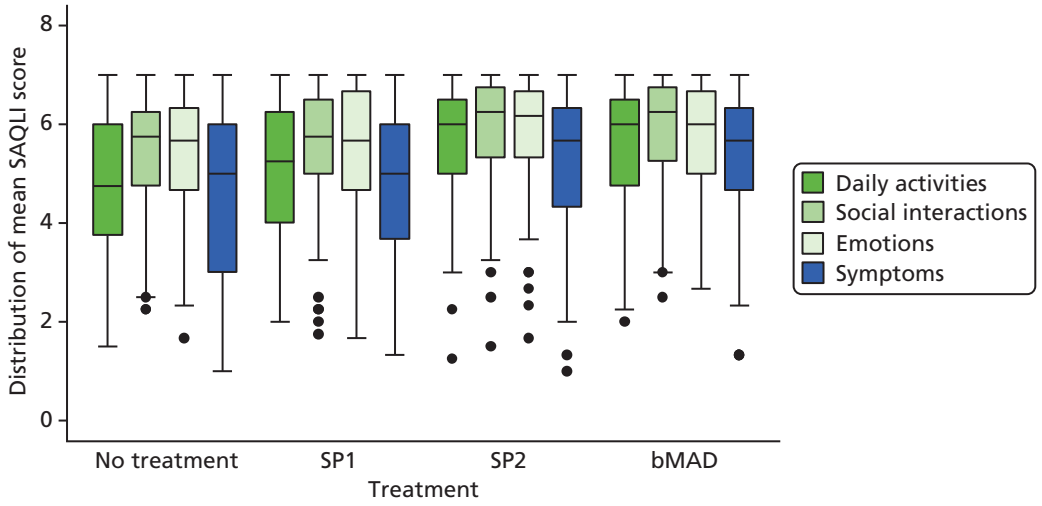

FIGURE 9 Box plots of the mean score for each domain of the SAQLI.

Short Form questionnaire-36 items

Summaries of results for the SF-36 standardised PCS and MCS are shown in *Table 21* and *Figures 10* and *11*. Predictably, this general HRQoL instrument is less sensitive to differences between the treatments than the disease-specific instruments, with only the comparison between the SP1 and SP2 showing a borderline significant difference in PCS in favour of the SP2. There was a similar borderline significant increase in the MCS for the bMAD compared with the SP1.

Protrusion achieved

The protrusion achieved was measured for all three devices at Papworth Hospital (*Table 22*). The SP1 achieved the greatest protrusion, being 0.89 mm (95% CI 0.42 to 1.37 mm; $p < 0.001$) greater than the SP2 and 0.66 mm (95% CI 0.17 to 1.14 mm; $p = 0.008$) greater than the bMAD. In a model that contained the degree of protrusion, MAD and time period, protrusion did not influence AHI [hazard ratio (HR) 0.997, 95% CI 0.991 to 1.001; $p = 0.206$]. Protrusion did have a small effect on the probability of a response to treatment (see earlier section on predictors of response to treatment).

Learning effect

The SP1 and SP2 devices were moulded and protruded by patients independently; in contrast, in the case of the bMADs, protrusion was determined by a medical professional. Variability between the mean protrusion values for each device may have been the result of a variety of factors, including patient-determined compared with clinician-determined protrusion and previous experience of wearing a device on the trial. For example, the SP1 was moulded at the start of that treatment period. Therefore, in patients with SP1 as their second or third device, jaw protrusion may have been either more or less depending on acclimatisation to jaw protrusion and any positive or negative effects experienced while

TABLE 21 Summary of results from mixed-effects model for the SF-36 standardised PCS and MCS ($n = 83$)

PCS ($n = 83$)	Mean (SD)	Coefficient	95% CI	p-value	Global p-value
Constant		41.61 (1.58)	38.51 to 44.71	< 0.001	
Difference in PCS compared with no treatment					
No treatment	43.06 (12.86)	–	–	–	0.058
SP1	42.73 (12.22)	−0.17 (0.84)	−2.27 to 1.92	0.990	
SP2	45.11 (12.33)	2.42 (1.17)	0.38 to 4.45	0.145	
bMAD	43.12 (13.81)	0.48 (1.22)	−1.74 to 2.70	0.386	
MCS ($n = 83$)	**Mean (SD)**	**Coefficient**	**95% CI**	**p-value**	**Global p-value**
Constant		45.24 (1.27)	42.75 to 47.72	< 0.001	
Difference in MCS compared with no treatment					
No treatment	46.20 (10.78)	–	–	–	0.112
SP1	46.87 (9.63)	0.89 (1.02)	−1.10 to 2.88	0.380	
SP2	47.34 (11.24)	1.20 (0.93)	−0.62 to 3.01	0.198	
bMAD	48.81 (9.00)	2.72 (1.20)	0.36 to 5.08	0.024	

Note
Period effects not shown.

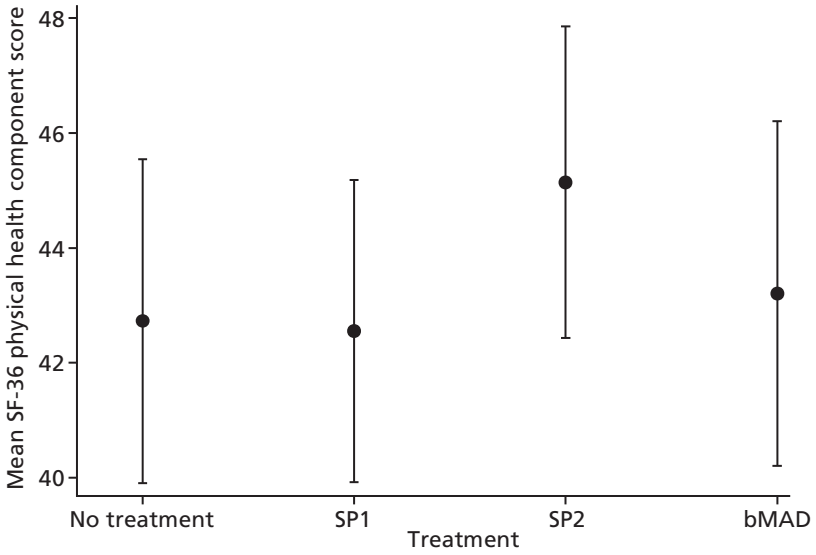

FIGURE 10 Standardised SF-36 physical health summary.

using previous devices. A few patients may have been unintentionally guided by their experience of the bMAD-fitting process. Six patients commented that they had found the visit to the maxillofacial team for bMAD fitting useful in subsequently informing SP2 moulding, including protrusion. Two patients commented that the bMAD-fitting experience helped when they later moulded the SP1. Two others did not describe inadvertent dental guidance, but found the SP1 easier to fit having already made the SP2 mould.

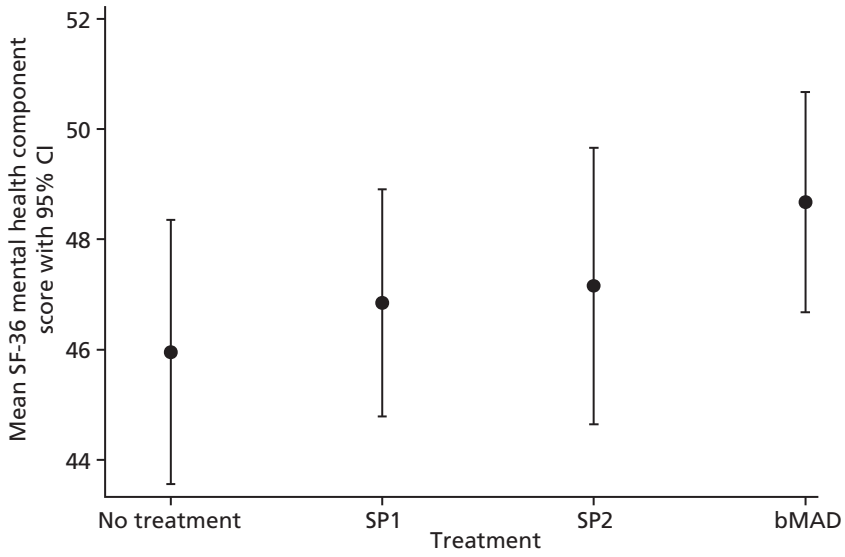

FIGURE 11 Standardised SF-36 mental health summary.

TABLE 22 Mean device measurements

Device	Measured of percentage protrusion	Unit/category	Total ($n = 90$)	Min.	Max.
SP1	Measured protrusion	M = mm	5.65 (2.12)	1	11
		Missing	14		
	Percentage protrusion		62.63 (22.08)	10	100
		Missing	15		
SP2	Measured protrusion	mm	4.75 (2.50)	–2	11.5
		Missing	11		
	Percentage protrusion		51.66 (26.42)	–25	100
		Missing	12		
bMAD	Measured protrusion	mm	4.99 (1.89)	1	10
		Missing	9		
	Percentage protrusion		55.18 (19.72)	9.09	100
		Missing	11		

Max., maximum; min., minimum.

Safety reporting

Driving

Eighty-seven (97%) patients in TOMADO reported that they were drivers at baseline and three (3%) were not. Eighty-six patients drove a car, two a motorbike, three a heavy goods vehicle and 16 drove other vehicles including a fork lift truck, jeep, van, minibus and tractor. *Table 23* records patient-reported sleepiness while driving. There was a clear improvement in sleepiness while driving, and in the requirement for interruption to journeys, during all periods of MAD use compared with no treatment, but little difference between MADs. During the trial there were only three reported cases of 'nodding off' (none of which resulted in a collision) and five collisions while driving. No collisions resulted in an injury to anyone involved other than the patient, and one collision resulted in an injury to the patient, who required treatment and advice from a health-care professional.

TABLE 23 Patient-reported sleepiness associated with driving

Driving-related question	Response	No treatment ($n = 75$)	SP1 ($n = 78$)	SP2 ($n = 75$)	bMAD ($n = 74$)
Sleepy while driving	Never	43 (59%)	54 (72%)	55 (75%)	56 (78%)
	Rarely	16 (22%)	11 (15%)	13 (18%)	5 (7%)
	Occasionally	11 (15%)	9 (12%)	5 (7%)	10 (14%)
	Frequently	3 (4%)	1 (1%)	0	1 (1%)
	Always	0	0	0	0
	Missing[a]	2	3	2	2
Nodded off driving	Yes	1 (1%)	1 (1%)	1 (1%)	0
	No	72 (99%)	74 (99%)	72 (99%)	72 (100%)
	Missing	2	3	2	2
Pulled off road	Yes	11 (15%)	4 (5%)	7 (10%)	4 (6%)
	No	62 (85%)	71 (95%)	66 (90%)	68 (94%)
	Missing	2	3	2	2
Collisions	Yes	1 (1%)	0	2 (3%)	2 (3%)
	No	72 (99%)	75 (100%)	71 (97%)	70 (97%)
	Missing	2	3	2	2

a All missing data arose because the patient had not driven in the past 4 weeks.

Partner-evaluated snoring scale

Fifty sleeping partners of trial patients completed the snoring VAS for all four periods (*Tables 24* and *25* and *Figure 12*). This showed a clear improvement for all MADs compared with no treatment, and between the SP1 and the two more sophisticated devices.

Adverse events

There were four SAEs during the trial. There was one case of sick sinus syndrome with atrial flutter and one case of hypoglycaemia during periods of no treatment, both considered possibly related to OSAH, one case of complete heart block and one case of non-specific chest pain during bMAD use, both considered possibly related to OSAH and MAD use. These occurred in four separate patients and all events were resolved within 7 days.

TABLE 24 Summary of effects from mixed-effects model for the partner-rated VAS for snoring ($n = 50$)

Snoring ($n = 50$)	Mean (SD)	Coefficient	95% CI	*p*-value	Global *p*-value
Constant		66.65	59.80 to 73.49	< 0.001	
Difference in VAS compared with no treatment					
No treatment	71.7 (16.2)	–	–	–	< 0.001
SP1	46.7 (24.1)	−23.22	−29.78 to −16.66	< 0.001	
SP2	35.6 (23.1)	−34.08	−41.85 to −26.31	< 0.001	
bMAD	32.4 (23.0)	−37.47	−45.31 to −29.63	< 0.001	

Higher scores indicate greater problems.
Note
Period effects not shown.

TABLE 25 Comparison of the partner-rated snoring scale between different MADs

Comparison	Observed contrast	95% CI	*p*-value
SP2 with SP1	−10.86	−18.90 to −2.83	0.008
bMAD with SP1	−14.25	−23.56 to −4.94	0.003
bMAD with SP2	−3.39	−11.38 to 4.60	0.406

Note
These comparisons are *not* adjusted for multiple comparisons. Differences are significant at 5% level according to the Bonferroni method if the *p*-value is < 0.017.

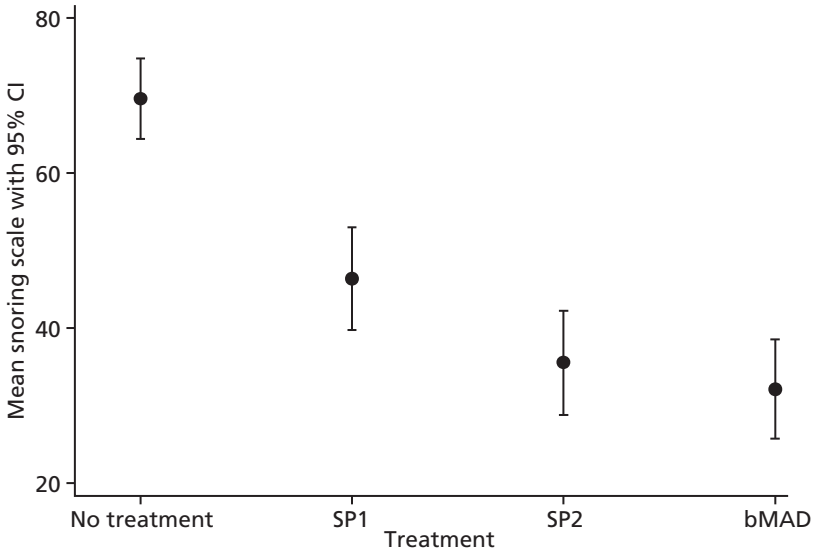

FIGURE 12 Partner-evaluated snoring scale.

A total of 851 minor AEs were recorded in 86 patients who enrolled in the trial (*Table 26*). These were mainly mouth discomfort and excess salivation. They were recorded equally frequently for all three MADs and less frequently during the no-treatment periods. Among patients who withdrew from the study, there were 63 AEs in 12 patients, mainly mouth discomfort (52, 83%). Almost all minor AEs in both completers and withdrawals were classed as probably related to MADs (528 events in 85 patients) or possibly related to both OSAH and MAD use (174 events in 54 patients) by an independent sleep physician.

Specific events included in each category are given in *Appendix 9*.

TABLE 26 All reported AEs during the trial with number of patients affected in brackets

Type of AE	No treatment (*n* = 78)	SP1 (*n* = 81)	SP2 (*n* = 78)	bMAD (*n* = 77)	Total
General	32 (24)	38 (24)	35 (25)	34 (26)	139 (47)
Dryness/bad taste/numbness	12 (10)	26 (20)	30 (24)	21 (18)	89 (39)
Discomfort/mouth problems	18 (13)	135 (60)	124 (52)	148 (74)	425 (83)
Excessive salivation	2 (2)	37 (32)	19 (18)	34 (29)	92 (48)
Cold related	14 (13)	25 (17)	34 (26)	24 (18)	97 (46)
Infection	2 (2)	6 (6)	0 (0)	1 (1)	9 (8)
Total	80 (45)	267 (73)	242 (68)	262 (76)	851 (86)

Trial-based economic analysis

Data completeness

Data were formatted as a four-period ($n = 83$) observation panel, including participants with at least one completed treatment period and for whom complete data on QoL and resource use were available. Of the 83 people, 77 provided complete EQ-5D-3L and resource use data for the SP1, SP2 and control periods, and 75 for the bMAD and control periods.

Seventy-four participants provided complete EQ-5D-3L and resource use data for all intervention periods. Data completeness was similar for the SF-6D ($n = 76$ for SP1, SP2 and control, and $n = 76$ for bMAD and control period).

Costs

Table 27 shows that the SP1 device cost the least (£1.62) pro rata over the 4-week trial period, followed by SP2 (£9.85), and that the bMAD is considerably more expensive (£28.64). The mean non-device costs during the no-treatment period were £78.50, while they were £73.02 for SP1, £53.58 for SP2 and £76.25 for bMAD (*Table 27*). *Figure 13* shows box plots of total costs for each group. While costs were similarly clustered for each trial group, SP2 had the narrowest spread of cost. The bunching of outliers close to the upper quartile tend to comprise patients with more frequent primary care (e.g. to dentist or GP) or outpatient visits and these occurred in all groups. However, in both the control and bMAD groups, a few patients incurred very high costs as a result of rare events such as an atrial flutter, pacemaker implantation and hypertension with chest pain.

Combining the device and resource use costs and comparing each intervention with control over the 4-week intervention period shows that the SP1 compared with control was £4 less (SE £21), and that SP2 was £15 less on average (SE £21), but that the mean cost of bMAD was £26 greater than mean costs in the control group (SE £28) (*Table 27*). Differences were not statistically significant.

TABLE 27 Trial-based comparison on costs incurred over 4 weeks

Intervention cost components	No treatment ($n = 78$)	SP1 ($n = 81$)	SP2 ($n = 78$)	bMAD ($n = 77$)
Device costs (fixed)	–	£21.00	£128.00	£350.00
Measurement for device	–	–	–	£110.37
Fitting of device	–	–	–	£92.04
Additional fitting visit if required (average across all patients)	–	–	–	£5.98[a]
Subtotal	**–**	**£21.00**	**£128.00**	**£558.39**
Device lifespan (months) (fixed)	–	12	12	18
Fixed cost of intervention – pro rata (4 weeks) subtotal	–	£1.62	£9.85	£28.64
	Mean (SE)	***Mean (SE)***	***Mean (SE)***	***Mean (SE)***
Variable resource use cost (4 weeks)	£78.50 (£19.97)	£73.02 (£10.47)	£53.58 (£8.05)	£76.25 (£24.40)
Total 4-week costs	**£78.50 (£19.97)**	**£74.64 (£10.47)**	**£63.43 (£8.05)**	**£104.89 (£24.39)**

a Five participants required an additional fitting visit for bMAD, cost at £92.04. Average across all participants = £5.98.

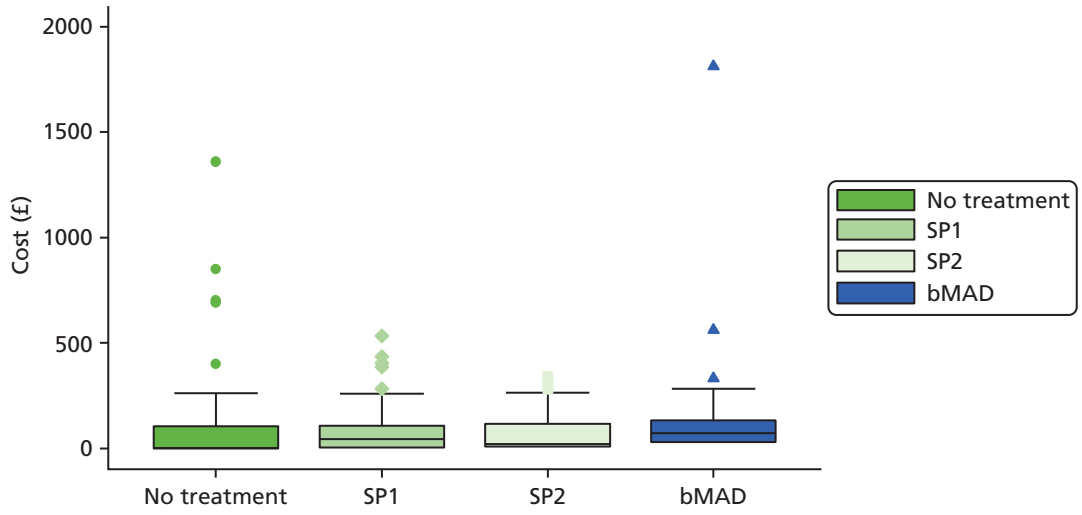

FIGURE 13 Box plots of total cost during each 4-week treatment period.

Quality-adjusted life-years

Figures 14 and *15* show the distribution of the QALY scores at baseline and by treatment group using the EQ-5D-3L and SF-6D. The EQ-5D-3L shows that the SP2 and bMAD have better profiles, with more people scoring around 0.078 or above and bMAD also having fewer people with scores around zero. Of those people with low outlying QALY scores, one person had consistently low scores during baseline and all four intervention periods and another at baseline and three treatment periods. The remaining differences show two participants with QALYs outside the lower IQR while on the SP2 and bMAD, and one participant during the no-treatment period. In only one case did the participants who reported lower EQ-5D-3L QALY scores also accrue higher costs, and this was during the no-treatment phase.

The mean QALY score based on the EQ-5D-3L data for the control period was 0.065 (SE 0.002). To give some perspective, 4 weeks in perfect health is associated with a QALY score of $(1 \times 4)/52 = 0.0769$. The control score is, therefore, less than perfect health, equating to a QALY score of 0.065. The difference in EQ-5D-3L QALY values for each MAD compared with no treatment (see *Appendices 10* and *11*) was 0.0009 (SE 0.001) for SP1, 0.0009 (SE 0.001) for SP2 and 0.0018 (SE 0.001) for bMAD (see *Table 28*). Although the gain was greatest for bMAD, there was substantial uncertainty, shown by the large SEs. The 95% CI for the effectiveness of each device compared with control spanned zero (i.e. no statistically significant effect).

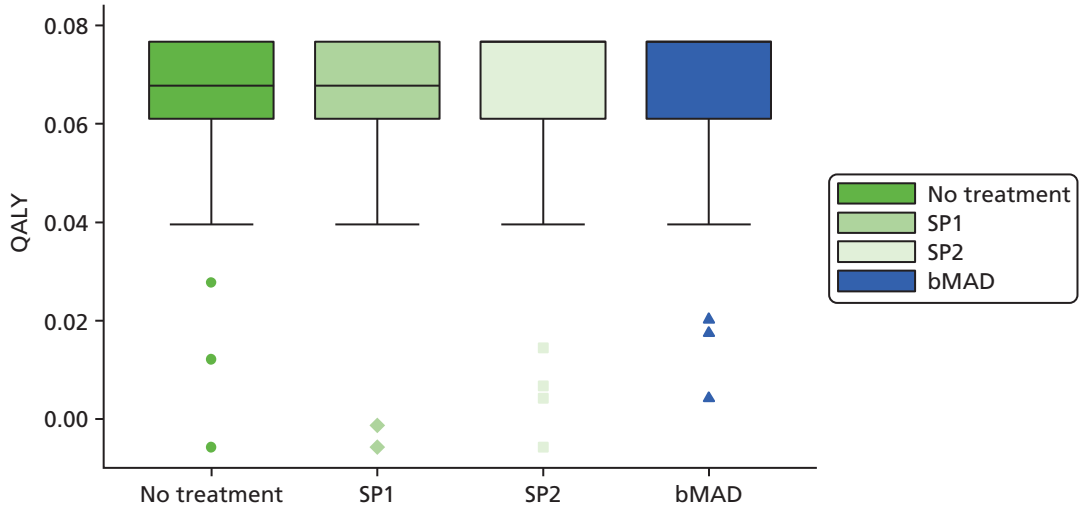

FIGURE 14 Box plot of EQ-5D-3L QALY results by treatment.

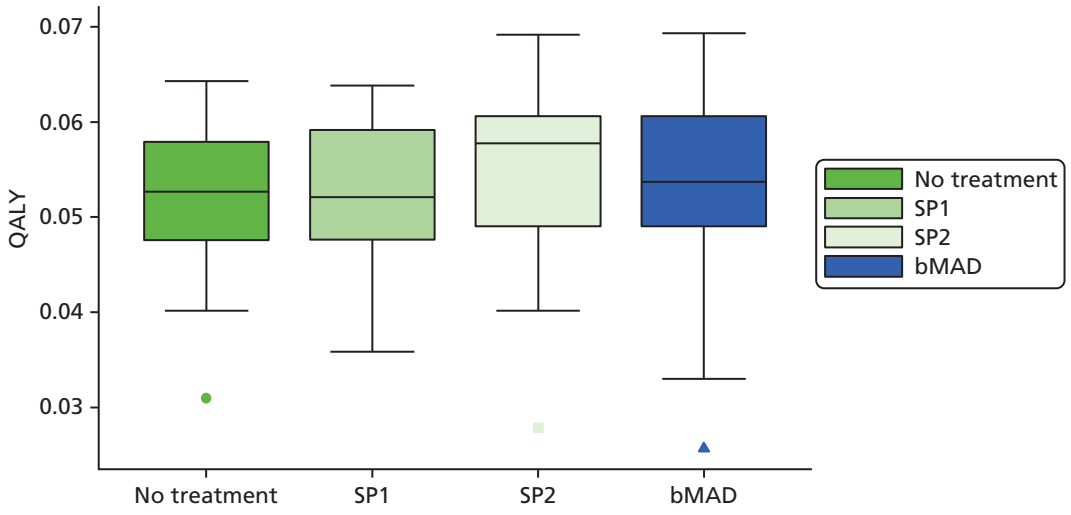

FIGURE 15 Box plot of SF-6D QALY results by treatment.

The SF-6D showed that the SP2 conferred the best health outcomes, with mean QALY score around 0.057, followed by bMAD and no treatment, around 0.053, and SP1, around 0.052. The one participant recorded as an outlier using SF-6D QALYs had fewer QALYs on no treatment, SP2 and bMAD. As with the EQ-5D-3L QALYs, those with low outlying QALY values were not necessarily those with higher costs. The mean QALY score from the mixed-effects model for the control period was 0.053 (SE 0.0008). The difference in SF-6D QALYs (see *Appendices 11* and *12*) compared with no treatment during the 4-week intervention period was 0.0004 (SE 0.0008) for the SP1, 0.0019 (SE 0.0007) for SP2 and 0.0009 (SE 0.0009) for the bMAD. Of all the MADs, the SP2 showed the greatest change in QALYs compared with control and was also the only intervention with a statistically significant difference ($p = 0.013$).

Cost-effectiveness

Table 28 shows that the ICERs were negative for the SP1 and SP2 compared with control, i.e. costs were lower and outcomes better for the two interventions than for no treatment. Note that EQ-5D-3L QALY differences between devices were small and non-significant. Of these two, the SP2 is more beneficial as costs were lower than the SP1.

Table 28 also shows that bMADs have the greatest impact on QALY gain, and at a cost of £14,900 per additional QALY gained, would be considered a cost-effective treatment compared with control. However, compared with the SP2, the bMAD costs an additional £46,000 per QALY (£105 – £64)/(0.0667 – 0.0658 QALYs). These results are mirrored by the net monetary benefit, which shows that the SP2 achieved the highest INMB, compared with no treatment, at £33 per 4 weeks assuming a WTP of £20,000 per QALY (*Table 28*).

The uncertainty around estimates of cost per QALY gained is represented in the cost-effectiveness planes (*Figures 16–18*) and CEAF (*Figure 19*). These indicate the results are robust. The CEAF (*Figure 19*) shows the SP2 to be most cost-effective up to a WTP per QALY of £39,800, at which point the bMAD supersedes it (39% likelihood of being cost-effective compared with 35% for the SP2). Below a WTP of £5000 per QALY only SP2 is more cost-effective than no treatment. Deterministic sensitivity analyses also showed that results are robust to using only complete case analysis as well as changes in a device's price and lifespan (see *Appendix 13*, *Figures 36–39*). When the bMAD price exceeds £525 or average lifespan falls < 14 months, it no longer has a positive INMB. When the price of the bMAD falls to below £60, or its length of life extends to beyond 3 years (with no change in the SP1), it becomes more cost-effective than the SP1. However, even when assuming the same price for the bMAD of £60 or that its lifetime is at least 5 years, the bMAD remains less cost-effective than the SP2.

TABLE 28 Trial-based comparison of costs and QALYs from devices against control

Cost-effectiveness components	No treatment ($n = 78$)	SP1 ($n = 81$)	SP2 ($n = 78$)	bMAD ($n = 77$)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Total costs over 4 weeks				
Total cost[a]	£78.50 (£19.97)	£74.64 (£10.47)	£63.43 (£8.05)	£104.89 (£24.39)
Incremental cost (MAD – no treatment)	–	–£3.87 (£21.38)	–£15.08 (£20.62)	£26.39 (£27.94)
Total utility over 4 weeks				
QALY[b]	0.0649 (0.0017)	0.0658 (0.0017)	0.0658 (0.0019)	0.0667 (0.0017)
Incremental QALY (MAD – no treatment)	–	0.00094 (0.00105)	0.00088 (0.00123)	0.00177 (0.00147)
Cost-effectiveness measure (UK £, 2011)				
ICER	–	dominant	dominant	£14,876
INMB (WTP = £20,000) vs. no treatment	–	£23	£33	£9

a Resource use and total costs by intervention, estimated using a mixed-effects model controlling for baseline data. All costs in 2011/12 (£).
b QALY scores calculated using the area under the curve method to represent the true QALY score for the 4-week intervention period to be consistent with the costs presented. Based on EQ-5D-3L responses.

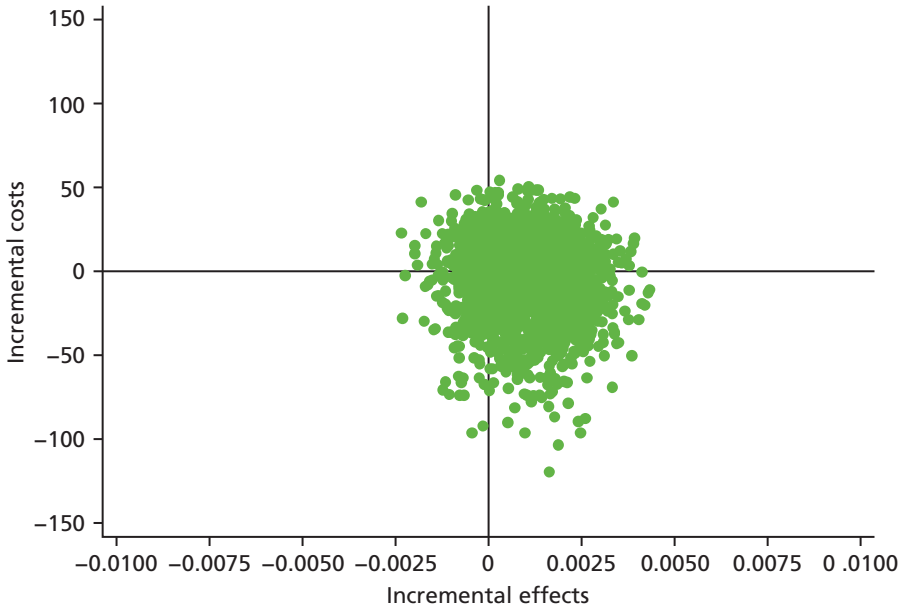

FIGURE 16 Incremental cost-effectiveness plane: SP1 compared with no treatment.

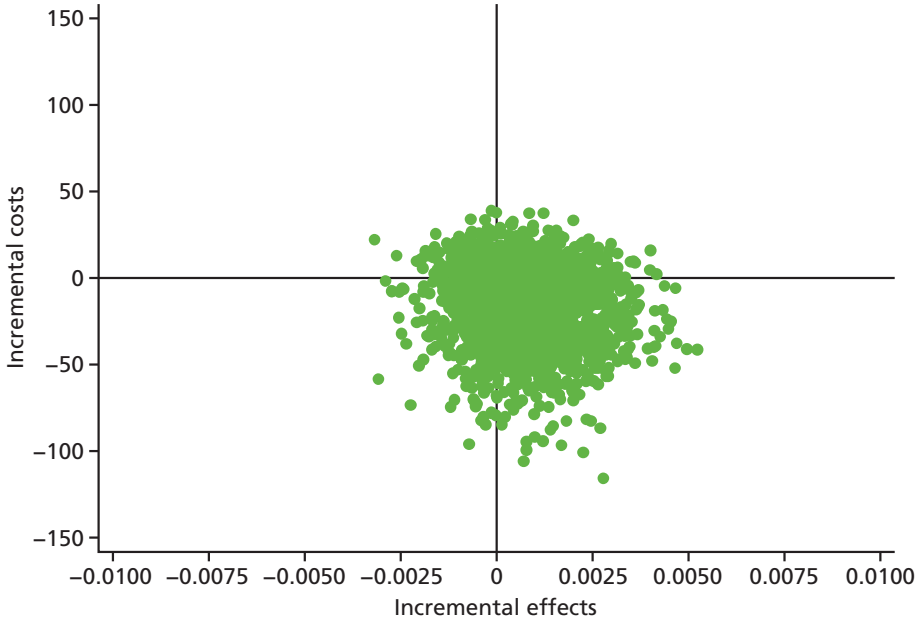

FIGURE 17 Incremental cost-effectiveness plane: SP2 compared with no treatment.

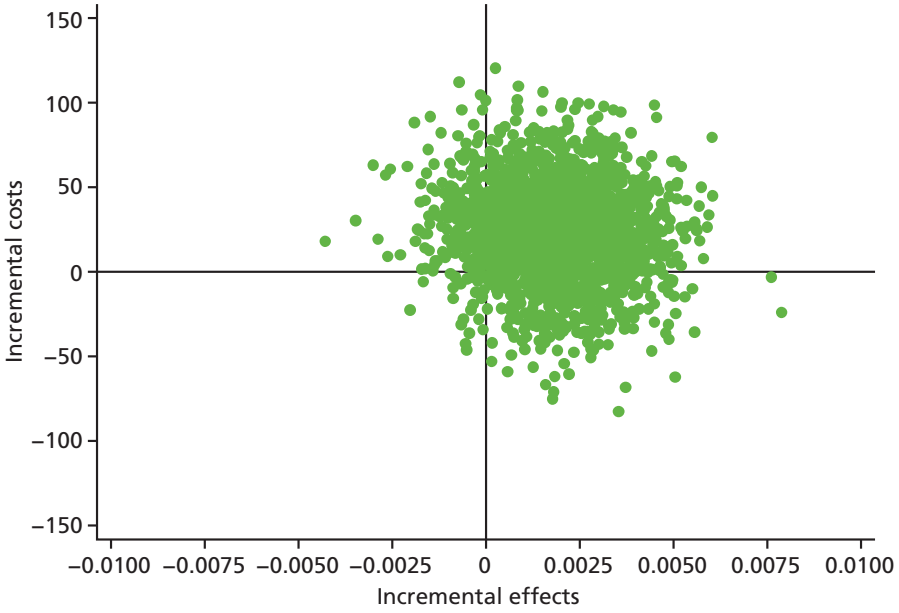

FIGURE 18 Incremental cost-effectiveness plane: bMAD compared with no treatment.

The cost-effectiveness analysis was repeated using the SF-6D data for health outcomes. Compared with no treatment, the SP1 has a QALY gain of 0.0004 (SE 0.0007) with the same cost saving described above (−£4 vs. control), meaning the SP1 was both cheaper and more effective, dominating no treatment. However, neither the difference in costs compared with no treatment nor the difference in health outcomes was statistically significant. The SP2 had a statistically significant improvement in health outcomes when compared with no treatment of 0.0019 (SE 0.0007) QALYs, with a *p*-value equal to 0.013. Combined with the costs saving of £15 over 4 weeks compared with no treatment, showing the SP2 to be dominant over no treatment; being both cheaper and more effective than no treatment. The bMAD provided an improvement

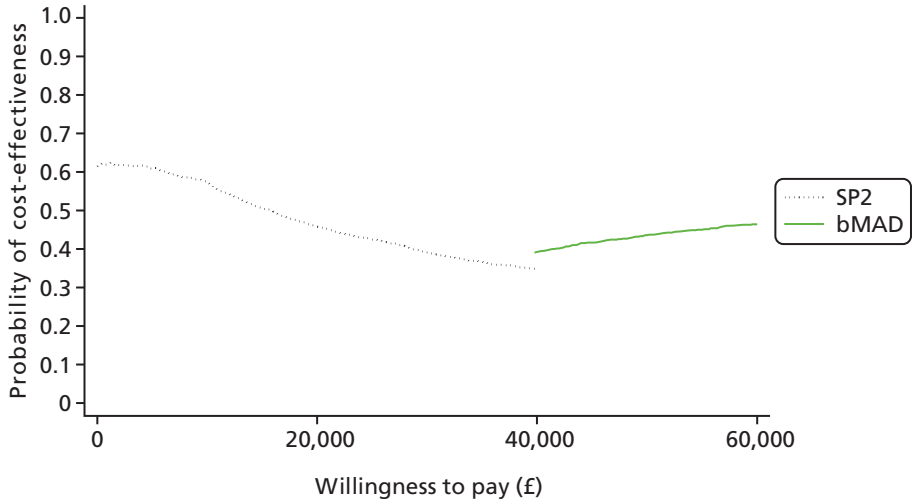

FIGURE 19 Cost-effectiveness acceptability frontier for each MAD compared with no treatment.

in health outcomes compared with no treatment of 0.0009 (SE 0.0009) QALYs, although this was not statistically significant. The bMAD cost £26 more than the no-treatment control, giving an ICER of £30,743 per QALY.

Applying a WTP per QALY of £20,000 the INMB of each treatment compared with control was calculated. The INMB for the SP1 was £12, for the SP2 £52 and for the bMAD £9. Probabilistic sensitivity analysis was used to produce the CEAC and CEAF based on the SF-6D results (*Appendix 13*, *Figure 44*) representing the uncertainty in costs and QALY estimates. This analysis found the SP2 to have the highest probability of being the most cost-effective treatment at all WTP thresholds per QALY. Above a WTP of £20,000, the SP2 had a probability of being the most cost-effective in excess of 95% compared with the SP1, bMAD or no-treatment alternatives.

Summary and discussion

The TOMADO showed that, in mild to moderate OSAH, non-adjustable MADs improved objective and subjective health outcomes over no treatment. Additional improvements diminished with increasing MAD sophistication, but the consistent results across outcomes suggest genuine effects. All devices were cost-effective compared with no treatment based on the point estimates of costs and QALYs. However, differences in EQ-5D-3L QALYs between devices were small and generally non-significant. Probabilistic analysis, accounting for uncertainty in costs and QALYs, showed that the SP2 was the most cost-effective up to a WTP of £39,800/QALY. Above this WTP, the bMAD appeared most cost-effective. These conclusions were robust to a range of realistic assumptions about device costs and durability.

In *Chapter 3* the literature on clinical outcomes for both MADs and other treatment options for OSAH will be reviewed and will incorporate the results of the TOMADO into the wider evidence base using meta-analysis where possible. In the TOMADO study, there were few differences between the different MADs in both clinical outcomes and cost-effectiveness. Additionally, grouping of trials according to different types of MAD will result in imprecise estimates of treatment effects. Therefore, the meta-analyses and cost-effectiveness models will consider MADs as a single comparator, with some examination of the effect of using different MADs in the deterministic sensitivity analysis in *Chapter 4*.

Chapter 3 Systematic review and meta-analysis of trials of treatments for sleep apnoea–hypopnoea

Introduction

In this chapter, a meta-analysis of randomised controlled trials (RCTs) is provided in order to understand how the TOMADO study fits into the total evidence on effectiveness of treatments for OSAH, and to provide input into the decision analysis in subsequent chapters. The focus is on those outcomes of the AHI and ESS that will directly inform the decision analysis, although sleep-related QoL questionnaires that were part of TOMADO and which were identified in our searches are also reviewed. This work builds on previous reviews and meta-analyses of both MADs, by Lim *et al.*,[51] and CPAP, by McDaid *et al.*[8]

Lim *et al.*,[51] in a Cochrane review conducted in 2009, identified 17 RCTs involving 831 patients. They concluded that MADs were effective in reducing AHI, ESS score and other measures of sleep-disordered breathing compared with CM but they were less effective than CPAP. The effects on QoL scales and symptoms were unclear because of the small numbers of studies reporting results and the differences in instruments used, and a need for further research in this area was highlighted. Similarly, the effects of MADs on cardiovascular risks and BP were inconclusive because of small numbers of patients, short follow-up and differences between trials in the outcomes chosen. This review noted the heterogeneity in populations studied, particularly in severity of OSAH at baseline, which complicates comparisons between MADs and CPAP. Thus, it is important to stratify for baseline severity when comparing these two treatments.

McDaid *et al.*[8] was a health technology assessment and decision analysis published in 2009 that focused on the use of CPAP in OSAH, with both no active treatment and MADs used as controls in separate analyses. They identified 48 studies reporting any clinical effectiveness, 29 of which included ESS score as the primary outcome. Most studies included people with severe disease according to baseline AHI. The effect of treatment on ESS score compared with CM was related to this baseline severity, reinforcing the need for stratification. There was less evidence of a difference between CPAP and MADs on ESS score. Reasons for this were difficult to determine as a result of the small number of trials directly comparing these treatments, but others have also noted only moderate correlation between AHI and ESS score.[14] In common with the review by Lim *et al.*,[51] the results comparing secondary end points such as QoL and cardiovascular risks were inconclusive because of the small numbers of trials and patients, short follow-up and heterogeneous outcome measures. McDaid *et al.*[8] also developed a lifetime cost-effectiveness model and conducted extensive analysis, which will be reviewed further in the next chapter. In addition, the authors highlighted a number of areas requiring further study, including the need for robust information on secondary outcomes, such as QoL and cardiovascular outcomes and trials focusing on patients with mild disease.

Methods

Primary objectives

The primary objective was to update previously conducted systematic reviews of the effect on OSAH of treatment by MADs and by CPAP compared with each other and with no active treatment. However, this review will be stratified by severity of OSAH.

To estimate the effect on AHI and ESS score of treatment by MADs and by CPAP compared with each other and with controls in three meta-analyses of RCTs. Heterogeneity as a result of OSAH severity, trial methodology and duration of follow-up will be assessed. Results from this analysis will feed directly into the economic modelling in *Chapter 4*.

Secondary objectives

The secondary objectives were to estimate the effect on the secondary outcomes, daytime BP and the QoL scales SAQLI and FOSQ, of treatment by MADs and by CPAP compared with each other and with controls for use in the long-term cost-effectiveness model, for mild to moderate OSAH.

Long-term effects of treatment on cardiovascular risk and RTAs will be assessed as part of the decision model development described in *Chapter 4* and are not studied further here.

Search strategy

The systematic review searched for all RCTs of adult OSAH patients in which at least one arm was randomised to MAD or CPAP. Studies comparing two different MADs or two different types of CPAP delivery were excluded since the differences between treatment modalities are known to be small and numerous different devices were trialled. Animal studies and non-randomised studies were excluded. Trials published in a language other than English were excluded.

Information sources

The search strategy updated two existing systematic reviews[8,51] to August 2013 (see *Appendix 14* for full search strategies). The main stages of the search are described below:

1. All studies from the published McDaid *et al.*[8] systematic review were included. McDaid *et al.*[8] (York University Centres for Reviews and Dissemination and for Health Economics) searched 14 databases up to November 2006 and included all RCTs of CPAP compared with either MADs or a non-MAD control. This search was repeated in 2012 by McDaid *et al.*[8] and the results were shared with the TOMADO group. This search strategy was again replicated, by the same authors, to retrieve articles from March 2012 to August 2013 using MEDLINE, EMBASE and the Science Citation Index, the three most sensitive databases reported by McDaid *et al.*,[8] in order to identify recent trials.
2. The search by McDaid *et al.*[8] did not include studies of MADs against non-CPAP controls. Therefore, additional papers were identified from the review by Lim *et al.*,[51] and an updated version of the Lim strategy rerun to cover the period June 2008 to August 2013, using MEDLINE, EMBASE and the Science Citation Index.
3. Reference lists of papers were also searched and were supplemented by the research team's knowledge of the area to identify other trials missed in updated searches.

Inclusion criteria

All studies identified in the previously published McDaid *et al.*[8] and Lim *et al.* [51] searches were reviewed. For the subsequent searches, titles and abstracts were screened independently for relevance by two members of the TOMADO team (two of MB, MG, AC-J, RC and MP). Disagreements were resolved by consensus.

Patients
Full papers were retrieved for RCTs of adult patients (≥ 16 years) with newly diagnosed or existing OSAH of any severity and confirmed using an appropriate method such as PSG. Studies were excluded if OSAH was not the predominant diagnosis. Studies of patients with sleep-disordered breathing that was predominantly associated with heart disease, stroke or dementia were excluded.

Interventions
Any trial with at least one randomised comparison of (i) MADs (fixed or adjustable) with non-CPAP controls, (ii) CPAP (fixed or autotitrating) with non-MAD controls or (iii) MADs (fixed or adjustable) with CPAP (fixed or autotitrating) were included. Studies were excluded if they did not include at least one of these randomised comparisons. Trials in which the treatment duration was ≤ 1 week were excluded since this period was considered inadequate to produce a treatment effect. Conservative care included usual care, recommendation to lose weight or reduce alcohol consumption, sham device, placebo pill or postural device aimed at discouraging sleeping in the supine position. Although data were extracted in studies in which a surgical intervention was compared with either MADs or CPAP, this was not considered to be CM and the studies were excluded from the meta-analysis.

Trial methods
Both parallel-group and crossover designs were included. There were no period effects in the primary outcomes of the TOMADO crossover study in which a 1-week washout period was used. Moreover, the prevailing opinion is that treatment effects persist for only a short time after stopping.[8,33] Therefore, inclusion criteria did not include washout periods for crossover trials and results from all available periods were used in the analysis.

Outcome measurements
The primary outcomes were AHI and ESS score. Secondary outcomes were total SAQLI, total FOSQ, SBP, DBP, cardiovascular risk and incidence of RTAs. (Cardiovascular risk and RTAs will be reported in *Chapter 4*.)

Data extraction
For previously published reviews, estimates of treatment effects recorded in the relevant papers were used, with the exception of a small number of transcribing errors identified and corrected in this meta-analysis.[8,51] For the newly identified studies, information from full papers was extracted independently by two members of the TOMADO study team (two of MB, MG, AC-J, RC and MP) and entered onto a bespoke data extraction form. Any queries were resolved by consensus. Studies that were reported only as abstracts were included provided that they included sufficient information to confirm inclusion criteria and details of results that could be used in one of the meta-analyses. For the updated review of MADs, if data in the published abstract, index paper, or a related publication were unclear, the authors were approached for further information. Owing to the timescale of the study it was not possible to pursue authors of trials involving CPAP for data that were not published in the abstract, index paper, or a related publication.

Data extracted included details of the patient population and baseline characteristics, intervention and comparator, outcome measurements, details of trial methodology, treatment duration and results.

Mean differences between the groups for continuous outcomes, and SEs of the group differences, were extracted for the meta-analysis. Outcomes at the end of the treatment period were preferred. In a small number of studies only the change in the outcome measure was reported, and this was included on the basis that the expected values of baseline measurements in randomised trials should be equivalent, although the SEs may be inaccurate.

Quality assessment

The Jadad score was calculated as a measure of quality that also facilitated consistency with previous published reviews.[8,51] For studies from previously published reviews, the scores were reassessed and any discrepancies between published and new Jadad scores were resolved by discussion. For newly identified studies and where it was missing from studies in published reviews, the Jadad score was calculated by one reviewer and checked by a second.

Publication bias

Funnel plots were examined as an informal method of assessing publication bias. These plots showed little evidence of asymmetry but, with the exception of analyses of primary outcomes for comparisons of CPAP against CM, the numbers of studies were too small to allow more formal analysis.

Data analysis

Three separate series of meta-analyses were conducted, one for each of the comparisons (i) MAD with non-CPAP controls, (ii) MAD with CPAP and (iii) CPAP with non-MAD controls. Meta-analyses used random-effects methods and were implemented using *metan* and related commands in Stata version 13.0.[64] In brief, this model was formulated as follows. From each study, *i*, we have an estimate of the treatment effect compared with the control treatment as $\hat{\beta}_i$ and we assume that these estimates follow a Gaussian distribution with,

$$\hat{\beta}_i|\beta_i \sim N(\beta_i, \sigma_i^2) \tag{3}$$

where β_i is the underlying mean treatment effect and σ_i^2 is the standard error in trial *i*. We assume that the trials are exchangeable a priori and that the underlying trial parameters β_i are drawn from a Gaussian distribution with mean $\mu = E[\beta_i]$ and variance $\tau^2 = \text{Var}[\beta_i]$.

The methods used in Stata follow DerSimonian and Laird,[64] who take a classical approach to random-effects meta-analysis. The expected treatment effect μ is estimated as the weighted average,

$$\hat{\mu} = \sum \hat{\beta}_i \widehat{w}_i / \widehat{w}_i \tag{4}$$

where the weights are given by the inverse of the estimated total variance $\widehat{w}_i = 1/(\sigma_i^2 + \tau^2)$.

The SE of $\hat{\mu}$ is approximated by $\sqrt{(1/\sum \widehat{w}_i)}$ and an approximate 95% CI is given by,

$$\hat{\mu} \pm 1.96\sqrt{(1/\sum \widehat{w}_i)}. \tag{5}$$

Although the data analysis in TOMADO was consistent with an overdispersed Poisson distribution for AHI results, which is usual for an event rate, all other publications assumed that AHI followed a Normal distribution. Therefore, the TOMADO results were reanalysed assuming that AHI was Normally distributed, and this estimate is included in the meta-analysis for consistency. For studies in which the rate is of the order of 20, the Normal distribution is a valid approximation, but for smaller values the SEs will be biased, and this should be taken into account when interpreting results.[65] All other outcomes were assumed to be Normally distributed. The SE term σ_i^2 was estimated by the within-trial SE error. Where only 95% CIs were available the SE was estimated using (upper limit – lower limit)/3.92.

The FOSQ has been calculated according to the original scoring system[56] in some papers and according to the revision (manual scoring revision dated 11 July 2000) in others. Where possible, the scores have been recalculated according to the latter.

Heterogeneity between studies was represented by the I^2-statistic and the chi-squared test for heterogeneity.[66] In order to investigate the sources of heterogeneity, the combined treatment effects for AHI and ESS score were re-estimated in each of the following subgroups:

1. Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99), moderate (AHI 15–29.99 events/hour, DI 10–29.99) and severe (AHI > 30 events/hour, DI > 30).
2. Mean baseline ESS score: mild (0–9), moderate (10–15) and severe (16–24).
3. Study design: parallel and crossover.
4. Treatment duration for studies involving MADs: short (2–12 weeks) and long (> 12 weeks); and for studies of CPAP against CM: short (2–4 weeks) medium (5–12 weeks) and long (> 12 weeks).

In addition, trial results for mild and moderate OSAH groups were combined and results recalculated to feed into the economic model in *Chapter 4*.

Results

Quantity and quality of studies

Figure 20 summarises studies identified at each stage of the search process. The updated search conducted by York Centre for Health Economics, which was responsible for the McDaid *et al.*[8] review, and the two searches conducted by the TOMADO team identified 7341 references. After removing duplicates and adding in additional references from other sources, the total number screened for relevance was 4404. After screening, 83 full articles were retrieved and read in detail, of which 27 were eligible for inclusion in the study. These were combined with 44 studies identified from previous reviews that satisfied the inclusion criteria and that had not been superseded by a later publication from the same study. These 71 studies are listed in *Appendix 15*. Three studies included comparisons involving MADs, CPAP and CM and so each contribute to three separate comparisons, a total of 77 separate comparisons.[23,67,68] There was a greater number of studies of the effectiveness of CPAP than of MADs (*Figure 20*). The characteristics of the 56 excluded studies are listed in *Appendix 16*.

Summary of included studies

Summaries of the baseline characteristics for the included studies are shown in *Tables 29–31* for the three comparisons. There were 12 studies including 629 patients that compared MADs with CM, 13 studies with 746 patients comparing MADs with CPAP, and 52 studies with 5400 patients comparing CPAP with CM.

Patient characteristics

Most studies were conducted in males, with the reported proportion ranging from 65% to 100% (median 81%). The reported mean ages ranged from 44.0 years to 59.2 years. Most trial populations were overweight or obese with reported mean BMI ranging from 28.3 kg/m^2 to 35.1 kg/m^2.

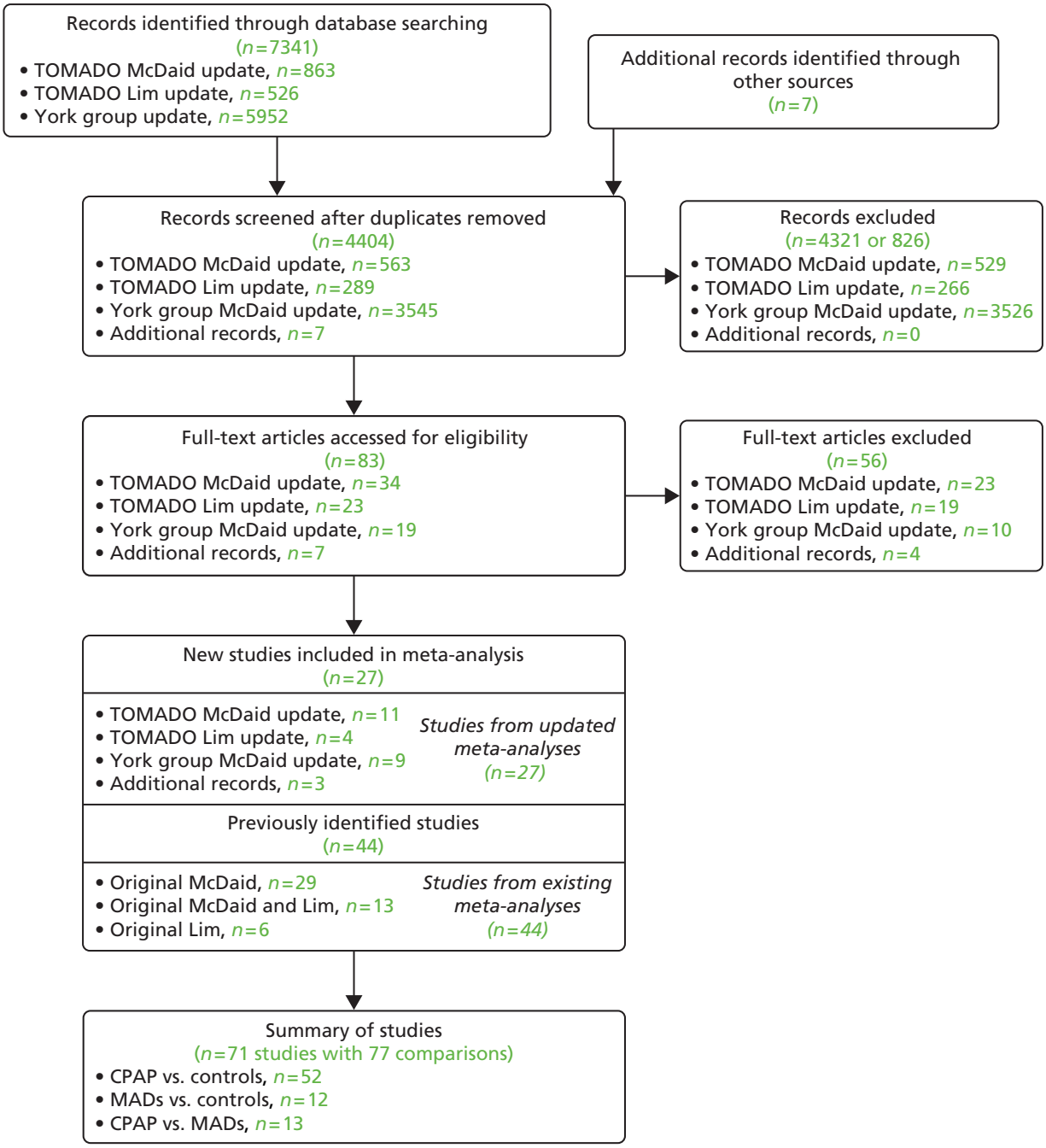

FIGURE 20 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

TABLE 29 Baseline characteristics of patients and study designs for trials of MADs compared with non-CPAP controls

Study	Design	Number randomised (analysed)	Baseline severity (AHI or DI)	Baseline symptom severity (ESS score)	Duration of each treatment (weeks)
Aarab 2011[68]	P	42	Moderate	Moderate	26
Andrén 2013[69]	P	72	Moderate	Moderate	13
Barnes 2004[23]	C	80	Moderate	Moderate	12
Blanco 2005[70]	P	24 (15)	Severe	Severe	13
Duran 2002[71]	C	44 (38)	Mild	NR	NR
Gotsopoulos 2002[72]	C	85 (73)	Moderate	NR	4
Hans 1997[73]	P	24	Moderate	NR	NR
Johnston 2002[74]	C	21 (18)	Severe	Moderate	4–6
Lam 2007[67]	P	67	Moderate	Moderate	10
Mehta 2001[75]	C	28	Moderate	NR	3
Petri 2008[76]	P	52	Severe	Moderate	4
TOMADO 2014[77]	P	90	Mild	Moderate	4

C, crossover; NR, not recorded or unclear; P, parallel.
Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).

TABLE 30 Baseline characteristics of patients and study designs for trials of MADs compared with CPAP

Study	Design	Number randomised	Baseline severity (AHI or DI)	Baseline symptom severity (ESS score)	Duration of each treatment (weeks)
Aarab 2011[68]	P	43	Moderate	Moderate	26
Barnes 2004[23]	C	80	Moderate	Moderate	12
Engelman 2002[22]	C	51 (48)	Severe	Moderate	8
Ferguson 1996[78]	C	27	Moderate	NR	17
Ferguson 1997[79]	C	24 (19)	Moderate	NR	17
Fleetham 1998[80]	P	101	Severe	Moderate	12
Hoekema 2008[81]	P	103	Severe	Moderate	8
Gagnadoux 2009[24]	C	59	Severe	Moderate	8
Lam 2007[67]	P	68	Moderate	Moderate	10
Olson 2002[82]	C	24	NR	NR	14
Phillips 2013[52]	C	122	Moderate	Moderate	4
Randerath 2002[83]	C	20	Moderate	NR	6
Tan 2002[84]	C	24 (21)	Moderate	Moderate	8

C, crossover; NR, not recorded or unclear; P, parallel.
Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).

TABLE 31 Baseline characteristics of patients and study designs for trials of CPAP compared with non-MAD controls

Study	Design	Number randomised	Baseline severity (AHI or DI)	Baseline symptom severity (ESS score)	Duration of each treatment (weeks)
Aarab 2011[68]	P	43	Moderate	Moderate	26
Arias 2005[85]	C	27	Severe	NR	12
Arias 2006[86]	P	23	Severe	NR	12
Ballester 1999[87]	P	105	Severe	Moderate	12
Barbé 2001[88]	P	55	Severe	Mild	6
Barbé 2012[89]	P	725	Severe	Mild	156
Barnes 2002[90]	C	42	Mild	Moderate	8
Barnes 2004[23]	C	80	Moderate	Moderate	12
Becker 2003[91]	P	60	Severe	Moderate	9
Campos-Rodriguez 2006[92]	P	72	Severe	Moderate	4
Chakravorty 2002[93]	P	71	Severe	Severe	12
Coughlin 2007[94]	C	35	Severe	Moderate	6
Craig 2012[95]	P	391	Mild	Mild	26
Diafera 2013[96]	P	100	Severe	Moderate	13
Drager 2006[97]	P	16	Severe	NR	12
Drager 2007[98]	P	24	Severe	Moderate	17
Durán-Cantolla 2010[99]	P	340	Severe	Moderate	12
Engleman 1996[100]	C	16	Severe	NR	3
Engleman 1997[101]	C	18	Mild	Moderate	4
Engleman 1998[102]	C	23	Severe	Moderate	4
Engleman 1999[103]	C	37	Mild	Moderate	4
Faccenda 2001[104]	C	71	Severe	Moderate	4
Haensel 2007[105]	P	50	Severe	NR	2
Henke 2001[106]	P	45	Severe	Severe	2
Hoyos 2012[107]	P	65	Severe	Moderate	12
Hui 2006[108]	P	56	Severe	Moderate	12
Jenkinson 1999[109]	P	107	Moderate	Severe	4
Kaneko 2003[110]	P	21	Severe	Mild	4
Kushida 2012[25]	P	1105	Severe	Moderate	26
Lam 2007[67]	P	67	Moderate	Moderate	10
Lee 2012[111]	P	71	Severe	Moderate	3
Lozano 2010[112]	P	75	Severe	Mild	13
Mansfield 2004[113]	P	55	Moderate	Moderate	12
Marshall 2005[114]	C	31	Moderate	Moderate	3
Monasterio 2001[115]	P	142	Moderate	Moderate	24
Montserrat 2001[116]	P	46	Severe	Severe	6

TABLE 31 Baseline characteristics of patients and study designs for trials of CPAP compared with non-MAD controls (*continued*)

Study	Design	Number randomised	Baseline severity (AHI or DI)	Baseline symptom severity (ESS score)	Duration of each treatment (weeks)
Norman 2006[117]	P	33	Severe	Moderate	2
Pepperell 2002[34]	P	118	Severe	Severe	4
Phillips 2011[118]	C	20	Severe	Moderate	8
Redline 1998[119]	P	111	Moderate	Moderate	8
Robinson 2006[120]	C	35	Moderate	Mild	4
Sharma 2011[121]	C	90	Severe	Moderate	13
Siccoli 2008[18]	P	102	Severe	Moderate	4
Simpson 2012[122]	P	36	Severe	NR	12
Skinner 2004[123]	C	10	Moderate	Moderate	4
Skinner 2008[124]	C	20	Moderate	Moderate	4
Spicuzza 2006[125]	P	25	Severe	NR	4
Tomfohr 2011[126]	P	71	Severe	Moderate	3
von Känel 2006[127]	P	28	Severe	NR	2
Weaver 2012[128]	P	281	Mild	Moderate	8
Weinstock 2012[129]	C	50	Severe	NR	8
West 2007[130]	P	42	NR	Moderate	12

C, crossover; NR, not recorded or unclear, P, parallel.
Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).

In general, CPAP trials were conducted in patients with higher AHI/ESS score at baseline. Two trials did not give sufficient information to determine baseline AHI. Of the 51 comparisons of CPAP with non-MAD controls that did record average baseline AHI, 35 (69%) were in patients with an average AHI > 30 events/hour (severe OSAH) compared with three of the 12 (25%) trials comparing MAD with non-CPAP controls. Most trials (7 of 12, 58%) comparing MAD with non-CPAP controls were in patients with moderate AHI at baseline. For direct comparisons of MAD with CPAP, one did not record baseline AHI; eight of the remaining 12 (67%) reported moderate and four (33%) reported severe baseline OSAH according to AHI on average.

Average baseline ESS score, the main subjective measure of daytime sleepiness, was available for 60 comparisons. All nine trials comparing MAD with CPAP and seven of the eight (88%) trials comparing MAD with non-CPAP controls reported moderate mean baseline ESS score. Of the 43 comparisons of CPAP with non-MAD controls, six (14%) had mild and five (12%) had severe mean baseline ESS score; the remaining 32 reported moderate baseline daytime sleepiness.

Intervention and comparators

Of the 25 trials involving MADs, 13 (52%) used adjustable devices, 10 (40%) used fixed devices and two (8%) did not report the type. In 13 trials (52%), the MADs were compared with CPAP. Of the others, nine (36%) used a sham MAD and one compared MADs with a placebo tablet, one with conservative treatment and one with no treatment.

Of the 65 trials involving CPAP, most (54, 83%) used fixed CPAP, six (9%) were autotitrating and five (8%) did not report this information. Excluding the 13 trials comparing CPAP with MADs, 29 of 52 (56%) compared CPAP with a sham version, seven (13%) with placebo tablet and nine (13%) with conservative treatment or no treatment.

Study design

The median number of cases randomised in MAD compared with control trials was 48 (range 21–91). The corresponding median number for MADs compared with CPAP was 51 (range 20–122) and, for CPAP compared with control, the median was 52 (range 10–1105). Duration of treatment during trials was generally short, with 60 of 76 trials (79%) that reported it having a treatment period of ≤ 12 weeks. Nine of 13 trials (69%) in which MADs were compared with CPAP had a crossover design, compared with 6 of 12 trials (50%) comparing MAD with other controls and 16 of 52 (31%) comparing CPAP with other controls.

Study quality

The Jadad score[131] was calculated as a broad measure of quality of the studies and this was available for 69 of the 71 trials. Two studies comparing MADs against CPAP were available only in summary form in previous reviews, so that Jadad scores could not be calculated.[80,82] Of the 69 studies with Jadad scores, 68 (99%) were clearly described as randomised and one was not.[125] The method of randomisation was judged 'clearly described and appropriate' in 31 trials (45%). Only 27 trials (39%) were described as double blind, 25 of which compared CPAP with a sham device and two compared a MAD with a non-therapeutic device. The method of blinding was judged 'clearly described and appropriate' in 19 of the 27 trials (70%). Withdrawals and drop-outs were clearly described in 60 (87%), with no differences between trial comparisons in this regard. The mean Jadad score was 2.9 in comparisons of MADs with non-CPAP controls, 2.3 in MADs against CPAP comparisons and 3.1 in CPAP against non-MAD controls, with the lower mean scores in head-to-head comparisons mainly attributable to the difficulty in blinding when two active treatments are compared.

Assessment of effectiveness

Results are organised by outcome measure, with each section including the three comparisons, MADs with non-CPAP control, MADs with CPAP and CPAP with non-MAD control.

Primary outcome I: apnoea–hypopnoea index

Mandibular advancement devices compared with non-continuous positive airway pressure controls

Twelve studies, including TOMADO, and 629 patients provided an estimate of the effect of AHI, but one of these[69] provided only a point estimate and could not be included in the meta-analysis (*Figure 21*). After combining the studies, the mean difference (reduction) in AHI for MADs compared with control groups was −9.29 (95% CI −12.28 to −6.30; $p < 0.001$). There was significant heterogeneity between studies ($I^2 = 60\%$; $p = 0.005$). *Figure 22* suggests that this partly arises from differences in baseline AHI, although the relationship is not monotonic and heterogeneity within these strata remains. Note that only two studies were in patients with mild OSAH and the treatment effect for these studies differed by more than nine events per hour. Seven studies reported baseline ESS score, of which six had moderate EDS according to ESS score; the other had severe EDS. Restricting analysis to the six studies with moderate EDS according to baseline ESS score resulted in less heterogeneity ($I^2 = 35$; $p = 0.177$), with mean difference in AHI as a result of MADs of −6.69 (95% CI −8.98 to −4.41) (*Table 32*). Six of the 11 studies had a crossover design and these studies had more heterogeneous results than parallel-group trials (*Table 32*). Treatment effects were greater in crossover trials than in parallel-groups designs, although the difference was not large. In addition, treatment effects in trials of short duration were larger than in longer-term trials, which may indicate reduced compliance over time or progression in the underlying mechanisms of OSAH.

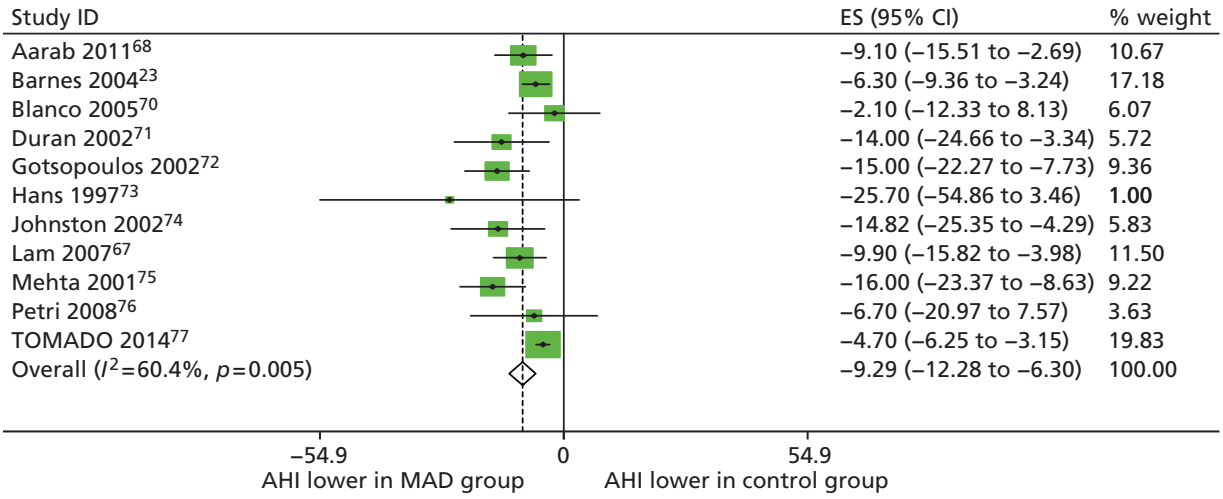

FIGURE 21 Meta-analysis of AHI results from trials of MADs compared with CM. Note that weights are from random-effects analysis. ES, effect size.

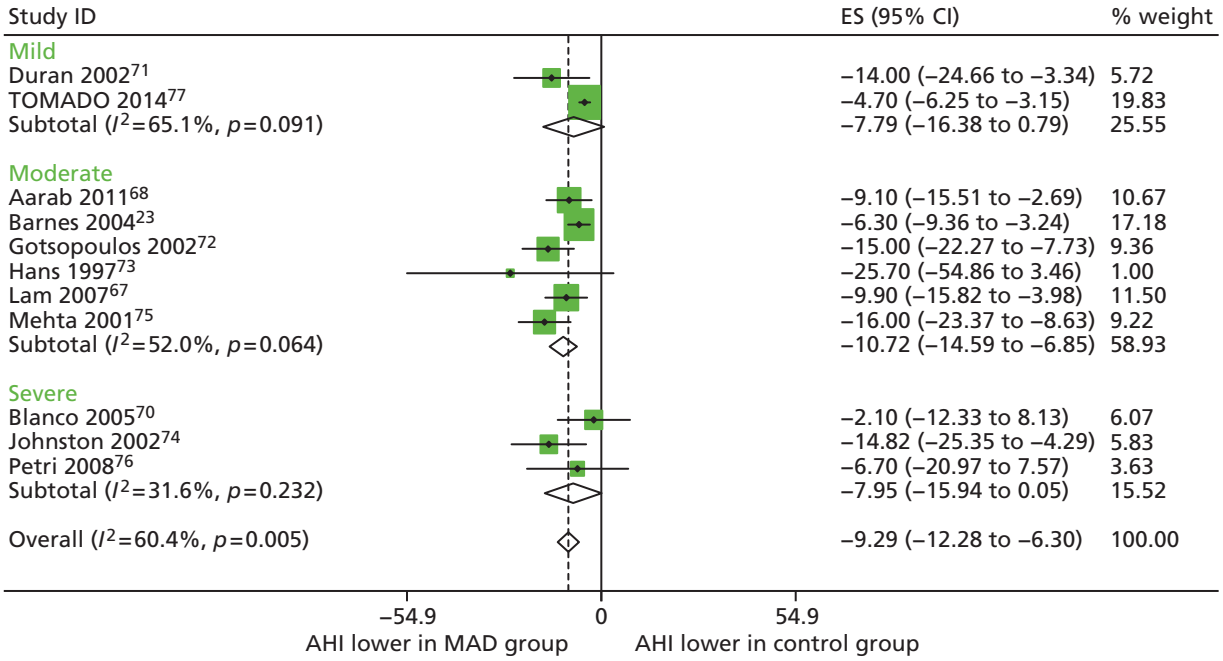

FIGURE 22 Meta-analysis of AHI results from trials of MADs compared with CM, stratified by baseline AHI. Note that weights are from random-effects analysis. Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30). ES, effect size.

TABLE 32 Subgroup analysis of AHI results (events per hour) for comparison of MADs with non-CPAP controls (negative estimates favour MAD)

Subgroup	Number of studies	Difference in AHI: MAD–control (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Mild	2	−7.79 (−16.38 to 0.79)	0.075	65%	0.091
Moderate	6	−10.72 (−14.59 to −6.85)	< 0.001	52%	0.064
Severe	3	−7.95 (−15.94 to −0.05)	0.051	32%	0.232
Baseline ESS score					
Moderate	6	−6.69 (−8.98 to −4.41)	< 0.001	35%	0.177
Severe	1	−2.10 (−12.33 to 8.13)	0.687	–	–
Trial design					
Crossover	6	−10.17 (−14.27 −6.07)	< 0.001	76%	0.001
Parallel	5	−8.57 (−12.39 to −4.75)	< 0.001	0%	0.533
Duration of treatment					
2–12 weeks	8	−9.69 (−13.27 to −6.12)	< 0.001	68%	0.003
> 12 weeks	3	−6.78 (−13.24 to −0.33)	0.039	23%	0.560
Overall MAD compared with control					
Overall	11	−9.29 (−12.28 to −6.30)	< 0.001	60%	0.005

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.

Mandibular advancement devices compared with continuous positive airway pressure

Thirteen trials including 746 patients compared MADs with CPAP. The estimated overall difference in AHI was 7.03 events/hour (95% CI 5.41 to 8.66 events/hour; $p < 0.001$), with post-treatment AHI being lower in those treated with CPAP than in those treated with MADs (*Figure 23*). Again there was important heterogeneity between study results, with smaller studies[78–80,82] and early studies[75–80] estimating greater effects than larger and later studies. No MADs–CPAP head-to-head comparisons were reported in patients with mild baseline AHI (*Table 33*). Estimates of the difference in post-treatment AHI were consistent and were not related to baseline AHI, baseline ESS score, trial design or duration of treatment, with all significantly lower after CPAP (*Table 33*).

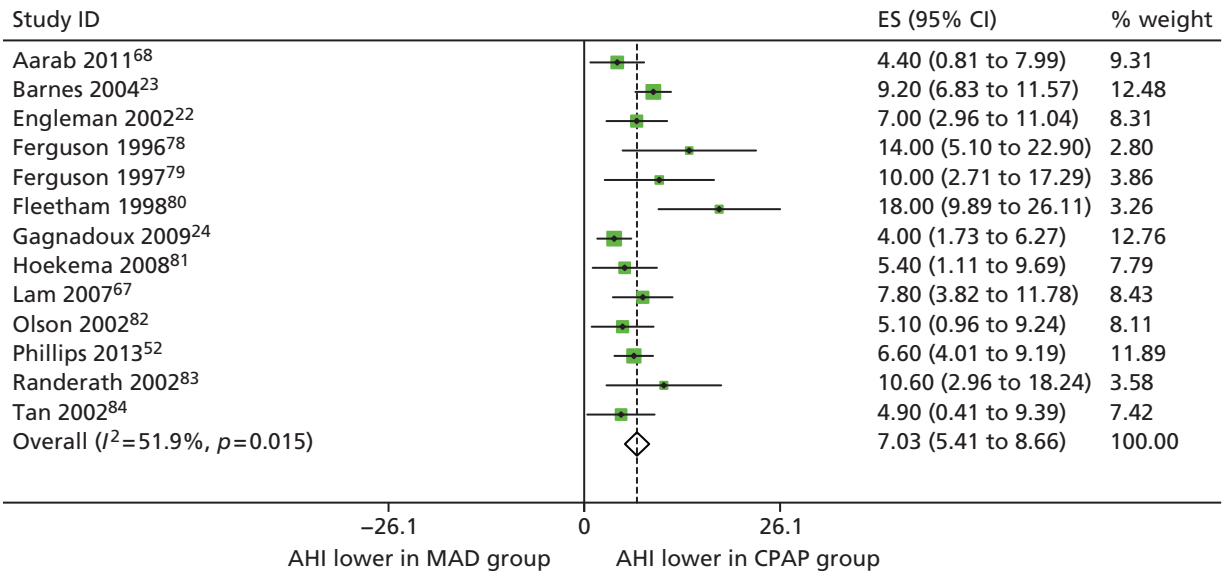

FIGURE 23 Meta-analysis of AHI results from trials of MADs compared with CPAP. Note that weights are from random-effects analysis. ES, effect size.

TABLE 33 Subgroup analysis of AHI results (events per hour) for comparison of MADs with CPAP (positive estimates favour CPAP)

Subgroup	Number of studies	Difference in AHI: MAD–CPAP (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Moderate	8	7.48 (5.77 to 9.19)	< 0.001	28%	0.203
Severe	4	7.22 (3.20 to 11.25)	< 0.001	74%	0.010
Baseline ESS score					
Moderate	9	6.70 (4.86 to 8.54)	< 0.001	57%	0.098
Trial design					
Crossover	9	6.91 (5.11 to 8.71)	< 0.001	48%	0.054
Parallel	4	7.72 (3.58 to 11.87)	< 0.001	69%	0.022
Duration of treatment					
2–12 weeks	9	7.19 (5.25 to 9.12)	< 0.001	59%	0.013
> 12 weeks	4	6.78 (3.25 to 10.31)	< 0.001	42%	0.157
Overall MAD compared with CPAP					
Overall	13	7.03 (5.41 to 8.66)	< 0.001	52%	0.015

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.
Treatment duration for studies involving MAD: short (2–12 weeks) and long (> 12 weeks); and for studies of CPAP against no active treatment controls: short (2–4 weeks), medium (5–12 weeks) and long (> 12 weeks).

Continuous positive airway pressure compared with non-mandibular advancement device controls

Of the 52 trials comparing CPAP with CM, 25 trials including 1596 patients reported post-treatment AHI. The estimated effect from combining these studies was −25.37 (95% CI −30.67 to −20.07; $p < 0.001$) (*Figure 24*). There was a significant amount of heterogeneity between study results, both overall and within strata. Some of this is explained by baseline AHI, and the potential for treatment effect is naturally governed by the extent of disease in the population. Only one of these studies was in patients with mild baseline AHI[128] and the estimated mean effect in this trial was small at −2.40 events/hour (95% CI −3.67 to −1.13 events/hour). Moreover, the mean difference in AHI between CPAP and control patients

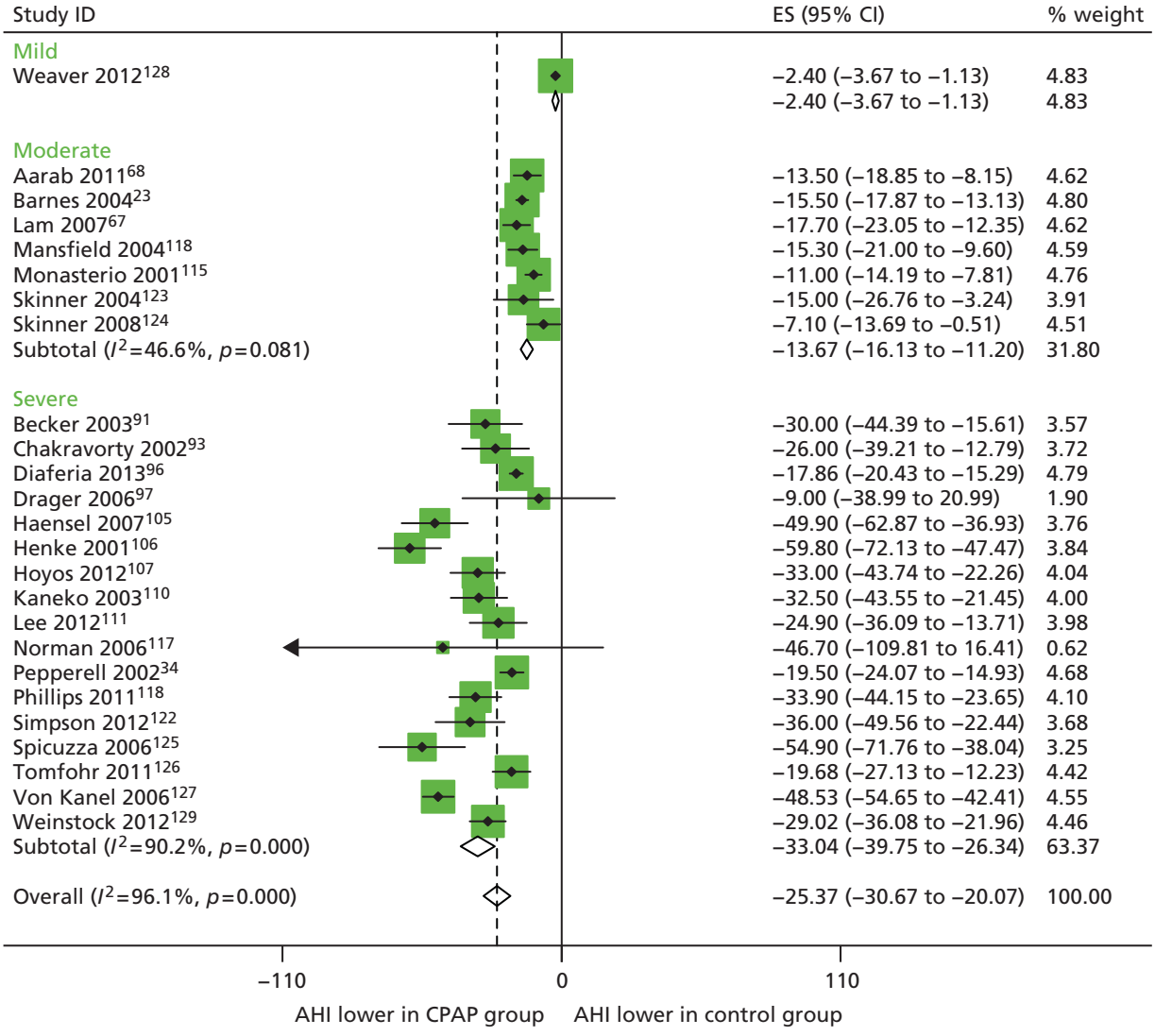

FIGURE 24 Meta-analysis of AHI results from trials of CPAP compared with CM, stratified by baseline AHI. Note that weights are from random-effects analysis. ES, effect size.

increased with baseline severity, from −13.67 (95% CI −16.13 to −11.20) for moderate OSAH according to AHI at baseline to −33.04 (95% CI −39.75 to −26.34) for severe (*Table 34*). The pattern was somewhat different for groups defined by the baseline measure of subjective daytime sleepiness, i.e. the ESS score. Only one study reported mild baseline EDS according to ESS score[110] but had severe baseline OSAH according to AHI, so that the estimated effect of CPAP on AHI was large at −32.50 (95% CI −43.55 to −21.45) (*Table 34*). However, the studies in patients with moderate baseline EDS according to ESS score reported a smaller effect of CPAP compared with controls than those with severe baseline EDS. There was some evidence that the treatment effect was lower for crossover trials than for parallel-group trials and for trials with longer treatment duration (*Table 34*).

TABLE 34 Subgroup analysis of AHI results (events/hour) for comparison of CPAP with non-MAD controls (negative estimates favour CPAP)

Subgroup	Number of studies	Difference in AHI: CPAP–control (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Mild	1	−2.40 (−3.67 to −1.13)	< 0.001	–	–
Moderate	7	−13.67 (−16.13 to −11.20)	< 0.001	47%	0.081
Severe	17	−33.04 (−39.75 to −26.34)	< 0.001	90%	< 0.001
Baseline ESS score					
Mild	1	−32.50 (−43.55 to −21.45)	< 0.001	–	–
Moderate	15	−17.54 (−22.51 to −12.56)	< 0.001	95%	< 0.001
Severe	3	−34.73 (−58.90 to −10.57)	0.005	95%	< 0.001
Trial design					
Crossover	5	−19.71 (−27.95 to −11.48)	< 0.001	87%	< 0.001
Parallel	20	−27.08 (−33.68 to −20.48)	< 0.001	97%	< 0.001
Duration of treatment					
2–4 weeks	11	−32.90 (−43.78 to −22.02)	< 0.001	93%	< 0.001
5–12 weeks	11	−22.34 (−29.84 to −14.85)	< 0.001	96%	< 0.001
> 12 weeks	3	−14.25 (−19.03 to −9.46)	< 0.001	82%	0.004
Overall CPAP compared with controls					
Overall	25	−25.37 (−30.67 to −20.07)	< 0.001	96%	< 0.001

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.
Treatment duration for studies of CPAP against no active treatment controls: short (2–4 weeks), medium (5–12 weeks) and long (> 12 weeks).

Primary outcome II: Epworth Sleepiness Scale

Mandibular advancement devices compared with non-continuous positive airway pressure controls

Of the 12 studies, 10 reported a point estimate of the effect of ESS score on MADs, but only nine reported sufficient data to allow calculation of the SE of the treatment effect. These nine studies included 485 patients and the combined treatment effect on ESS score was −1.64 (95% CI −2.46 to −0.82) (*Figure 25* and *Table 35*). Again there was significant heterogeneity between study results, with small studies[70,73] more likely to report large treatment differences. Only the TOMADO study was conducted in patients with mild OSAH according to AHI at baseline, and the effect on ESS score was between, and of a similar order to, estimates from trials in patient groups with moderate and severe baseline AHI. Patients from one trial by Blanco *et al.*[70] reported severe baseline EDS according to ESS score and also reported a large treatment effect. This trial was small, randomising 12 patients to either an advanced or a non-advanced mandibular device for a period of 3 months, and reporting on 20 patients who completed treatment. Excluding this trial and restricting analysis to the six trials that had a moderate baseline EDS according to ESS score resulted in a combined treatment difference of −1.36 (95% CI −2.07 to −0.64; $p < 0.001$). Owing to the small number of trials and the large influence of Blanco's study it is not possible to reliably assess reasons for heterogeneity further.

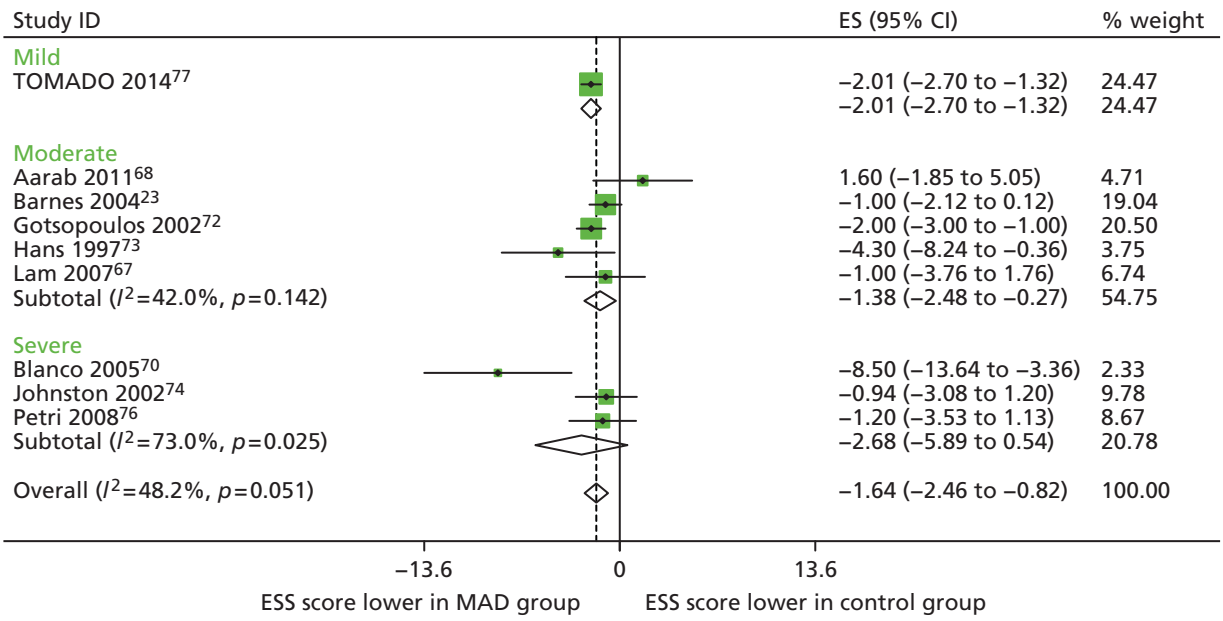

FIGURE 25 Meta-analysis of ESS score results from trials of MADs compared with CM, stratified by baseline AHI. Note that weights are from random-effects analysis. Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30). ES, effect size.

TABLE 35 Subgroup analysis of ESS score results for comparison of MADs with non-CPAP (negative estimates favour MADs)

Subgroup	Number of studies	Difference in ESS score: MAD–controls (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Mild	1	−2.01 (−2.70 to −1.32)	< 0.001	42%	0.142
Moderate	5	−1.38 (−2.48 to −0.27)	0.150	73%	0.025
Severe	3	−2.68 (−5.89 to 0.54)	0.103	48%	0.051
Baseline ESS score					
Moderate	6	−1.36 (−2.07 to −0.64)	< 0.001	–	–
Severe	1	−8.50 (−13.64 to −3.36)	0.001	55%	0.037
Trial design					
Crossover	4	−1.75 (−2.25 to −1.25)	< 0.001	2%	0.380
Parallel	5	−2.18 (−4.80 to 0.44)	0.102	68%	0.015
Duration of treatment					
2–12 weeks	7	−1.75 (−2.22 to −1.28)	< 0.001	0%	0.521
> 12 weeks	2	−3.26 (−13.15 to 6.63)	0.518	90%	0.001
Overall MAD compared with controls					
Overall	9	−1.64 (−2.46 to −0.82)	< 0.001	48%	0.051

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.
Treatment duration for studies involving MAD: short (2–12 weeks) and long (> 12 weeks).

Mandibular advancement devices compared with continuous positive airway pressure

Of the 12 studies directly comparing MADs and CPAP, 10 trials and 675 patients contributed to the meta-analysis of ESS score results, with a combined estimate of 0.67 (95% CI −0.11 to 1.44; $p = 0.093$) (*Figure 26*). The positive estimate indicates that the post-treatment ESS score was lower (better) in the CPAP group. There was less between-study heterogeneity in this analysis and the results of stratified analysis show that any treatment effect is small, with clinically significant differences likely only for those with severe baseline OSAH according to AHI (*Table 36*). However, the number and size of trials remains too small to make reliable conclusions, particularly regarding mild OSAH.

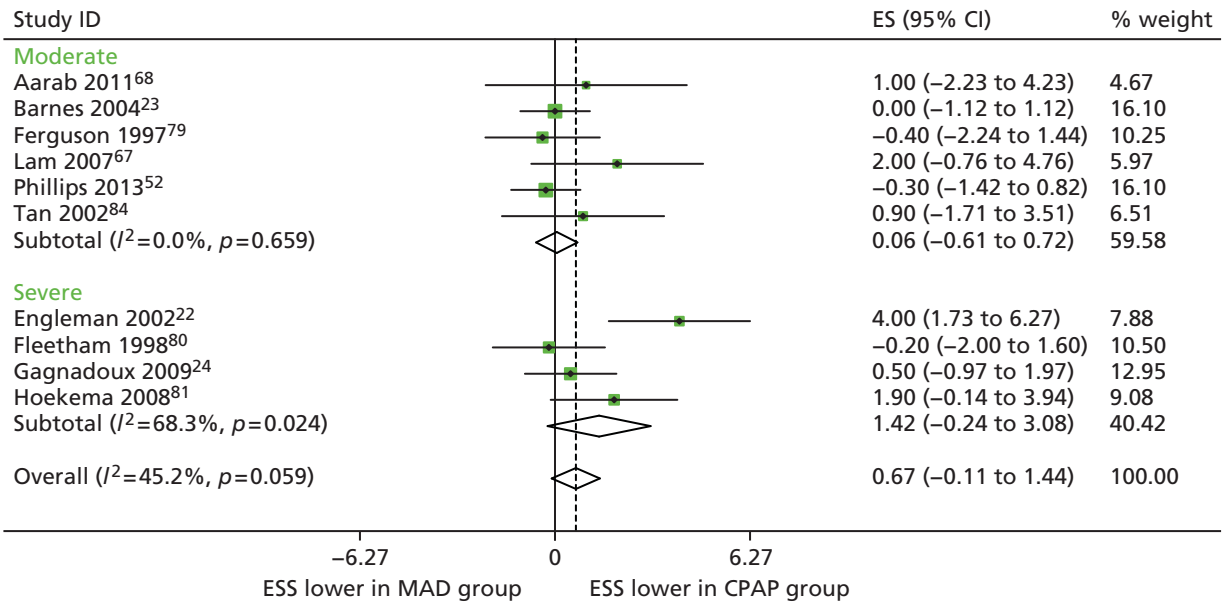

FIGURE 26 Meta-analysis of ESS score results from trials of MADs compared with CPAP, stratified by baseline AHI. Note that weights are from random-effects analysis. ES, effect size.

TABLE 36 Subgroup analysis of ESS score results for comparison of MADs with CPAP (positive estimates favour CPAP)

Subgroup	Number of studies	Difference in ESS score: MAD–CPAP (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Moderate	6	0.06 (–0.61 to 0.72)	0.864	0%	0.659
Severe	4	1.42 (–0.24 to 3.08)	0.094	68%	0.024
Baseline ESS score					
Moderate	9	0.81 (–0.04 to 1.65)	0.062	49%	0.049
Trial design					
Crossover	6	0.54 (–0.48 to 1.57)	0.301	60%	0.030
Parallel	4	0.97 (–0.16 to 2.11)	0.093	0%	0.399
Duration of treatment					
2–12 weeks	8	0.82 (–0.09 to 1.73)	0.078	55%	0.031
>12 weeks	2	–0.06 (–1.66 to 1.54)	0.944	0%	0.461
Overall MAD compared with CPAP					
Overall	10	0.67 (–0.11 to 1.44)	0.093	45%	0.059

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.
Treatment duration for studies involving MAD: short (2–12 weeks) and long (> 12 weeks); and for studies of CPAP against no active treatment controls: short (2–4 weeks), medium (5–12 weeks) and long (> 12 weeks).

Continuous positive airway pressure compared with non-mandibular advancement device controls

Thirty-eight of the 52 trials comparing CPAP with non-MAD controls reported the estimated post-treatment effect on ESS score, with 4894 patients included in the comparisons. These trials are plotted in *Figure 27* and the combined estimate of treatment effect on ESS score was −2.23 (95% CI −2.76 to −1.71; $p < 0.001$). Again there is significant heterogeneity, and some stratified analyses are reported in *Table 37*. In common with AHI, the effect of CPAP on ESS score increases with baseline AHI severity, from −1.23 (95% CI −2.19 to −0.27) for the mild group to −2.64 (95% CI −3.44 to −1.84) for the severe group. A similar but steeper effect is seen with increasing baseline ESS score, the effect increasing from −0.83 (95% CI −1.16 to −0.51) for mild baseline EDS according to ESS score to −4.99 (95% CI −6.51 to −3.47) for severe EDS according to ESS score. The trial design has less impact on outcomes but longer duration of treatment is associated with decreasing treatment effect, which again mirrors the analysis of AHI.

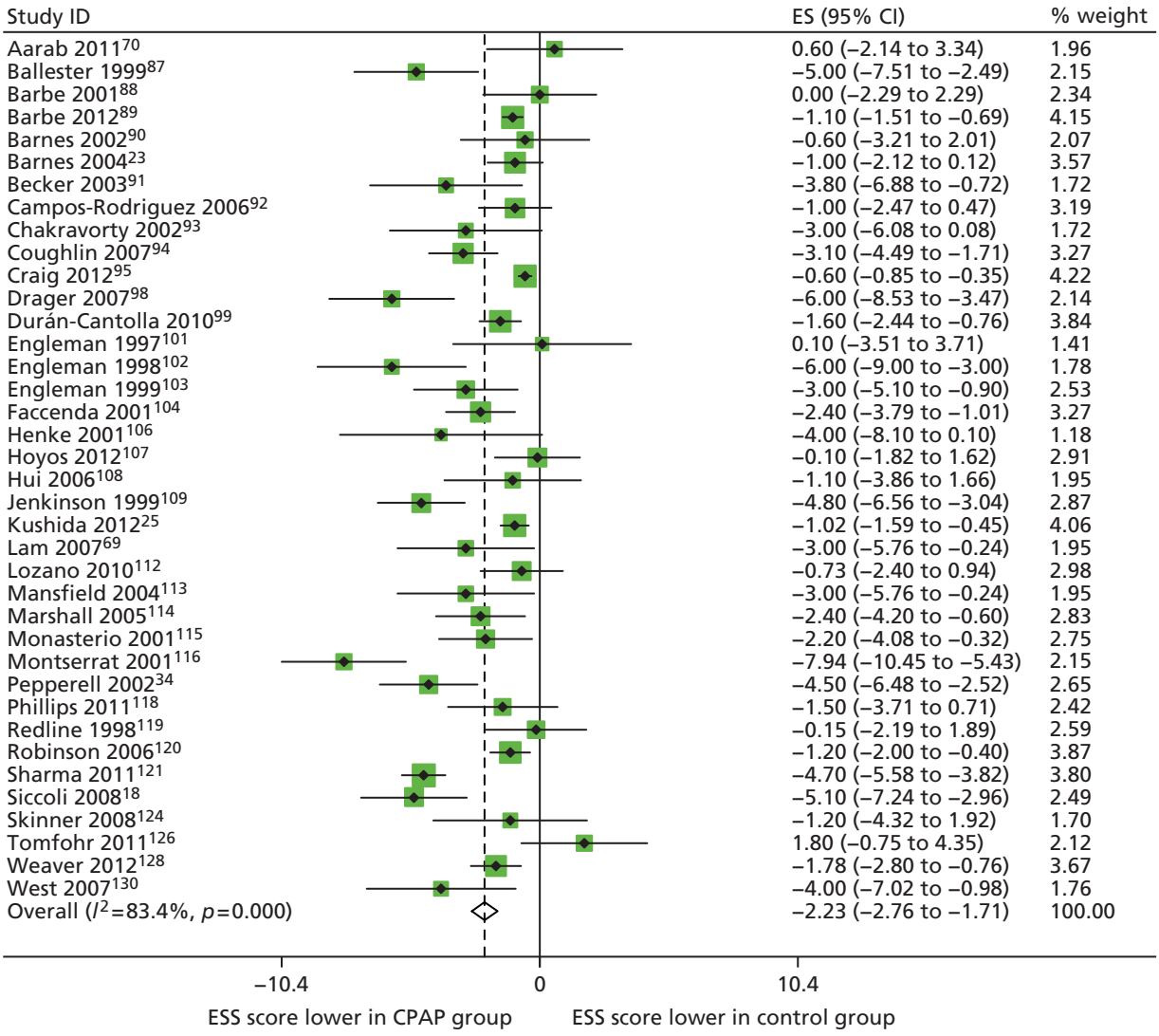

FIGURE 27 Meta-analysis of ESS score results from trials of CPAP compared with CM. Note that weights are from random-effects analysis. ES, effect size.

TABLE 37 Subgroup analysis of ESS score results for comparison of CPAP against non-MAD controls (negative estimates favour CPAP)

Subgroup	Number of studies	Difference in ESS score: CPAP–control (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Baseline AHI					
Mild	5	−1.23 (−2.19 to −0.27)	0.012	59%	0.045
Moderate	10	−1.82 (−2.73 to −0.92)	< 0.001	60%	0.008
Severe	22	−2.64 (−3.44 to −1.84)	< 0.001	86%	< 0.001
Baseline ESS score					
Mild	5	−0.83 (−1.16 to −0.51)	< 0.001	30%	0.222
Moderate	28	−2.19(−2.84 to −1.53)	< 0.001	76%	< 0.001
Severe	5	−4.99 (−6.51 to −3.47)	< 0.001	46%	0.115
Trial design					
Crossover	12	−2.32 (−3.33 to −1.31)	< 0.001	79%	< 0.001
Parallel	26	−2.15 (−2.74 to −1.55)	< 0.001	82%	< 0.001
Duration of treatment					
2–4 weeks	13	−2.58 (−3.66 to −1.51)	< 0.001	75%	< 0.001
5–12 weeks	17	−2.20 (−3.02 to −1.39)	< 0.001	68%	< 0.001
> 12 weeks	8	−1.87 (−2.83 to −0.90)	< 0.001	93%	< 0.001
Overall CPAP compared with controls					
Overall	38	−2.23 (−2.76 to −1.71)	< 0.001	83%	< 0.001

Mean baseline AHI/DI: mild (AHI 5–14.99 events/hour, DI 5–9.99); moderate (AHI 15–29.99 events/hour, DI 10–29.99); and severe (AHI > 30 events/hour, DI > 30).
Mean baseline ESS score: mild (0–9); moderate (10–15); and severe (16–24).
Study design: parallel and crossover.
Treatment duration for studies of CPAP against no active treatment controls: short (2–4 weeks), medium (5–12 weeks) and long (> 12 weeks).

Secondary outcome I: daytime blood pressure

Mandibular advancement devices compared with non-continuous positive airway pressure controls

Of the trials included, five with a total of 394 patients compared daytime SBP and DBP. Two trials were in patients with mild baseline AHI and three with moderate baseline AHI. The combined estimate of the effect of MADs on SBP was small −1.13 mmHg (95% CI −2.17 to −0.10 mmHg; $p = 0.032$) (*Table 38*). Similarly, the effect of MADs on daytime DBP was small, −0.64 mmHg (95% CI −1.70 to 0.49 mmHg; $p = 0.265$). There were too few trials in this analysis to allow stratification by patient and design characteristics.

Mandibular advancement devices compared with continuous positive airway pressure

Three trials with 270 cases with moderate baseline AHI provided treatment effects for daytime SBP and DBP in head-to-head comparisons of MADs and CPAP. There was little difference in post-treatment BP outcomes in these trials, with effect estimates that were neither clinically nor statistically significant (*Table 38*). Again further analysis of these results is not possible.

Continuous positive airway pressure compared with non-mandibular advancement device controls

Fifteen studies reported daytime BP from 1772 patients (*Figures 28* and *29*). The combined effect of CPAP on SBP was −2.36 mmHg (95% CI −3.65 to −1.06 mmHg; $p < 0.001$). Again a smaller difference was estimated for DBP of −1.49 mmHg (95% CI −2.17 to −0.80 mmHg; $p < 0.001$). As CPAP trials are generally conducted in patients with more severe OSAH, these results have been stratified for baseline AHI level in *Table 38* and show that the effect of CPAP on both SBP and DBP increased with increasing AHI.

TABLE 38 Summary of results of analysis of SBP and DBP

Subgroup	Number of studies	Difference in BP (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
SBP (mmHg)					
MAD–controls	5	−1.13 (−2.17 to −0.10)	0.032	0%	0.433
MAD–CPAP	3	−0.09 (−2.27 to 2.08)	0.932	0%	0.729
CPAP–controls (all)	21	−2.36 (−3.65 to −1.06)	< 0.001	35%	0.059
CPAP–controls (mild AHI)	3	0.00 (−2.05 to 2.05)	0.999	0%	0.406
CPAP–controls (moderate AHI)	3	−3.44 (−7.96 to 1.08)	0.136	44%	0.170
CPAP–controls (severe AHI)	15	−2.84 (−3.65 to −1.06)	< 0.001	30%	0.126
DBP (mmHg)					
MAD–controls	5	−0.64 (−1.77 to 0.49)	0.265	43%	0.137
MAD–CPAP	3	−0.14 (−1.65 to 1.36)	0.851	0%	0.817
CPAP–controls (all)	21	−1.49 (−2.17 to −0.80)	< 0.001	13%	0.286
CPAP–controls (mild AHI)	3	−1.18 (−2.45 to 0.09)	0.068	0%	0.530
CPAP–controls (moderate AHI)	3	−1.39 (−3.81 to 1.04)	0.262	33%	0.225
CPAP–controls (severe AHI)	15	−1.59 (−2.53 to −0.65)	< 0.001	24%	0.193

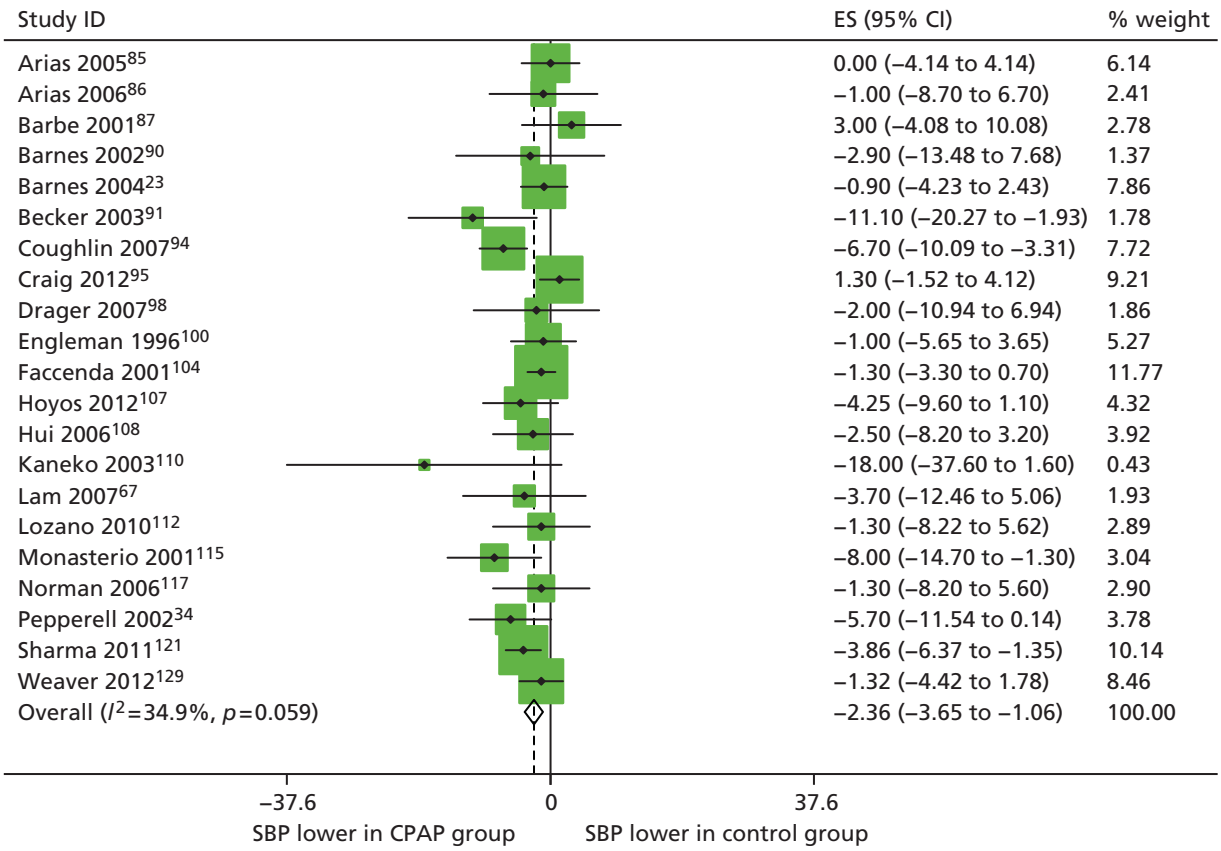

FIGURE 28 Meta-analysis of SBP results from trials of CPAP compared with CM. Note that weights are from random-effects analysis. ES, effect size.

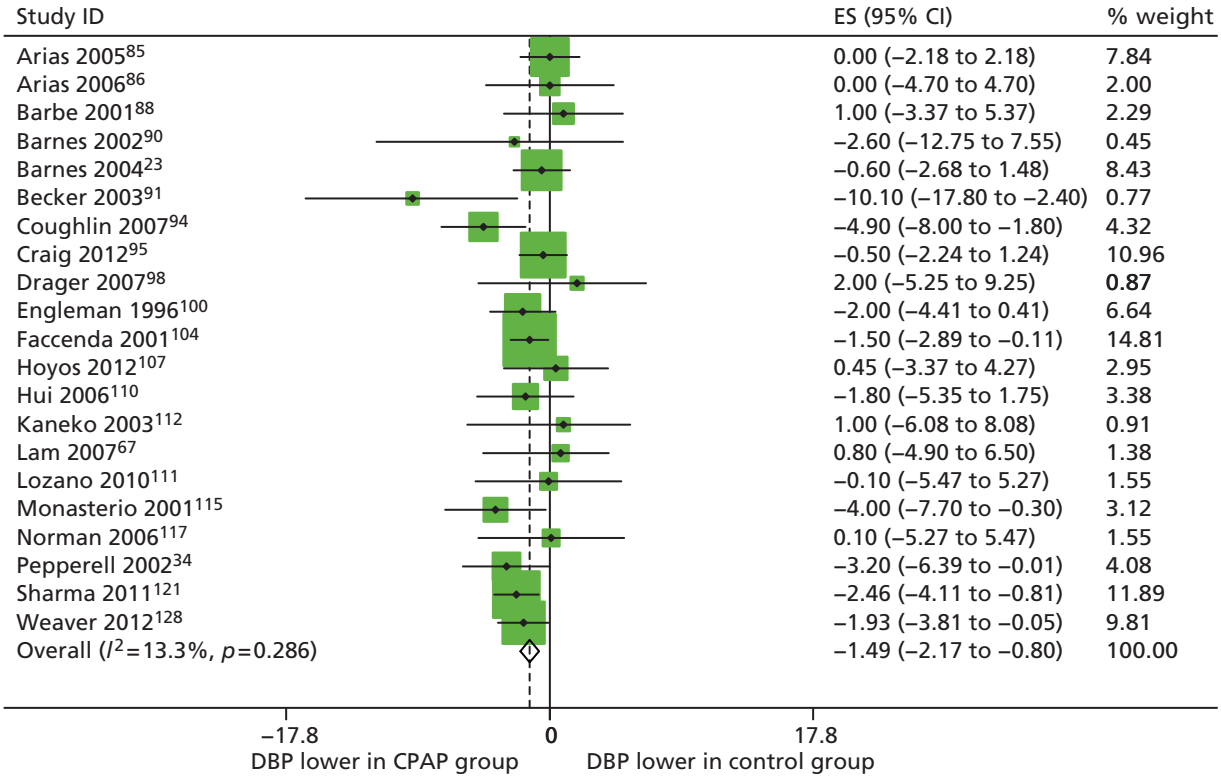

FIGURE 29 Meta-analysis of DBP results from trials of CPAP compared with CM, stratified by baseline AHI. Note that weights are from random-effects analysis. ES, effect size.

Secondary outcome II: sleep-related quality of life

Quality-of-life assessment was restricted to the two sleep-related QoL measures used in the TOMADO study (see *Chapter 2*), the SAQLI and the FOSQ, and to studies identified in the searches described above.

Mandibular advancement devices compared with non-continuous positive airway pressure controls

In our review, only two trials (including TOMADO in *Chapter 2*)[67] reported results of the SAQLI (157 patients) and three trials[23,70] (including TOMADO in *Chapter 2*) reported on the FOSQ (194 patients). Combined results for total SAQLI and FOSQ scores are given in *Table 39* and show a small improvement in both scores, but small numbers and some heterogeneity between studies mean it is not possible to draw reliable conclusions.

Mandibular advancement devices compared with continuous positive airway pressure

Three trials (193 patients) reported SAQLI results in comparisons of MADs and CPAP. The combined results suggest that these two treatments are equally effective in terms of total SAQLI score (*Table 39*). Similarly, the difference between the treatments in overall FOSQ score was small (in favour of MAD) and had a *p*-value of 0.261 for the treatment effect. This was based on four trials and 356 patients.

Continuous positive airway pressure compared with non-mandibular advancement device controls

The SAQLI was recorded in only three trials (211 patients) comparing CPAP with CM. The combined estimate of treatment effect was similar to that reported in comparisons of MADs and CM (*Table 39*). Although the mean difference of 0.58 is statistically significant the clinical relevance is unclear. Flemons and Reimer[132] suggest that a change of 1 point is the minimum clinically important difference for the total SAQLI score, and this difference falls into the range 0.5–1.0, which these authors termed 'an indeterminate area in which the signal-to-noise ratio is likely to be poor'. There was a greater number of trials reporting FOSQ, and the results of combining these trials are shown in *Table 39*. There was a small effect on total FOSQ score favouring CPAP based on nine studies and 764 patients.

TABLE 39 Summary of results from QoL measures

Measurement	Number of studies	Difference in total score (95% CI)	*p*-value for effect	I^2	Heterogeneity *p*-value
Total SAQLI					
MAD–controls	2	0.51 (0.35 to 0.67)	< 0.001	0%	0.954
MAD–CPAP	3	–0.05 (–1.25 to 1.03)	0.760	0%	0.950
CPAP–controls	3	0.58 (0.27 to 0.88)	< 0.001	0%	0.829
Total FOSQ					
MAD–controls	3	0.96 (–0.17 to 2.10)	0.097	57%	0.098
MAD–CPAP	4	0.39 (–0.29 to 1.06)	0.261	53%	0.094
CPAP–controls	9	0.41 (–0.09 to 0.92)	0.109	32%	0.159

Summary and discussion

These meta-analyses have shown that MADs result in a significant improvement in post-treatment AHI and that the estimate of effect is similar irrespective of baseline AHI. In contrast, CPAP produces an improvement that is more than three times that of the combined estimate for MADs. However, the majority of trials involving CPAP focus on patients with high baseline AHI, and there is strong evidence that the treatment effect, compared with CM, is related to baseline AHI. In head-to-head trials of MADs and CPAP, the combined estimates again favour CPAP, but none was conducted in patients with low baseline AHI. This evidence would suggest that CPAP results in a greater overall effect on post-treatment AHI, but that the improvement over MADs is likely to be lower in mild disease.

The effect of MADs on subjective daytime sleepiness assessed by ESS follows a similar pattern, but the differences in treatment effects between MADs and CPAP are smaller and are not significant in head-to-head comparisons. From trials of CPAP against CM, the estimated effects are strongly related to baseline EDS severity and, to a lesser extent, baseline AHI. When trials of similar baseline characteristics are compared, there is little difference between the effects of MADs and CPAP on post-treatment ESS score when assessed against CM, and this is reinforced by the results from head-to-head trials.

There is some evidence that the treatment effects are stronger in trials with short duration of treatment, which would suggest either that non-compliance increases with time or that treatments become less effective over time for other reasons. This will be discussed further in *Chapter 5*.

The number of trials reporting daytime SBP and DBP was small. There were many other papers that reported a range of markers of hypertension. Given the timescale of the project, we chose to concentrate on markers that will be used in the decision models, a full review of hypertension being outside the scope of the project. Our analyses showed that there was a small but significant effect of CPAP and MADs on SBP compared with CM and that there was little difference between these two active treatments. Small but important differences were observed for DBP. These findings are remarkable given the short follow-up of most of the trials identified and are encouraging signs that a reduction in cardiovascular risk is possible for both MADs and CPAP. Again the size of the effect on BP was related to baseline AHI in CPAP trials, reinforcing the similarity of MADs and CPAP effects on BP when trial populations are comparable.

The small number of trials reporting results from the main sleep-related QoL questionnaires is disappointing and does not allow reliable conclusions. There is evidence of small treatment differences for the SAQLI between MADs and CM and between CPAP and CM, but the size of the differences are unlikely to be clinically relevant. The total SAQLI score effects for these two comparisons are similar (0.51 and 0.58 units) and consistent with the head-to-head comparisons, which showed no difference between the two active treatments. The treatment effects for the total FOSQ score were less precise and none was significant at traditionally applied levels.

In almost all comparisons there was significant heterogeneity between trials, some of which could be explained by baseline severity, design and treatment duration, but there remained unexplained heterogeneity. Although we used random-effects meta-analysis to provide unbiased point estimates and robust estimates of precision, further elucidation of the sources of heterogeneity would be useful.

Chapter 4 Long-term cost-effectiveness of oral mandibular devices compared with continuous positive airway pressure and conservative management

Introduction

The results of the within-trial economic analyses based on the TOMADO study data presented in *Chapter 2* showed that that all three of the MADs trialled are cost-effective compared with no treatment for mild to moderate OSAH. The within-trial cost-effectiveness analysis suggests that the SP2, or a similar semi-bespoke device, should be offered as first-line treatment and that dentally fitted bespoke devices should be reserved for those who cannot produce the mould for, or tolerate, a semi-bespoke device. However, there were no statistically significant differences in treatment effects between devices in the base case and results reflect only the observed 4-week follow-up period, comparing each device with no treatment as well as between devices. This chapter presents a cost-effectiveness analysis incorporating long-term effects, to address uncertainties regarding the long-term use of MADs for the treatment of mild to moderate OSAH.

Obstructive sleep apnoea–hypopnoea is a chronic condition and is associated with considerable long-term morbidities, which cannot be fully reflected by a within-trial cost-effectiveness analysis with a short follow-up. For example, large cohort studies have shown that OSAH is associated with hypertension,[133] which will have long-term cardiovascular implications including stroke.[134] The morbidities associated with OSAH are likely to manifest themselves after long-term disease. Excessive daytime sleepiness caused by OSAH also increases the risk of RTAs.[135] These relatively rare events are unlikely to be reflected adequately in short-term trial data.

The long-term and rare events associated with OSAH have survival, QoL and health-care resource use implications, which are important to incorporate in a cost-effectiveness analysis to inform decision-making. While TOMADO's follow-up period was restricted to 4 weeks, partly because of the crossover nature of the trial and the length of follow-up required for gathering data on the primary clinical outcome (AHI), this length of follow-up is common among other studies of interventions to treat OSAH (see *Chapter 3*). To address longer-term cost-effectiveness, several economic models have been developed.[136–142]

Decision-makers also need to be able to compare MADs with other relevant interventions not included in TOMADO. Therefore, an economic model that is able to bring together a range of data sources to chart the long-term morbidities associated with OSAH, as well as symptomatic relief and changes in HRQoL provided by different treatments, is required. The NICE Technology Appraisal 139 defined the potentially suitable treatment options for mild to moderate sleep apnoea as CPAP, MAD or CM.[37] CPAP therapy was recommended in the first instance and oral devices were shown to be cost-effective against CM as an alternative. However, uncertainties remain about the role MADs may play in the treatment of sleep apnoea.

Following a literature search of economic models for OSAH, McDaid *et al.*[8] found a number of key limitations with existing economic evaluations:

- studies did not use the full range of clinical evidence available to estimate the impact of treatment on sleepiness
- a lack of trial-based evidence to compare utility values associated with different treatment options
- limited data on long-term impact of OSAH in terms of cardiovascular risk, RTAs and HRQoL
- the existing evaluations did not examine all the relevant comparators.

To address these limitations, McDaid *et al.*[8] developed a new model to investigate the cost-effectiveness of CPAP compared with MADs and conservative care. To adequately characterise OSAH and its treatment, and ensure that the model was clinically representative, the structure was established from a systematic review used to inform clinical effectiveness, consultation of existing cost-effectiveness literature and opinion of clinical experts involved in the technology assessment process. It made good use of available trial data through a systematic review and meta-analysis of RCTs. The modelling process also followed NICE methodological guidance and used the reference case[37] to increase generalisability.

The perspective, structure, capabilities and treatment options which had been incorporated into the McDaid *et al.*[8] model corresponded to the aims of this evaluation and, therefore, their peer-reviewed model formed the starting point of the long-term economic evaluation. Their conclusion that key uncertainties included the cost-effectiveness of MADs and, hence, the role they should play in the treatment of OSAH, also serves to highlight the importance of the new research in this chapter: 'It remains unclear precisely what type of devices may be effective and in which populations with OSAH. The effectiveness of dental devices compared with CPAP in mild and severe disease populations remains unclear'.[8]

The objectives of the economic analysis presented in this chapter were therefore to update and adapt the York model where necessary to (i) reflect emerging data since the model was built and (ii) focus on the mild/moderate severity patient population. This updated model was then used to assess the cost-effectiveness of MADs, compared with CM and CPAP therapy.

This chapter begins with a summary of the McDaid *et al.*[8] model. It is followed by a description of how parameterisation was completed on the basis of literature searches undertaken to identify potential new sources of data and the incorporation of the TOMADO results into modelling. Results of the analysis of the long-term cost-effectiveness of MADs compared with CPAP and CM for mild/moderate OSAH sufferers are then presented, as incremental cost per QALY. The discussion of these results with the main policy interpretation is left to *Chapter 5*.

The McDaid et al. *model*

McDaid *et al.*[8] developed a state-transition Markov model to assess the long-term cost-effectiveness of CPAP therapy compared with MAD and CM as part of a NICE technology appraisal.[37] The model charted the movement of a hypothetical cohort of 50-year-old men, with characteristics pooled from a meta-analysis of clinical trials of OSAH interventions. Patients were typically overweight (mean BMI = 30 kg/m^2) and had high BP (SBP = 130 mmHg). Baseline EDS, measured by mean ESS score, was 12. Various CPAP devices provided by different manufacturers were treated as one class of intervention. The large numbers of differing MADs used in trials were pooled for an overall treatment effect. CM involved a one-off consultation with a GP, with some level of lifestyle advice on how to reduce or cope with symptoms better. Outcomes were summarised as an incremental cost per QALY for each intervention. The model structure is explained briefly below.

Given the chronic nature of OSAH, the McDaid *et al.*[8] model adopted a lifetime horizon and incorporated the possibility of CVEs, strokes and involvement in RTAs, as well as accounting for symptomatic effects of OSAH on QoL. Patients started in an OSAH state and were able to move into a number of different health states [OSAH post coronary heart disease (CHD), OSAH post stroke and death], reflecting morbidities linked to long-term OSAH suffering. The model ran on a yearly cycle to chart a hypothetical cohort of 10,000 patients over time.

Figure 30 provides a diagrammatic representation of the model. Elliptical boxes represent health states and square boxes represent events. Arrows show the direction of transitions between health states and the occurrence of events. All members of the cohort started in the OSAH state and could stay in that state, unless a transition occurred, until death. They could move into the post-CHD state if they experienced an acute CVE and survived. This state allowed for the increased morbidity and mortality associated with having had a first CHD event. If they did not survive, they moved to the absorbing death state. If they did

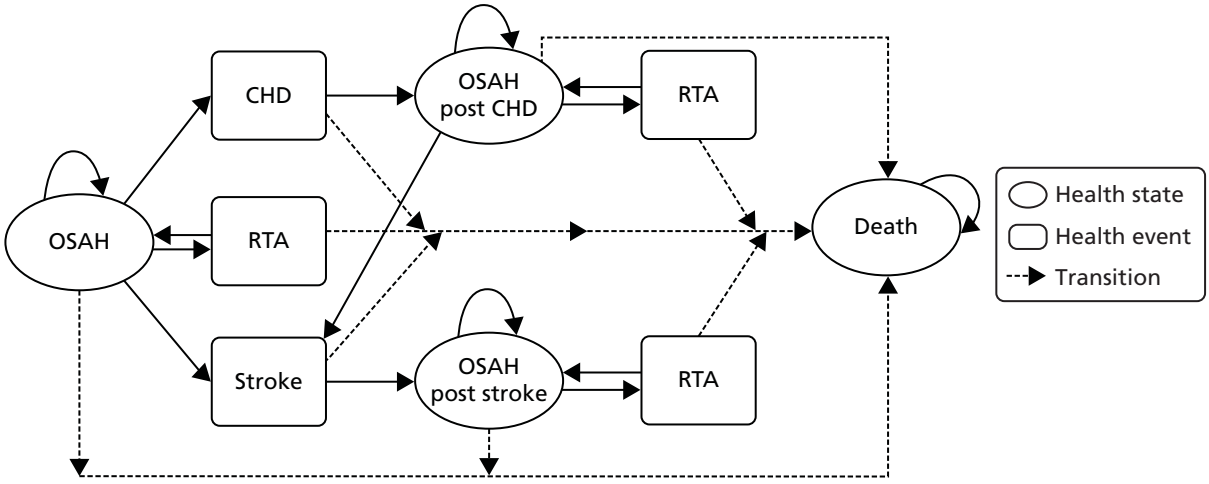

FIGURE 30 Long-term model structure developed by McDaid *et al.*[8]

survive, they could remain in this post-CHD state until death, or experience a RTA (fatal or non-fatal) or suffer a stroke. If they survived a RTA, they remained in the same health state post event. If they survived a stroke, they moved to the OSAH post-stroke state, where they were again able to remain until death or experience a RTA. They were not able to move back to a CHD state once they had suffered a stroke. Patients who had a disabling stroke were assumed to no longer be able to drive and, hence, a proportion of those in the post-stroke state were not able to have a RTA event.

Patients could suffer a stroke while in the initial OSAH state, in which case, if they survived, they would move to the post-stroke health state. Here they would be subject to the increased risk of mortality and morbidity following the first event. Provided the stroke was not disabling they could experience a RTA (fatal or non-fatal). Patients in the initial OSAH state may at some point have experienced a RTA and, provided it was not fatal, would stay in the OSAH state until another transition or death.

Movements between states were determined by a set of transition probabilities, derived from various sources. In the base case, transitions that relate to CVEs and risk of stroke were informed by the Framingham risk equation, utilising information on baseline characteristics of an OSAH population to calculate the probability of a CVE (*Table 40*). Differences in SBP observed under the treatment options (from a meta-analysis of RCTs) were used in the Framingham equation to differentiate the risk of CVEs and strokes under each intervention. The equation is based on Weibull models, meaning that predicted risk is non-linear with respect to each risk factor. McDaid *et al.*[8] tested whether or not use of mean BPs would

TABLE 40 Model cohort characteristics for use in the Framingham equation

Parameter	Mean	Source
Age (years)	51	TOMADO mean
SBP	130	TOMADO mean
Smoking (0 = no; 1 = yes)	0	Assumption (TOMADO 25% smokers)
Total cholesterol (mg/dl)	224	Coughlin *et al.*[143]
HDL cholesterol (mg/dl)	43	Coughlin *et al.*[143]
Diabetes (0 = no; 1 = yes)	0	Assumption (TOMADO 7% diabetic)
ECG-LVH (0 = no; 1 = yes)	0	Assumption
Baseline ESS score	11.9	TOMADO mean

ECG, electrocardiogram; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy.

bias the results using a set of individual patient data. From the equation, the risk of CVEs and stroke were predicted using BP for each patient, and the mean taken. This was compared with risk calculated based on the mean of group BPs. The risk calculated by the two different methods was the same to two decimal places and, so, use of aggregate-level data did not significantly bias results. The equation was used to calculate the 4-year probability of an event, with a piece-wise exponential used to convert this into a yearly probability to correspond to the cycle length.

Long-term observational studies were consulted for estimates of the increased risk of mortality following events relating to stroke and CHD once an initial event had occurred.[144,145] The underlying risk of RTAs (fatal and non-fatal) was estimated from Department of Transport[146] data and was adjusted based on the OR of RTAs given treatment with CPAP compared with no treatment, taken from an updated meta-analysis by Ayas *et al.*[136] Given a lack of data on the likelihood of a RTA when using MADs, the ratio of ESS scores for MAD treatment compared with CM was applied to the OR for RTAs of CPAP compared with CM. Symptomatic relief provided by different interventions was accounted for using evidence from a meta-analysis of ESS scores, which were mapped to a QoL scale, in the absence of good HRQoL data. Regression techniques were used to estimate an algorithm for expressing utility changes, as measured by EQ-5D-3L and SF-6D pre-scored preference questionnaires to changes in ESS score. Utilities and costs were assigned to each of the health states and differed depending on the intervention being received. Each health event had an associated utility loss and acute cost attached to the event.

Costs of interventions were estimated in 2005 prices (£), incorporating the cost of devices and any on-going resource usage associated with maintenance and replacement, including equipment, staff time and overheads. CPAP device costs were acquired from McDaid *et al.*[8] Estimation of resource use during the titration process was taken from a manufacturer's submission to NICE, which included data elicited from a group of clinicians regarding proportion titrated by different methods in clinical practice to ascertain appropriate costs. The machine was assumed to have a lifespan of 7 years (clinical opinion) and masks replaced annually. It was assumed that the MADs being used was a Thornton Adjustable Positioner® (Airway Management Inc., Dallas, TX, USA), commonly in use at the time and this was costed according to NHS Dental contract costs, given the lack of an appropriate NHS cost of the device. The lifespan of a MAD was assumed to be 2 years (clinical opinion) compared with 12–18 months in the TOMADO study. Unit costs for NHS resource use (sleep specialist consultations, nurse appointment and GP consultations) were taken from nationally available NHS reference costs, as well as unit costs published by the Personal Social Services Research Unit (PSSRU).[58,147] Published sources were consulted for estimates of the cost of other morbidities (CHD, stroke and RTAs) associated with OSAH. Two economic evaluations which had estimated costs of an acute CHD (and on-going treatment costs of chronic conditions) and stroke events in a NHS setting were used.[148,149] RTA costs were taken from UK Department of Transport estimates.[146] Cost and effects were discounted at 3.5% per annum.

The modelling was implemented in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and results presented as ICERs representing the long-term mean cost per QALY gained for the different interventions. Uncertainty was explored using probabilistic techniques, by attaching distributions to input parameters and randomly sampling from them, performing 10,000 iterations to produce estimates of the distributions of the outcome. This uncertainty was summarised using CEACs, showing the likelihood that any given device is cost-effective at a given WTP threshold.

Results from McDaid *et al.*[8] indicated a 78% probability that CPAP was cost-effective for the hypothetical cohort at a threshold of £20,000 per QALY. At this WTP, MADs and CM had a probability of being cost-effective of 21% and 1%, respectively. Sensitivity analysis suggested that CPAP had the highest probability of being cost-effective over a wide range of WTP thresholds, even for mild and moderate subgroups, though the probability of MADs being cost-effective increased for milder subgroups.

Updating model parameter values

For this cost-effectiveness analysis, the parameters used to populate the economic model were revisited, to update where necessary and possible. Treatment effects were restricted to a mild/moderate severity group of OSAH sufferers and taken from the meta-analyses presented in *Chapter 3*, which incorporated both TOMADO and other RCT data. Within-trial effects were used in a sensitivity analysis to investigate potential between device differences in long-term cost-effectiveness. Other data from TOMADO used in the model included costs and HRQoL. The remaining data for the economic model were produced following replication of searches first performed by McDaid *et al.*[8] on cardiovascular risk and sleep apnoea, HRQoL data, and RTA risk and sleep apnoea. A new review on compliance of CPAP and MADs was also conducted. The decision about whether or not new evidence was chosen in preference to that already parameterising the model was based on the following criteria:

- evidence was specific to a mild to moderate OSAH population
- estimates were UK specific or more relevant to the NHS
- data were more robust (based on characteristics such as sample size and study design)
- evidence was contemporary compared with previous estimates or
- new evidence facilitated improved modelling (for instance longer-term data or enabling structural improvements) of OSAH and its treatment.

Cardiovascular risk and obstructive sleep apnoea–hypopnoea syndrome

McDaid *et al.*[8] recognised CVEs as a major source of morbidity associated with OSAH and modelled accordingly. Based on literature searches, the evidence established a link between OSAH and CVD, the strongest with regards to OSAH being a risk factor in hypertension,[150,152] though there remained some doubt about whether or not it is an independent risk factor. For this reason, and given a lack of data on long-term outcomes for treatment of OSAH, CVEs were linked to OSAH using a risk score which accounts for the increased risk from raised BP.

In order to account for uncertainties around OSAH and cardiovascular risk, assess the current understanding of the link between OSAH and CVD, and allow for any long-term evaluation of interventions, the literature search of CVD and its role in OSAH was updated. Although some of the RCTs identified by the systematic review in *Chapter 3* had investigated longer-term CVD outcomes under treatment, the majority did not and instead focused on intermediate outcomes, mainly BP. Follow-up was often not sufficiently long to capture these rare events.

Literature search

A search of MEDLINE for 2007–2013 to find articles that referenced OSAH and CVD used a subset of terms that could be encompassed into CVD (e.g. stroke, heart disease, hypertension) which was very similar to that performed by McDaid *et al.*[8] (see details in *Appendix 14*). The original search had also looked for RTA literature, but this was left to an additional search. The search yielded over 500 papers, which were screened by title and abstract. The focus was on identifying new analyses of primary data, including observational studies not identified as part of the systematic review of *Chapter 3* and previous reviews. The majority were excluded as they were not related to OSAH, and 82 were shortlisted, of which 24 were examined in more detail. The 57 excluded were guidelines, commentaries, editorials, letters or case reviews ($n = 18$); duplicates or duplicating clinical trial data already identified in the systematic review (see *Chapter 3*) ($n = 2$) [e.g. referring to a different patient population (e.g. focused on central apnoeas or a younger population) ($n = 16$)]; did not consider the association between OSAH and CVD risk ($n = 10$); were not in the English language; or had only abstracts available ($n = 11$). Owing to the heterogeneity between studies in methodology and markers of hypertension used, a narrative review is provided rather than a formal meta-analysis.

Several studies explored the link between OSAH and CVD. Two studies showed the high prevalence of cerebrovascular lesions[153] and hypertension[154] among an OSAH population. In the former,[153] the prevalence of silent lacunar infarction among 192 patients with moderate and severe OSAH

(AHI ≥ 15 events/hour) was higher than among the controls and the patients with mild OSAH ($p < 0.0001$). In a population of 125 hypertension sufferers, OSAH was present in 64%, a much higher prevalence than in the general population.[154] A small case–control study ($n = 50$) found that nearly 60% of patients who had had a stroke and ischaemic attacks displayed OSAH.[155] In a case–control study (63 cases and 63 matched controls), patients with resistant hypertension (inclusion criteria: BP > 140/90 mmHg, using at least three BP-lowering drugs, including a diuretic), 45 of the case subjects were found to be OSAH sufferers compared with 24 of the controls ($p < 0.001$).[156] Logistic regression gave those with OSAH an OR for suffering from resistant hypertension of 4.8 (95% CI 2.0 to 11.7). A case-matched study of 227 OSAH patients used multiple variable regression to estimate an OR for coronary heart failure of 5.47 (95% CI 1.06 to 28.31) for OSAH sufferers compared with controls.[157]

Several articles analysed data from large cohort studies, with mixed results indicating OSAH as an independent risk factor for hypertension:

- Young *et al.*,[133] in a subset of data from the Wisconsin Sleep Cohort ($n = 1549$), found an OR for 4-year incidence of hypertension (defined as BP > 140/90 mmHg or treatment with antihypertensives) of 2.0 (95% CI 1.2 to 3.2) for patients with an AHI of 5–15 events/hour compared with patients with an AHI < 5 at baseline; patients with an AHI > 15 had an OR for 4-year incidence of hypertension of 2.9 (95% CI 1.5 to 5.6) compared with patients with an AHI < 5 at baseline.
- Marin *et al.*[158] looked at a cohort of control subjects (AHI < 5 events/hour) and OSAH sufferers ($n = 1889$) treated with CPAP therapy. They estimated an adjusted HR for incident hypertension compared with controls which was greater among patients with untreated OSAH; among those ineligible for CPAP therapy, HR was 1.33 (95% CI 1.01 to 1.75), compared with 1.96 (95% CI 1.44 to 2.66) among those who declined CPAP therapy and 1.78 (95% CI 1.23 to 2.58) among those non-adherent to CPAP therapy. All displayed higher rates of hypertension than control subjects.
- O'Connor *et al.*[159] using data from the Sleep Heart Health Study ($n = 2470$ men) after a mean of 2 years of follow-up and based on the same definition of hypertension, observed an OR (adjusted for age, sex, race and time since baseline) of 2.19 (95% CI 1.39 to 3.44) for people with an AHI of > 30 events/hour compared with an AHI of 0.0–4.9 events/hour, though this relationship became weaker (and not significant) for lower AHI. When adjusted for further baseline characteristics (BMI, waist-to-hip ratio and neck circumference) the OR was 1.50 (95% CI 0.91 to 2.46) suggesting a moderate but not significant association, which was again further weakened for lower AHI.
- Kapur *et al.*[160] used the same dataset and demonstrated that the relationship is stronger if patients are stratified by AHI and sleepiness. They estimated an adjusted OR of 3.04 (95% CI 1.33 to 6.04) for an AHI > 30 and experiencing frequent sleepiness (≥ 5 days).
- Using the same definition of hypertension (based on BP or taking hypertensive medication), the Vitoria Sleep Cohort[161] of 1180 patients showed similar results. The crude OR suggested an association, with respiratory disturbance index (RDI) of > 14 compared with 0.0–2.9 giving an OR of 2.61 (95% CI 1.75 to 3.89). An OR greater than 1 held for lower strata of RDI, which were all significant. However, when adjusted for age, sex, BMI, neck circumference, alcohol, coffee and tobacco consumption, and fitness level the OR for RDI > 14 compared with an RDI of 0.0–2.9 was 0.98 (95% CI 0.62 to 1.57), which suggests obstructive sleep apnoea (OSA) is not an independent risk factor.

Other data from the Sleep Heart Health Study ($n = 5422$) suggest that OSAH is associated with a higher chance of suffering a stroke (OR 2.86, 95% CI 1.10 to 7.39, at an AHI of > 19 events/hour).[4] The point estimate of the OR was similar in lower severity OSAH, but the difference was not statistically significant. Martínez-Garcia *et al.*[162] undertook a prospective observational study offering CPAP to OSAH patients, with 7 years' mean follow-up ($n = 223$) of non-fatal CVEs. For a group of patients with an AHI > 20 who had not been able to tolerate CPAP, they estimated a HR, using Cox-adjusted proportional regression, of 2.87 (95% CI 1.11 to 7.71).

Several of the articles ($n = 9$) were review papers combining existing prospective evidence on the association between hypertension, CVD (including stroke), mortality and OSAH.

Several reviews examined the mechanisms involved in OSAH's role in hypertension.

In a 2009 review, Bradley and Floras[5] state: 'Data from animal models, epidemiological studies, and RCTs provide strong evidence that OSAH can cause hypertension, and that its treatment can lower BP. Indeed, OSAH might well be the commonest treatable cause of secondary hypertension.' The same authors were involved in a subsequent review in which Kasai *et al.*[163] noted the higher prevalence of OSAH among a CVD population (47–83%). They suggest that repetitive apnoeas expose the heart and circulatory system to 'noxious stimuli' which can lead to CVD through OSAH's causal role in negative intrathoracic pressure, autonomic dysregulation, oxidative stress, inflammation, endothelial dysfunction, platelet activation and hypercoagulability. Although no quantitative synthesis of data was undertaken, Kasai *et al.*[163] asserted that 'data from epidemiological studies and randomised clinical trials strongly suggest that OSA is a common and treatable risk factor for development of hypertension, heart failure, arrhythmias, and stroke, especially in men'. However, they also proposed that the relationship may be bidirectional. Kato *et al.*[164] also conclude that the pool of evidence relating OSAH to CVD is growing, and state that this is strongest in relation to the role of OSAH in hypertension. Monahan and Redline[165] corroborate assertions around improved understanding of pathophysiological basis of the association of OSA and CVD and note the 'modest improvements in BP associated with continuous positive airway pressure (CPAP) use'.

Two reviews note that BP is lowered by treatment of OSAH. Calhoun[166] explores the mechanism of OSA-induced hypertension and presents results of four meta-analyses suggesting that BP is lowered by CPAP treatment [SBP lowered by 1.38 mmHg (not significant), 2.46 mmHg, 1.64 mmHg and 0.95 mmHg (not significant)] and data included in Monahan and Redline[166] corroborate this. No cohort studies that show long-term treatment effects (with estimates of ORs or relative risks) for interventions used to treat OSAH were identified.

Several reviews also highlighted the role of OSAH in stroke.

Loke *et al.*[134] conducted a meta-analysis which included nine prospective studies ($n = 8400$) investigating OSAH and CVD outcomes and suggested an association between OSAH and strokes (OR 2.24, 95% CI 1.57 to 3.19) and heart disease (OR 1.56, 95% CI 0.83 to 2.91), though the relationship was not statistically significant for the latter. Wallace *et al.*[167] conducted a qualitative review of sleep-related disorders and stroke. The authors comment on the established association between OSAH and stroke, citing evidence from the Sleep Heart Health Study and the Wisconsin Sleep Cohort referred to earlier, and state the case for screening stroke patients for OSAH. In another review, Dyken and Im[168] conclude that OSAH is independently associated with a range of stroke factors but note that, while there is some evidence that treatment can reduce BP, there is a lack of definitive RCT data on overall stroke risk. Portela *et al.*[169] and Caples[170] echo the findings of both these reviews.

However, recognition of a lack of good trial data was a recurrent theme. Monahan and Redline[165] allude to the need for well-powered clinical trials investigating long-term CVD outcomes in OSAH under treatment. Kohli *et al.*[171] and Parati *et al.*[172] make similar conclusions regarding the gaps in current evidence.

While the role of OSAH in CVEs is still somewhat unclear, new evidence does suggest an association. However, there is still a lack of good-quality evidence on the long-term cardiovascular and stroke outcomes of treatment of OSAH, for patients using both CPAP and MADs. There is greater understanding since McDaid *et al.*[8] addressed the literature, of the potential causal factors relating to OSAH and CVD and stroke,[164,165] but they are probably multifactorial and may be bidirectional.[163]

As McDaid *et al.*[8] found, evidence still seems to be strongest in supporting the role of OSAH in hypertension. Analysis of data from large cohort studies (the Wisconsin Sleep Cohort)[133] showed an association, especially among men, but there remains conflicting evidence (The Sleep Heart Health Study;[159] Vitoria Sleep Study[161]). Based on these findings and the BP data found in randomised trials,

the use of the Framingham risk equation was not modified on the basis of data published since the McDaid *et al.* modelling exercise. The characterisation of risk through an algorithm such as the Framingham equation, which uses differences in BP to differentiate CVE risk between baseline and post intervention, seems appropriate given the lack of good data on long-term outcomes. Baseline risk is defined by characteristics taken from TOMADO and a study investigating the role of OSA and metabolic syndrome by Coughlin *et al.*[143] Other cardiovascular inputs to the model are given in *Table 41*.

While the Framingham equation was used in the base case, an additional source of the relative risk associated with a reduction in SBP was identified. Lewington *et al.*[174] pooled data from 61 cohort studies to estimate the relationship between BP and vascular mortality. Adjusting for regression dilution, at ages 60–69 years the relative risk of a stroke for a 20 mmHg reduction in SBP is 0.43 and the relative risk of CHD is 0.54. Given the linear relationship, a proportional change for a 1 mmHg reduction was taken. This analysis also suggests that the reduction in risk is proportional, independent of pre-treatment BP. The baseline risk from the Framingham equation was taken. The proportion of disabling strokes was taken from a large RCT of over 6000 patients comparing interventions for secondary prevention of vascular events.

Road traffic accident risk

To incorporate the change in risk of RTAs following treatment for OSAH, McDaid *et al.*[8] updated a meta-analysis first undertaken by Ayas *et al.*[136] with one additional study by Barbé *et al.*[175] with the eight studies in the Ayas *et al.*[136] review. All of these studies had before-and-after designs, based on actual RTA events pre- and post-CPAP therapy. Barbé *et al.*[175] collected 2 years of collision information retrospectively from participants prior to the study and then prospectively recorded events for 2 years while using CPAP. This study reported a relative risk, but gave event numbers which were used to calculate an OR compatible with the Ayas *et al.*[136] data. Results from the nine studies were pooled to give an OR of 0.168 (95% CI 0.100 to 0.230) after treatment with CPAP. This suggests that the odds of a RTA are reduced by nearly six times when CPAP treatment is initiated. While this effect size is quite large, the underlying rate of a RTA[176] was extremely low (non-fatal: male = 0.0089 per year, female = 0.0082 per year; fatal: male = 0.00014 per year, female = 0.00006 per year).

The rates of RTAs in the model were updated using data derived from the National Travel Survey for 2010[177] and UK Data Archive data from 2010 on RTAs,[178] which presented equivalent contemporary data to those used by McDaid *et al.*[8] The risk was calculated based on the number of UK driving licences held and the numbers of fatal traffic accidents and traffic accidents involving serious and slight injury for 2010. These rates are given in *Table 42*.

TABLE 41 Coronary heart disease and stroke parameters

Parameter	Mean	SD	Source
Relative risk of death following CHD	3.2	0.30	Rosengren *et al.*[144]
Relative risk of death following stroke	2.3	0.18	Dennis *et al.*[145]
Proportion of strokes that are disabling	0.309	–	Diener *et al.*[173]

TABLE 42 Underlying risk of RTAs

Parameter	Mean	SD	Source
Rate of non-fatal RTAs for males	0.0062	pop^n	Department of Transport[146]
Rate of fatal RTAs for males	7.11×10^5	pop^n	Department of Transport[146]
Rate of non-fatal RTAs for females	0.0053	pop^n	Department of Transport[146]
Rate of fatal RTAs for females	2.91×10^5	pop^n	Department of Transport[146]

The search used by McDaid *et al.*[8] was rerun to identify new studies conducted between 2007 and 2013 relating to OSAH and the risk of RTAs.

Literature search

The search (see terms used in *Appendix 14*) identified 32 articles, which were screened for relevance. Nineteen were excluded on the basis that they were commentaries or editorials ($n = 3$); duplicates ($n = 1$), referred to the wrong patient population (e.g. non-OSAH patients, elderly population) ($n = 5$); did not consider RTA risk ($n = 6$); were not in the English language; or only had abstracts available ($n = 4$). Of the 13 studies reviewed in greater detail only two related to observed RTA risk post treatment.[179,180] These two articles were meta-analyses of RTA risk post OSAH treatment. One additional study considered simulated driver performance before and after CPAP treatment.[181] The other nine included clinical effectiveness and cost-effectiveness studies and case–control studies comparing OSAH risk with healthy populations.

The two new meta-analyses pooling data on the impact of CPAP on RTAs were:

- Tregear *et al.*[180] analysed nine studies, including one additional study by Scharf *et al.*[182] that did not appear in the Ayas *et al.*[136] and McDaid *et al.*[8] meta-analyses. However, the Tregear *et al.*[180] analysis also omitted one study by Suratt and Findley[183] that Ayas *et al.*[136] and subsequently McDaid *et al.* had included. The Suratt and Findley[183] article is available only in abstract form and may have been excluded by Tregear *et al.*[180] given their criteria that all studies must be published in full. It is not clear why the study by Scharf *et al.*[182] was not included in the Ayas *et al.*[136] review, which McDaid *et al.*[8] subsequently updated. Tregear *et al.*[180] estimated an OR of 0.278 (95% CI 0.220 to 0.350) for the risk of a RTA post CPAP treatment compared with pre-intervention. This is higher than, but comparable to, the OR of 0.168 estimated by McDaid *et al.*[8]
- Antonopoulos *et al.*[179] performed an analysis of real accidents, accident near misses and simulated driving performance. Ten studies of real accidents (including the Suratt and Findley[183] data) were included. As in the review by Ayas *et al.*,[136] the Scharf *et al.*[182] study was absent, but this review did include another study by Minemura[184] that was not in the McDaid *et al.*[8] or Tregear *et al.*[180] analyses. While the study by Minemura[184] may have been excluded by Tregear *et al.*[180] because of their inclusion criterion that studies should involve more than 20 patients, the reason for omission from the Ayas *et al.*[136] review is unknown. An OR of post-CPAP compared with pre-CPAP RTA risk of 0.21 (95% CI 0.12 to 0.35) was estimated and pooled data on driving simulator performance showed a significant improvement in performance post treatment.

An additional study, by Hoekema *et al.*,[181] based on a prospective simulator-based investigation of driving performance of 20 OSAH patients and 16 controls, was also found. OSAH patient simulator performance was compared with the control group before and after 8 weeks of CPAP ($n = 10$) and MAD ($n = 10$) treatment. Patients randomised to each group were subject to 25 minutes of driving simulation and lapses of attention were observed. The results suggested significant differences in performance post treatment, similar for both CPAP and MADs.

Given the difficulty in ascertaining the reason for inclusion of studies and the effect it leads to in differences of ORs pooled by the two new meta-analyses and the McDaid *et al.*[8] analysis, the OR of experiencing a RTA of 0.17 from McDaid *et al.*[8] was retained. The two newly identified estimates of the reduction in RTA risk post treatment are of similar magnitude, but the Tregear *et al.*[180] estimate was used in a scenario analysis, as it suggested the smallest effect size. Given that this estimate is specific to CPAP, the approach to the comparison of MADs with CM followed the method of McDaid *et al.*[8] That is, a multiplier based on the relative treatment effects on ESS score of CPAP versus CM and MADs versus CM was applied to the OR of RTA for CPAP versus CM. These rates are presented along with other treatment effects in *Table 42*.

Health-related quality of life

During their systematic review, McDaid *et al.*[8] highlighted the paucity of data regarding HRQoL and OSAH. To characterise cost per QALY using the NICE reference case, utility scores are needed for each treatment.

As these were lacking, and a large number ($n = 27$) of the trials in the systematic review of treatment effects had reported ESS scores, McDaid *et al.*[8] used the surrogate end point of ESS score as a proxy for differences in utility. Three sets of individual patient-level data (two measuring ESS and SF-36 profile in the same patients and one that measured ESS, SF-36 profile and EQ-5D-3L data in the same set of patients) were used to map ESS scores to EQ-5D-3L and SF-6D values (based on tariffs published by Brazier *et al.*[63] and Dolan[61]) using regression analyses. The results of this process indicated that a unit fall in ESS score is associated with an increase in utility, based on a SF-6D ($n = 294$) value of 0.0095 (95% CI 0.0070 to 0.0123) and based on an EQ-5D-3L ($n = 94$) value of 0.0097 (95% CI 0.0019 to 0.0175).

The systematic review presented in *Chapter 3* highlights the remaining dearth of RCT data on OSAH and HRQoL. In trials that did include some measurement of QoL, it was predominantly limited to disease-specific measures (SAQLI and FOSQ). However, one study did use generic instruments to measure HRQoL. In a double-blind randomised trial of 102 men who received a real or sham CPAP device, Siccoli *et al.*[18] used the SF-36 and SF-12 4 weeks after treatment to measure impact of CPAP therapy on HRQoL. This population was defined as having moderate/severe OSAH. In the intervention group, scores on several domains of the SF-36 (Emotional Well-being, Vitality, Role Emotional and Social Function) were significantly higher than those in the sham group. Using the SF-12, the mean PCS difference was 58.8 compared with 72.4 and the mean MCS was 63.5 compared with 77.9, both differences being 'significant'. However, a utility score based on these short-form surveys was not presented.

While TOMADO included the EQ-5D-3L and SF-36, these data were relatively short term and specific only to MAD. Therefore, further searches were undertaken to identify other potential sources of HRQoL utility data from generic instruments, for use in the modelling.

Literature search

A search first performed by McDaid *et al.*[8] was replicated for 2007–13, using MEDLINE, to identify data not included in the systematic review reported in *Chapter 3*, i.e. including observational trials that might offer a robust data source.

The search yielded over 700 potentially relevant articles, which were screened by title and abstract for relevance. The aim was to identify studies of OSAH which included a treatment (either CPAP or MADs) and measured QoL using the EQ-5D-3L or SF-36/SF-12 pre-scored preference questionnaires. Seventy-one papers were examined in greater detail (see list in *Appendix 15*, along with the search terms).

Of the 72 papers examined further, only two captured generic QoL data. A prospective study by Tsara *et al.*[185] reported SF-36 profiles for 135 patients (120 with severe and 15 with mild/moderate OSAH based on AHI) before and after CPAP therapy in a sleep unit at a general hospital in Greece. These data suggested improvements in QoL post CPAP treatment, though this was not expressed as a utility score. Improvements for men were observed in all domains except Pain (Physical Role, Physical Function, Emotional Well-being and Vitality: $p < 0.01$; General Health, Role Emotional and Social Function: $p < 0.05$), with the greatest change in General Health. Women displayed a significant improvement only in Role Physical ($p < 0.01$). Antic *et al.*[186] collected data as part of a randomised trial of nurse-led care for moderate to severe OSAH patients. One hundred and thirty-five OSA patients were included, with SF-36 measurement 3 months after treatment with CPAP in three sleep centres in Australia. SF-36 domains were not presented, but the authors reported that the vitality component was significantly correlated with objective adherence.

Neither of the additional studies[185,186] considered MADs and the focus was in a more severe disease group than TOMADO is primarily focused on. The study by Siccoli *et al.*[18] does offer some robust trial data regarding CPAP treatment effects that could have been converted to SF-6D but, again, these are in a group of patients with moderate to severe disease. TOMADO collected data for a mild to moderate group using MADs, which suggested there may be some improvements in HRQoL after treatment, but these results were not significant for generic instruments.

Bearing in mind these limitations and the desire to utilise the synthesised systematic review of treatment effects, the clinical end point of ESS was again mapped to utility. As TOMADO provided more data points than had been available to McDaid *et al.*,[8] these data were used to estimate a relationship, mapping observed ESS scores to utility measures. The resulting algorithm then converted ESS score treatment differences into post-treatment utility changes.

Mapping Epworth Sleepiness Scale score to European Quality of Life-5 Dimensions three-Level version and Short Form questionnaire-6 Dimensions

TOMADO presented a large dataset of both SF-36 and EQ-5D-3L data for people with mild to moderate OSAH. Given repeated measurements, it yielded 402 data points of ESS score and SF-6D and 404 data points of ESS score and EQ-5D-3L that could be used in a regression-based mapping exercise to estimate an algorithm mapping ESS to utility scores. The algorithms for SF-6D and EQ-5D-3L were estimated using a linear mixed-effects regression model. The ESS score was an explanatory variable; a dummy variable was used to control for differences in baseline utility and participants were included as a random effect. These models rely on an assumption that the residuals are Normally distributed, though this may not always hold.[187] The models are shown in *Table 43* for SF-6D and *Table 44* for EQ-5D-3L.

Figure 31 shows that the residuals appear to be reasonably close to normality for SF-6D, but less so for the EQ-5D-3L. This is consistent with our a priori knowledge of the discrete nature of the EQ-5D-3L, the ceiling effect often observed in relatively healthy groups of patients[188] and the findings of the McDaid *et al.*[8] mapping exercise. Other studies of utility indices derived from EQ-5D-3L in OSAH sufferers confirm this phenomenon and suggest that SF-6D may display a distribution closer to normality.[189]

The results of this regression analysis indicate that a 1-unit decrease in the ESS is associated with a 0.0061 ($p < 0.001$) rise in utility based on EQ-5D-3L and a 0.0067 ($p < 0.001$) rise in utility based on the SF-6D instrument. For probabilistic sensitivity analysis the estimated variance matrix from the linear mixed models was used when sampling from the parameter distributions. The baseline utility of the population in the economic model was estimated based on the mean baseline ESS score of patients in TOMADO. The coefficients in the mapping equations estimated from the TOMADO data were similar to, but slightly lower than, those estimated by McDaid *et al.*[8] This should be expected as the population of patients recruited to TOMADO had mild to moderate OSAH and so represented a subsection of the range of disease severity.

Treatment effects of the use of MADs and CPAP from the meta-analyses of ESS scores in *Chapter 3* were converted into utility increments using the algorithm. The baseline utility was estimated based on the mean ESS score of the trial participants in the TOMADO. The utilities used in the model are shown in *Table 45*.

TABLE 43 Mixed-effects model for mapping ESS scores and utility based on SF-6D ($n = 402$)

Variable	Coefficient	SE	*p*-value	95% CI
ESS	–0.0067	0.0011	0.000	–0.0087 to –0.0046
Baseline	–0.0020	0.0079	0.799	–0.0175 to 0.0134
Constant	0.7529	0.0116	0.000	0.7302 to 0.7756

TABLE 44 Mixed-effects model for mapping ESS scores and utility based on EQ-5D-3L ($n = 404$)

Variable	Coefficient	SE	*p*-value	95% CI
ESS	–0.0061	0.0020	0.003	–0.0101 to –0.0020
Baseline	0.0139	0.0145	0.340	–0.0146 to 0.0423
Constant	0.9094	0.0220	0.000	0.8664 to 0.9525

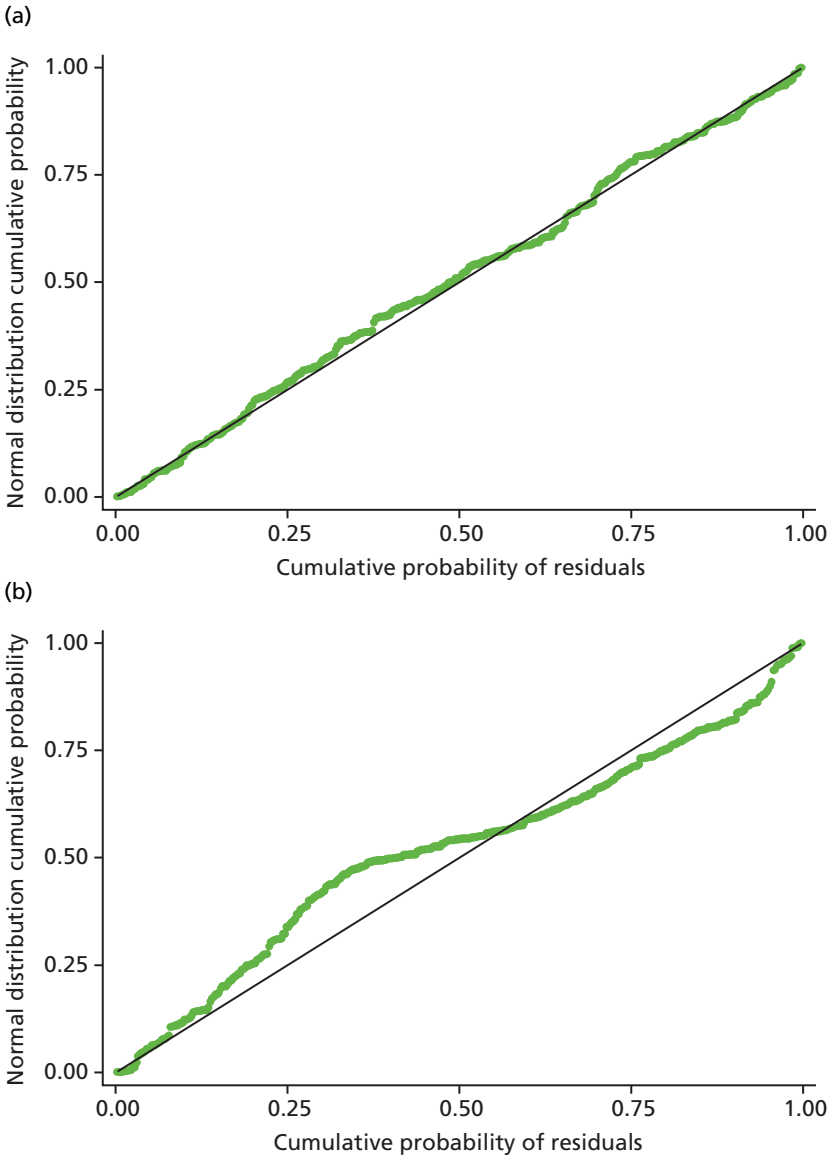

FIGURE 31 Residuals from linear model mapping ESS to (a) SF-6D; and (b) EQ-5D-3L utility scores.

TABLE 45 Utilities for CVEs and RTAs

Utility	Mean	SD	Source
OSAH untreated (baseline)	Baseline ESS score × −0.006 + 0.91	–	TOMADO EQ-5D-3L mapping algorithm
OSAH treated with MAD	$\Delta ESS_{MAD\text{-}CM} \times -0.006$	–	TOMADO EQ-5D-3L mapping algorithm
OSAH treated with CPAP	$\Delta ESS_{CPAP\text{-}CM} \times -0.006$	–	TOMADO EQ-5D-3L mapping algorithm
Stroke (decrement)	−0.0524	0.0002	Sullivan and Gushchyan[190]
CHD (decrement)	−0.0635	0.0001	Sullivan and Gushchyan[190]
RTA	0.6200	0.2700	Currie *et al.*[191]
Age (decrement per year)	−0.0007	0.0000	Sullivan and Gushchyan[190]

McDaid *et al.*[8] relied on data from a study conducted by Sullivan and Ghushcyan,[190] which used EQ-5D-3L data from a panel of 38,678 patients to estimate decrements associated with a range of chronic diseases. The utility associated with a RTA was based on EQ-5D-3L data from a data repository 6 weeks after an inpatient episode for injuries sustained from a RTA in the UK. No additional robust sources of utility data were identified and these values were retained.

Compliance

McDaid *et al.*[8] used a study by McArdle *et al.*[45] of long-term (median follow-up = 1.8 years) CPAP use in Scotland ($n = 1155$) to inform compliance in the model. This prospective observational study collected data on patients offered CPAP therapy. The mean ESS score of patients starting CPAP at baseline was 12 and AHI was 30 events/hour. Patients who refused CPAP therapy had a lower mean AHI of 22, though this was not shown to be a significant predictor of CPAP acceptance. Continued CPAP usage was significantly associated with AHI, with a HR estimate (relative risk of stopping CPAP) using Cox proportional regression of 2.48 (95% CI 1.79 to 3.40) for AHI < 15 relative to AHI ≥ 15. The study also reported a HR for stopping CPAP of 1.92 (95% CI 1.41 to 2.61) for an ESS score < 10 relative to an ESS score > 10. A Kaplan–Meier curve of CPAP use over 5 years was used to calculate yearly probabilities of patients stopping CPAP. The proportion still using CPAP was 0.84 at year 1, 0.74 at year 2, 0.73 at year 3 and 0.68 at year 4. After 4 years, a plateau was observed and, so, it was assumed that all patients who had not stopped using CPAP would continue to use the device indefinitely. In the absence of equivalent data for MADs, McDaid *et al.*[8] assumed compliance was equal to that of CPAP.

A search was conducted to identify new compliance data for both MADs and CPAP.

Literature search

The search of MEDLINE yielded 111 articles that were screened by title and abstract. The terms used are in *Appendix 14* and selection focused on long-term estimates. Studies were considered relevant if they included the use of MADs or CPAP for treatment of OSA and had at least 1 year mean follow-up, indicating a measure of compliance over time. Studies were limited to those with at least 50 patients. Thirty-eight were reviewed in more detail. Of these, many did not have at least a year of follow-up ($n = 11$), others did not present compliance data on continuation of treatment ($n = 10$), did not include more than 50 patients ($n = 3$) or ($n = 5$) were concerned with a different patient group (e.g. snorers). One was not available in full form.

Brette *et al.*[192] assessed long-term MAD use in a French cohort ($n = 140$) with mean AHI of 27 events/hour at baseline. The device assessed, 'uses thermoformed splints custom-fitted to the patient's dental arches based on moulds [sic]'. Compliance was determined by a one-off questionnaire at a mean of 2.75 years from treatment initiation, when 76% of patients were still using the device regularly. Vezina *et al.*[193] conducted a retrospective study ($n = 81$) of the use of two different MADs, a traction- and compression-based device, with mean follow-up of 3.6 years. Both devices were custom made from hard copolyester (outer layer) and soft polyurethane (inner layer), following dental impressions. They found that 59% of patients were still using the MADs. Ghazal *et al.*[194] conducted a long-term (mean follow-up of 3.5 years) randomised study of two MADs ($n = 103$). At follow-up, 62% and 46% of patients were still using the two different devices, the first being an IST (hard methylmethacrylate) and the latter a Thornton Anterior Positioner® (made of a laminated, hard–soft polymer with an inner soft polyurethane and an external hard polycarbonate component). In a prospective study with mean follow-up of 1.4 years, which included telephone survey follow-up, Gindre *et al.*[195] reported that 82% of patients ($n = 66$) were still using the device, on average 6 days a week. The majority of this group ($n = 50$) had moderate to severe sleep apnoea (mean AHI = 38.6), but had not been able to tolerate CPAP.

In a real-life study of CPAP compliance ($n = 303$), Galetke *et al.*[196] observed, after a median follow-up of 13 months, that 67% of participants were still regularly using the CPAP machine, while 27% had definitively discontinued use. Mean AHI in this group was 33 events/hour and mean ESS score was 9. A prospective study ($n = 158$) investigating titration methods for CPAP also collected some data on long-term compliance (median follow-up 1.9 years) and found that 77% were still using CPAP at 3 years.[197] Kohler *et al.*[198] conducted a long-term study of usage of CPAP in Oxford with median follow-up of 3.9 years. After 5 and 10 years, 81% and 70% of patients were still using CPAP. They also investigated covariates associated with adherence and found that only ODI was a significant factor, suggesting that more severe apnoea is associated with greater compliance, as McArdle *et al.*[8] demonstrated. However, subjective daytime sleepiness was not a significant factor.

Hoffstein[199] pooled data from 21 studies of MAD compliance, to produce an estimate of 56–68% of patients still wearing the device at 33 months, though some of these patients had very limited symptoms.

Estimates of CPAP compliance from Kohler *et al.*,[198] who conducted a large hospital record-based study of 600 patients in England, were used in our updated modelling. This gave 10-year data compared with the 4-year data from McAardle *et al.*[45] Based on mean AHI of 30 events/hour in the McAardle *et al.*[45] population and mean ODI of 28 events/hour, these groups can be considered to be of broadly similar severity, although mean ESS score is higher in the Kohler *et al.*[198] population. Though some compliance data regarding MADs were identified, the picture is unclear. The assumption that compliance for MADs was the same as for CPAP therefore remained unchanged. There is evidence to suggest that CPAP compliance is lower in milder severity groups, but there is no corresponding evidence that MAD compliance would necessarily be higher. Scenario analyses were therefore conducted to investigate the effect of different compliance rates for CPAP and MADs. Kohler *et al.*[198] estimated a HR of 0.97 for ODI. This means that a fall in ODI of 10 events/hour would represent an increase in risk of discontinuing CPAP therapy of 26%. There are no similar data on the relationship in MADs. Therefore, a one-way conservative adjustment to CPAP compliance was made, reducing it by 5% and 10% to observe the effect.

Mortality rates

Non-cardiovascular disease mortality, originally based on data from 2004 in McDaid *et al.*,[8] was updated using interim life tables (2009–11) and mortality statistics for 2010 from the Office for National Statistics.[200,201] The interim life tables gave age- and gender-specific mortality rates, from which the all-cause hazard was reduced according to the proportion of people who died of CHD and ischaemic heart disease. Underlying mortality rates for patients who have suffered a stroke or CVE were adjusted based on data from two long-term follow-up studies, and are shown in *Table 41*.

Modelling treatment effects

Treatment effects were taken from the meta-analysis presented in *Chapter 3* for mild to moderate OSAH. This analysis suggests that the difference in ESS score for CPAP and MADs are very similar: −1.62 and −1.61, respectively. In a scenario analysis, device-specific differences in ESS score observed in the TOMADO study to estimate cost-effectiveness for the SP1, SP2 and bMADs were used. Differences in BP were also taken from the meta-analysis, though, given the data, it was not possible to estimate specifically for a mild to moderate group. The risk of RTA was based on the CPAP treatment effect pooled by McDaid *et al.*[8] and the ratio of ESS score for MADs and CPAP. These effects are presented in *Table 46*. The base-case risk of RTA after use of MAD is shown, but in scenario analyses will differ according to the ESS treatment effect.

Resource use and costs

McDaid *et al.*[8] incorporated into the model the costs (at 2004/5 prices) relevant to the NHS and personal social services which included the cost of the three interventions (CM, CPAP and MADs) and on-going costs associated with their provision, as well as those of OSAH-related events (RTAs and CVEs).

TABLE 46 Modelled treatment effects

Parameter		Mean difference	SD	Source
ESS	MAD vs. CM (mild to moderate)[a]	−1.620	0.380	Meta-analysis (see *Chapter 3*)
	CPAP vs. CM (mild to moderate)	−1.610	0.340	Meta-analysis (see *Chapter 3*)
SBP	MAD vs. CM	−1.130	0.530	Meta-analysis (see *Chapter 3*)
	CPAP vs. CM	−2.360	0.660	Meta-analysis (see *Chapter 3*)
Risk of RTA	MAD vs. CM	0.167	–	McDaid *et al.*[8] and ratio of ESS treatment effects
	CPAP vs. CM	0.168	0.033	McDaid *et al.*[8]

a Mild to moderate based on mean baseline AHI of study participants.

The cost of CHD events was taken from an evaluation of cardiac medication. Briggs *et al.*[148] used data from a large trial ($n = 12,218$) extrapolated using Markov modelling to estimate 'background' costs as well as the costs associated with modelled events. From regression analyses on costs, McDaid *et al.*[8] were able to utilise the estimated cost for fatal CVEs (which tends to be somewhat lower than for non-fatal events) as well as the cost of an acute CHD event and on-going treatment of CHD. These data were assigned to the health states in the model and to the models for risk of CVEs. Similarly McDaid *et al.*[8] identified a study which would give the acute cost of a stroke and the on-going costs associated with being in a post-stroke health state. Bravo Vergel *et al.*[149] used long-term data from the Nottingham Heart Attack Registry (5 years) which gave details of frequency, timing of recurrent events and in-depth resource use. The costs of RTAs were taken from Department of Transport estimates of the NHS costs associated with fatal and non-fatal RTAs.

For the purpose of this cost-effectiveness analysis, costs were updated where possible and presented at 2011/12 prices. Where relevant, costs were increased for health-care service inflation using PSSRU price indices.[147] The costs of CPAP, MAD and CM are shown in *Table 47*. The cost of a CPAP machine was provided by Meditas and the cost of an auto-adjusting positive airway pressure (APAP) machine used in the titration process by Respironics. Information provided by ResMed in its submission to NICE[37] was taken to estimate the cost of starting CPAP therapy and on-going yearly costs. A survey of clinicians was used to estimate the cost of the titration process based on the proportions that undergo outpatient and inpatient titration and the method used. These data were assessed for face validity by the TOMADO clinical team. Outpatient visits in sleep clinics were updated for contemporary reference costs, as was the cost of specialist nurse time. The acute cost of CPAP therapy was estimated to be £173. Along with other annual costs and the assumption that the lifespan of a machine was 7 years, equivalent annual cost was estimated to be £252.

In the base case, the costs of MADs were assumed to be those of the SP2, as presented in *Chapter 2*. Based on clinical opinion it was assumed that, on average, a patient would have one annual follow-up with a sleep specialist. The lifespan of the device was assumed to be 1 year, based on the expectations of the manufacturer and clinical opinion, as no long-term evidence of replacement was available. Given the comparatively short lifespan and inability to return MADs for reuse, this was noted as a potential source of uncertainty and investigated in scenario analyses, along with using the costs for the SP1 (1-year lifespan) and the bMAD (a fully bespoke MADs assumed to have a lifespan of 18 months).

The costs of CM were taken to include a one-off consultation with a GP. This was taken from PSSRU estimates.[147]

TABLE 47 Costs associated with interventions (2011/12 prices; £)

Cost parameters	Mean	SD	Source
CM	36.00		PSSRU[147]
CPAP initial costs			
Unit cost of follow-up outpatient visit	105.89	47.08	NHS reference costs 2011/12[58]
Probability of having a follow-up outpatient visit	0.69	0.3	McDaid *et al.*[8]
Total cost of follow-up outpatient visit	*73.06*		
Probability of using APAP	0.81	0.19	McDaid *et al.*[8]
Probability of home titration	0.99	0.01	McDaid *et al.*[8]
APAP machine	499.00		Jenny Salmon, Phillips Respironics, 2013, personal communication
Number times CPAP/APAP used for dose titration	163		McDaid *et al.*[8]
Total cost APAP for dose titration	*3.06*		
Probability of using CPAP	0.19		McDaid *et al.*[8]
CPAP machine	230		Angela Dunnil, ResMed UK Ltd, 2013, personal communication
Total cost CPAP for dose titration	*1.41*		
Total cost of in-home titration	*2.72*		
Probability of inpatient titration	0.01		McDaid *et al.*[8]
Unit cost sleep study follow-up	722.80	263.56	NHS reference costs 2011/12[58]
Total cost of inpatient titration	*7.23*		
Probability of seeing a specialist nurse for titration	1		McDaid *et al.*[8]
Unit cost of 30-minute appointment with specialist nurse	44.50		PSSRU[147]
Total cost of specialist nurse involved in titration	*44.50*		
Probability of seeing a consultant for titration	0.4	0.4	McDaid *et al.*[8]
Unit cost of consultant appointment	105.89	47.08	NHS reference costs 2011/12[58]
Total cost of titration by consultant	*42.37*		
Unit cost of 30-minute appointment with technician	11.23		McDaid *et al.*[8] inflated
CPAP initial cost	*174.94*		*(73.06 + 2.72[a] + 7.23 + 44.5 + 42.37 + 11.23)*
CPAP on-going costs			
Interest rate	3.5%		NICE[37]
Estimate life of CPAP machine (years)	7		McDaid *et al.*[8]
Annual equivalent cost CPAP machine	*36.34*		*230/annuity factor*
Cost of CPAP mask	105.00		ResMed (50% full/50% nasal masks)
Estimated life of CPAP mask	1		McDaid *et al.*[8]
Annual equivalent cost CPAP mask	*92.43*		
Annual sundries	*17.33*		*McDaid* et al.[8] *inflated*
Annual follow-up	*105.89*		*NHS reference costs 2011/12*[58]
CPAP on-going annual cost	*251.99*		*(36.34 + 92.43 + 17.33 + 105.89)*

TABLE 47 Costs associated with interventions (2011/12 prices; £) (*continued*)

Cost parameters	Mean	SD	Source
MAD initial costs			
Thermoplastic device (SP1)	*21.00*		*TOMADO*[77]*, Chapter 2*
Semi-bespoke device (SP2)	*128.00*		*TOMADO*[77]*, Chapter 2*
Bespoke device (bMAD)	*552.00*		*TOMADO*[77]*, Chapter 2*
MAD on-going annual cost	*105.89*	*47.08*	*NHS reference costs 2011/12*[58]

a Weighted cost of CPAP/APAP titration.

The costs of CHD and stroke as modelled by McDaid *et al.*[8] were taken from robust long-term data sources. No new sources identified were able to reflect the acute costs of events and on-going costs associated with these conditions in a way that suited the modelling and so these costs were increased for general health service inflation. No new UK-specific estimates of the costs associated with RTAs were identified and so those used by McDaid *et al.*[8] were inflated to reflect 2011/12 prices. These are shown in *Table 48*.

Methods of analysis

The base case includes a hypothetical cohort of 10,000 men informed by the characteristics of the TOMADO population. These characteristics are shown in *Table 40*. ESS treatment effects were taken from the meta-analysis stratified to include studies of OSAH that fell into the mild to moderate range according to mean baseline AHI. Costs were based on the SP2 device, with an assumed lifespan of 12 months. All models incorporated the uncertainty around model input parameters by repeatedly sampling ($n = 15{,}000$) from the parameter distributions and recalculating model outputs conditional on each sample, in order to estimate the distribution of the outputs. Distributions were chosen dependent on the nature of the parameter being sampled. Gamma distributions were used for unit costs, Normal distributions were used for input parameters that were estimated from regression coefficients (including the Cholesky decomposition of mapped utility values) and log-Normal distributions were used for relative risks. Several scenario analyses were conducted, which still incorporated the probabilistic elements of the modelling and, where relevant, adjusted distributions of input parameters accordingly.

TABLE 48 Mean costs associated with CHD, stroke and RTAs

Cost	Mean	SD	Source
CHD and stroke			
Cost of fatal CVE	3561	434	Briggs *et al.*[148]
Acute cost of CHD	11,786	505	Briggs *et al.*[148]
Ongoing cost of CHD	886	138	Briggs *et al.*[148]
Acute cost of stroke	10,476	347	Bravo Vergel *et al.*[149]
Ongoing cost of stroke	2764	334	Bravo Vergel *et al.*[149]
RTA			
Cost of RTA (non-fatal)	3120	1942	Department of Transport[146]
Cost of RTA (fatal)	6297	1942	Department of Transport[146]

Scenario analyses were conducted to investigate sensitivity of outputs to:

- the lifespan of the interventions
- the cost of devices incorporating SP1 and bMAD costs
- ESS treatment effects observed in TOMADO
- reduced CPAP compliance in lower severity disease using a multiplier
- the time horizon
- use of an alternative source of the relative risk of vascular events given a reduction in SBP
- use of an alternative source for the effect of effective treatment of OSA on RTA events.

All results are presented as incremental cost per QALY. For the base case, uncertainty in the estimates is presented as the likelihood of being cost-effective at WTP thresholds of £10,000, £20,000 and £30,000 per QALY, the CEAC for a range of WTP thresholds and the CEAF to identify the most cost-effective treatment option over the range of WTP thresholds. All costs are in 2011/12 prices.

Results of the economic model

Base-case analysis

The results of the base case are presented in *Table 49*. This shows that MADs compared with CM are more costly but also more effective in patients with mild to moderate OSAH. The additional costs are a result of much higher treatment costs, with a reduction in RTA and CVE costs mitigating this difference somewhat. The ICER of MADs compared with CM is £6639 per additional QALY gained. CPAP compared with MADs is more expensive but more effective. The ICER of CPAP compared with MADs is £14,012 per QALY gained.

At a threshold value of £20,000/QALY, CPAP has the highest mean INMB compared with CM (£3879) and the probability that CPAP is cost-effective is 0.52. At a threshold value of £30,000/QALY, this probability increases to 0.55 with a mean INMB of £6914. Oral devices have a mean INMB compared with CM of £3794 at a threshold value of £20,000/QALY and the probability that they are cost-effective is 0.47. At a threshold value of £30,000/QALY, this probability decreases to 0.45 with a mean INMB of £6643.

TABLE 49 Cost-effectiveness results (base-case analysis)

Cost-effectiveness component	CM	MAD	CPAP
Intervention costs (mean)	£36	£3206	£3524
RTA costs (mean)	£1963	£713	£716
CVE costs (mean)	£4118	£4103	£4074
Total costs	£6116	£8022	£8307
Total QALYs	14.336	14.621	14.640
ICER (oral devices compared with CM and CPAP compared with MADs)		**£6687**	**£15,367**
Probability of cost-effectiveness			
At £10,000/QALY	0.16	0.46	0.38
At £20,000/QALY	< 0.01	0.47	0.52
At £30,000/QALY	0	0.45	0.55

Figure 32 depicts the uncertainty surrounding decisions of which approach is most cost-effective in the base-case analysis, for a range of values decision-makers may be willing to pay per QALY gained. It shows that at very low WTP thresholds, CM is the most likely to be cost-effective. Over the conventional range of £20,000–£30,000, CPAP has the highest likelihood of being the most cost-effective, with the decision becoming less uncertain as WTP per QALY increases. At a WTP of approximately £20,000/QALY the probability that CM is the most cost-effective falls to zero.

Figure 33 gives the CEAF for the base case. It shows the intervention which yields the highest mean net benefit over the range of WTP. It can be seen that, while MADs have the highest mean net benefit after a threshold of £6687, there does remain uncertainty of whether or not it is likely to be more cost-effective than CM. From £15,367, CPAP becomes cost-effective, and at this point the likelihood of MADs and CPAP being cost-effective is very similar, 0.48 and 0.49, respectively. At higher WTP, CPAP always has the highest mean net benefit and highest likelihood of being the most cost-effective, although with considerable uncertainty.

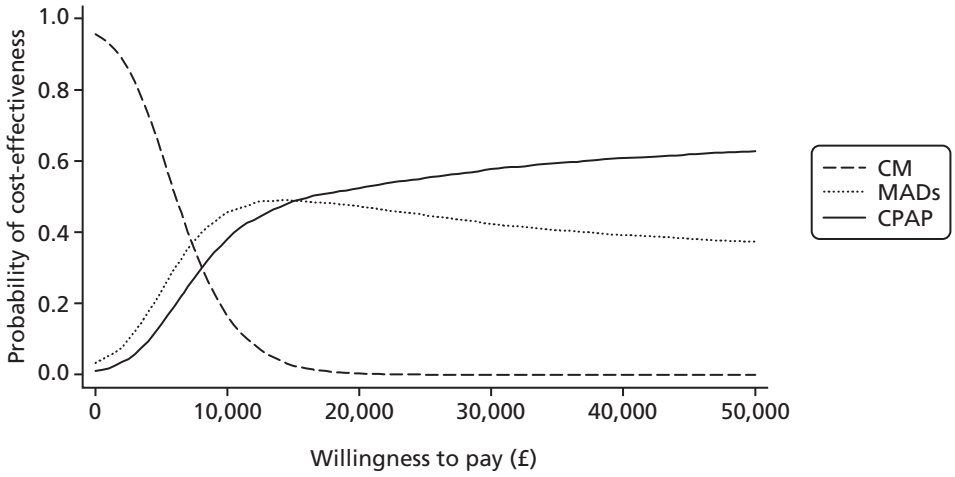

FIGURE 32 The cost-effectiveness acceptability curves (base-case analysis).

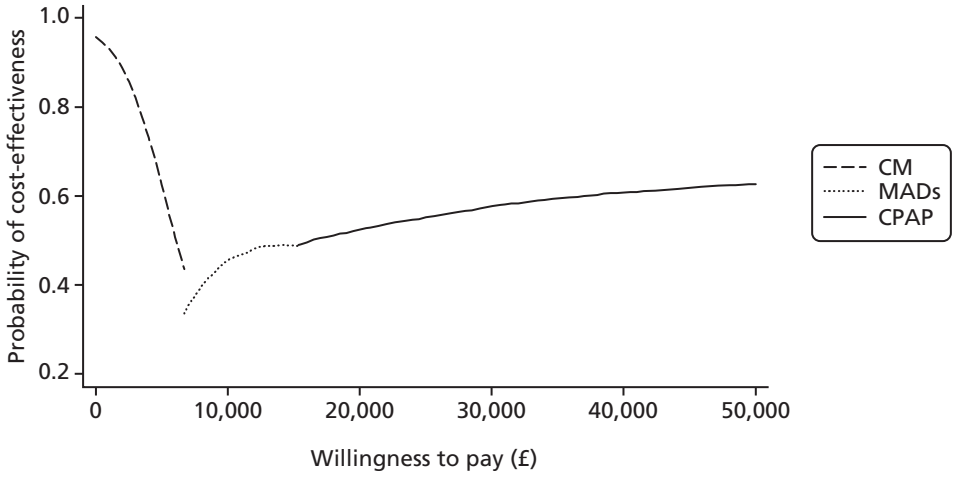

FIGURE 33 The cost-effectiveness acceptability frontier (base-case analysis).

Sensitivity analyses

A series of one-way deterministic sensitivity analyses were undertaken to explore the additional impact of changing specific input values on the cost-effectiveness results from the base case. These are presented in *Table 50*, which shows that decisions are not sensitive to the use of SF-6D utilities scores. This is also true for use of an alternative source of relative risk reduction associated with decreasing SBP. However, results and decisions are sensitive to assumptions about costs. For example, replacing device costs from SP2 with those for SP1 or bMAD costs leads to a different decision about the relative value of CPAP; in the case of SP1, CPAP would no longer be considered cost-effective (ICER = £89,182) by usual NICE threshold values, as the additional benefits of CPAP become relatively more expensive. Replacing SP2 device costs with bMAD leads to CPAP dominating bMAD as the benefits of CPAP are greater and costs are lower than bMAD. This is the case even if the lifespan of bMAD is assumed to be 2 years rather than 18 months.

The assumed lifespan of devices makes a difference to the optimum decision. A conservative estimate for the lifespan of the SP2 based on manufacturer and expert clinical opinion was 1 year. However, if the lifespan is increased to 18 months, SP2 becomes the most cost-effective intervention.

Use of device-specific costs and effects as observed in TOMADO indicates that SP2 dominates CPAP, given the comparatively higher QALYs gained. A comparison of bMAD with CPAP shows that both the costs and benefits of CPAP are lower. However, at a conventional threshold of £20,000 to £30,000 per QALY,

TABLE 50 Summary of ICERs following deterministic sensitivity analyses

	Type of deterministic sensitivity analysis	
	MADs vs. CM	CPAP vs. MADs
Base case	***£6687***	***£15,367***
Length life SP2 12 months – > 18 months	£4674	£44,066
Utility derivation		
EQ-5D-3L – > SF-6D QALYs	£8783	£16,225
Relative risk reduction for CVE associated with unit fall in SBP		
Reduction in cardiovascular risk associated from Lewington *et al.*[174]	£6741	£14,606
MAD costs		
SP1 device costs (assuming 12-month lifespan)	£1552	£89,182
bMAD costs (assuming 18-month lifespan)	£18,161	Dominant
bMAD costs (assuming 2-year lifespan)	£13,836	Dominant
TOMADO device-specific costs and treatment effects		
SP1 costs (12-month lifespan) and effects (ESS = –1.51)	£1656	£56,640
SP2 costs (12-month lifespan) and effects (ESS = –2.15)	£5425	Dominated
bMAD costs (18-month lifespan) and effects (ESS = –2.37)	£14,539	£57,907
Time horizon		
10-year time horizon	£8309	£90,998
RTA treatment effect		
Treatment effect from Tregear *et al.*, 2010[180] meta-analysis	£17,002	£16,428
Compliance		
CPAP compliance reduced by 5%	£6667	£40,668
CPAP compliance reduced by 10%	£6756	Dominated

the cost savings of CPAP compared with bMAD are larger than the value to 'compensate' for lower benefits of CPAP.

If a shorter time horizon is considered, CPAP becomes less cost-effective. This is because much of the benefit of CPAP results from its greater effectiveness in lowering BP. The benefits of reducing this risk factor for CVD would accrue later in patients' lives.

Summary and discussion

This chapter builds on a well-developed existing economic model, to assess the cost-effectiveness of MADs compared with CPAP and CM for patients with mild to moderate OSAH. Updated and new reviews of the evidence were conducted to reflect evidence that has emerged since the original modelling exercise and to better represent patients with mild to moderate OSAH. These covered the role of sleep apnoea in CVD, RTAs, HRQoL and long-term compliance by treatment.

Understanding of the mechanism of sleep apnoea on CVD has developed since the original model and, despite some conflicting evidence, the body of published studies indicates probable causality. However, there are still no reliable long-term data on cardiovascular outcomes under different treatment options for sleep apnoea. The model relies on differences in BP as proxies, reflected through prediction of risk using the Framingham equation, and direct evidence would improve the modelling. Data on BP from trials are heterogeneous and there are insufficient data to separate the effects by severity of disease. Data from new meta-analyses on the risk of RTA were used in sensitivity analysis rather than the base-case analysis because of difficulties in ascertaining the reasons for inclusion of papers. The use of generic measures of HRQoL in randomised trials to support conversion onto a utility scale is still rare, but TOMADO enabled a re-estimation of the relationship between ESS score and utility based on more data and for different levels of severity. The literature search for compliance data identified the longest-term follow-up study of CPAP compliance to date, but similarly robust data are still not available for MADs.

The meta-analysis presented in *Chapter 3* fed into the model and, by estimating a similar treatment effect for MADs and CPAP, indicates the likely importance of the cost of delivering the treatment options. The base-case analysis for MADs used trial data from *Chapter 2* based on the cost of SP2, with sensitivity analyses focusing on the cost of SP1 and bMAD as well as the length of life of the device. The costs of CPAP and CM were based on inflation-adjusted estimates from McDaid *et al.*[8] supplemented by company-supplied prices.

The results from the updated model suggest that, at conventional NICE thresholds of £20,000 to £30,000 per QALY, both MADs and CPAP are cost-effective compared with CM. CPAP is the preferred option, at a WTP per QALY of £15,000 and above. However, there is considerable uncertainty with CPAP having a 52% probability of being the most cost-effective option at £20,000 per QALY, compared with 47% for MAD. As cost per QALY increases to £30,000, the corresponding figures are 55% for CPAP and 45% for MAD. These suggest that MADs could be considered a legitimate treatment option for mild/moderate sleep apnoea, especially if CPAP is not tolerated.

The sensitivity analyses indicate that the cost of devices and their lifespan is important for the policy decision. For example, assuming costs for the bMAD, rather than the SP2, results in the CPAP being both more effective and less costly even with a 2-year lifespan for the bMAD. However, increasing the length of life of the MAD from 12 months to 18 months, or using SP1 costs in place of those for SP2, results in an increase in the incremental cost per QALY for CPAP relative to MAD to £44,066 and £90,998, respectively. Long-term data on the lifetime of MADs in routine practice would improve precision of estimates.

The sensitivity analysis also indicated the importance of compliance. Reducing compliance with CPAP by 5% increases the ICER of CPAP relative to MADs to £40,000/QALY. A reduction of 10% in compliance with CPAP means that QoL gains for CPAP over MADs are lost and the cost is higher. As there is evidence that, for milder sleep apnoea, compliance with CPAP falls and, therefore, that MADs may be more cost-effective, comparable compliance data for MADs are required to confirm or refute this.

Finally, the sensitivity analysis indicates the importance of the time frame of the analysis. Moving from a lifetime to a 10-year time horizon changes conclusions with respect to the relative value of CPAP and MADs; the cost per QALY of CPAP increases from £15,000 to £91,000 per QALY. This is largely because the cost of CPAP is not spread over a sufficiently long period and the value of the increased benefits (e.g. reduced CVD) is not accounted for.

Chapter 5 Discussion and conclusions

Summary of main findings

The Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea–hypopnoea

In an adequately powered and efficiently designed randomised study, TOMADO showed that, for patients with mild to moderate OSAH, the rate of apnoea/hypopnoea events per hour for each of the three non-adjustable MADs studied was significantly lower than with no treatment. Although the effect on AHI compared with no treatment increased with sophistication of the MAD, the between-device differences were small and not statistically significant at commonly used thresholds. Arbitrarily defined response to treatment was achieved in just under half the patients when using the SP2 and bMAD and in approximately one-fifth when using no treatment, compared with baseline measurements. The likelihood of response was most closely related to BMI at baseline and during the study. Results for 4% ODI, which is more commonly used in clinical practice in the UK, were very similar to those for AHI.

The effects of MAD on ESS score mirrored those for apnoea/hypopnoea events per hour, with the SP2 and bMAD having a greater effect than the SP1.

Although the trial treatments were administered over a short time period, some evidence of compliance with treatment emerged. This indicated that one reason for the poorer performance of the SP1 may be lower compliance, as shown by the shorter duration of use per night and greater likelihood of discontinuation during the treatment period. The SP1 was also less likely to be chosen as the preferred device by those patients who completed the trial. Similarly, partners of the trial patients reported improvements in snoring during MAD use, with the SP1 having a weaker effect than SP2 and bMAD.

The relationship between MAD treatment and sleepiness-related functioning and QoL (FOSQ and SAQLI) showed a similar pattern to that for AHI and ESS outcomes, with significant effects for all MADs compared with no treatment, and the SP1 performing less well than SP2 and bMAD. Detailed examination of the questionnaires suggested small improvements across all dimensions, but that scales measuring the effect of sleepiness on activities (FOSQ, SAQLI), general productivity (FOSQ) and symptoms (SAQLI) were particularly affected by MAD treatment. General HRQoL measures were largely insensitive to MAD treatment, with the exception that the SP2 was associated with significantly higher SF-6D QALYs compared with control (accounting for baseline differences).

A range of secondary outcome measurements were taken and the general messages from these outcomes were consistent with those of the a priori stated primary outcome (AHI) and main secondary outcome (ESS score). Although these secondary outcomes were useful indicators of patient compliance and QoL and give a more complete picture of the effects of MADs, they should not be overinterpreted or be used in combination as an indicator of the strength of the effects of different MADs.

There were few SAEs during the study period and, out of the four SAEs reported by four patients, three were short-term, cardiac-related events. Two were considered possibly related to OSAH and one was considered possibly related to OSAH or MADs because the patient was on MAD treatment at the time. Almost all patients reported at least one minor AE, with mouth discomfort and excess salivation being the main problems.

The short treatment period meant little opportunity to observe an effect of MADs on RTAs or CVEs, which are the desired longer-term implications of control of EDS. However, patients did report improvements in sleepiness during driving and fewer interruptions to journeys during MAD use.

The trial-based cost-effectiveness analysis was also limited by the short treatment period, but the improvements in HRQoL for all MADs compared with no treatment meant that all were cost-effective at a WTP of £20,000 per QALY. The SP2 was the most cost-effective MAD up to a WTP per QALY of £39,800.

Thus, based on TOMADO, while all MADs have significant benefits and few harms compared with no treatment, the SP2 appears to achieve more benefits than the SP1 and almost all the benefits of the more sophisticated bMAD. However, it achieves these benefits at a lower cost than the bMAD and, so, it can be recommended on cost-effectiveness grounds.

Meta-analysis

Cochrane reviews from Lim *et al.*[51] and Giles *et al.*,[33] and a meta-analysis from McDaid *et al.*,[8] were updated for the major outcomes that were included in TOMADO. The systematic review identified 12 studies including 629 patients comparing MADs with CM, 13 studies including 746 patients comparing MADs with CPAP and 52 studies including 5400 patients comparing CPAP with CM, all of which had an AHI or ESS score as one of the study end points. Study participants were predominantly middle-aged men who were overweight or obese. Trials including CPAP were generally conducted in patients with more severe OSAH according to AHI than trials of MADs with CM. CM included a range of treatments including sham devices, sham CPAP, placebo tablets, lifestyle advice and no treatment. Although we included only randomised trials, quality was variable, with many trials having fewer than 50 patients and treatment periods were generally short. Both parallel-group and crossover trials have been used.

Heterogeneity between studies, assessed by the I^2 statistic, was variable and often unreliable as a result of the small number of studies available. Some heterogeneity could be explained, particularly by baseline severity, but there remained unexplained heterogeneity. Although random-effects methods were used, the validity of combining trials in formal meta-analysis is questionable and cautious interpretation is required. Partly for this reason a network meta-analysis including all trials was not attempted.

Both MADs and CPAP resulted in significant improvements in AHI, with the greatest benefit evident in trials of CPAP against CM. However, the reduction in AHI was strongly related to baseline AHI, which is natural since a higher baseline allows greater scope for an absolute decrease. In head-to-head trials of MADs against CPAP, the performances of the two treatments were more similar and there were no head-to-head trials in patients with mild-range AHI.

Excessive daytime sleepiness assessed by the ESS is less variable than AHI so most trial populations were classed as having moderate baseline EDS. The differences between the effects of MADs and CPAP on subjective daytime sleepiness assessed by ESS were smaller and not significant in head-to-head comparisons. The estimated effects on EDS were strongly related to baseline severity and, to a lesser extent, baseline AHI. When trials of similar baseline characteristics were compared, there was little difference between the effects of MADs and CPAP on post-treatment ESS score when assessed against CM, and this is reinforced by the results from head-to-head trials. Treatment effects appeared to be stronger in trials with short duration of treatment, possibly reflecting a tailing-off of compliance over time.[45]

The meta-analysis did not provide much insight into the effect of treatment on daytime BP above previous meta-analyses. There was a large amount of heterogeneity in the methodology used for assessing surrogates of cardiovascular outcomes. Our meta-analysis focused on daytime SBP and DBP because it was included as the primary marker of hypertension in TOMADO and because it is used in the Framingham equation that provides input into the long-term economic model. There was a small effect of both CPAP and MADs on SBP compared with CM, with little to choose between the two.

Few trials, apart from TOMADO, have contributed to the literature on HRQoL so that it was difficult to draw reliable conclusions. In common with TOMADO, there was evidence for a significant improvement in HRQoL as a result of these treatments in the meta-analysis, but the size of the effects is unlikely to be clinically important. The paucity of information did not allow more detailed analysis of published HRQoL. Given the demonstrated clinical effectiveness of both CPAP and MAD, further trial-based studies of HRQoL are unlikely to be conducted, but observational studies to supplement existing trial data would be useful.

Cost-effectiveness

In order to assess the effect of CPAP and MADs on long-term outcomes, including cardiovascular hazards and RTAs, we reviewed and updated an economic model provided by the University of York Centre for Health Economics, developed for McDaid *et al.*[8] The model inputs were adapted to better represent patients with mild to moderate OSAH and updated to reflect new research since the original model was developed. Systematic searches of published literature were undertaken to update model inputs related to CHD and stroke risk, RTA rates, HRQoL and costs. In addition, data from TOMADO were used for device-specific costs and to create a more precise mapping function between ESS score and utility measures (both EQ-5D-3L and SF-6D) that would also be more applicable to patients with mild to moderate OSAH.

In the base case, using the SP2 as the 'standard' device, MADs were found to be more costly and more effective than CM in patients with mild to moderate OSAH, with an estimated ICER of £6687 per QALY. Compared with MADs, CPAP was more costly and more effective, with an estimated ICER of £15,367. While it was clear that both of these treatments were better than CM, there was substantial uncertainty in the choice, with probabilities of being cost-effective at a WTP of £20,000 per QALY of 47% for MADs and 52% for CPAP. Corresponding figures at a WTP of £30,000 per QALY are 45% for MADs and 55% for CPAP.

The results were sensitive to a number of parameter inputs. If the average lifespan of the SP2 is increased from 12 months to 18 months, the ICER for CPAP compared with MADs becomes £44,066, which is more than traditionally accepted WTP thresholds. Additionally, choice of device has an important effect on the economic decision, with the ICER for the SP1 compared with CM being £1552, and for the bMAD compared with CM being £13,836. The ICER for CPAP compared with the SP1 is high at £89,182, but CPAP is both cheaper and more effective than the bMAD. Using device-specific inputs for treatment effects further confirms the superiority of the SP2 as the most cost-effective treatment for patients with mild to moderate OSAH, although substantial decision uncertainty remains. Differential compliance rate for CPAP also reduces its cost-effectiveness so that MADs become both less costly and more effective if compliance to CPAP is of the order of 90% of SP2.

Strengths and limitations

Strengths

The TOMADO study was a relatively large and rigorously conducted RCT, with robust and precisely estimated treatment effects. To our knowledge, TOMADO is the first trial of MADs in mild to moderate OSAH with both clinical, patient-centred and cost-effectiveness outcomes. The interpretation of results is clear and consistent among different outcome measures. In contrast with most other published randomised trials, TOMADO included a detailed study of HRQoL. This showed consistency with clinical outcomes and highlighted the effects of MADs on activity, general productivity and symptoms. Although these effects might be described as modest, it is remarkable that they can be observed after a short period of treatment. TOMADO fed into updated meta-analyses that offered stronger insights into the relative effectiveness of MADs and CPAP in patients with OSAH. In addition, the effects of baseline severity

have been highlighted and used to explain some of the differences in effects between MADs and CPAP. TOMADO also fed into an updated model of the long-term cost-effectiveness of MADs and CPAP devices which was adapted, for the first time, to mild to moderate OSAH.

The study was applicable to general sleep practice as it recruited participants who had been referred from primary care to the sleep clinic at Papworth Hospital. The SP1 and SP2 devices used in the study are available in many countries and are similar to other thermoplastic and semi-bespoke MADs on the market. Although the bMAD was fitted and manufactured by a hospital maxillofacial laboratory, it was done using skills, materials and facilities common to dental sleep services.

Limitations

Women, younger patients and patients with a BMI in the normal range were under-represented in the patients included in TOMADO and other trials so that results may not be generalisable to these populations.

In evaluating three non-adjustable MADs representing a range of sophistication and cost, TOMADO could not also include an adjustable MAD (aMAD). These are increasingly recommended,[202,203] but are often more costly. They allow gradual titration of mandibular advancement according to tolerance and efficacy. This may give larger treatment effects by achieving ultimately greater jaw protrusion without lowering compliance, but whether or not aMADs are more effective than non-adjustable MADs remains unproven.

The aim for the bMAD was at least 50% maximal protrusion, but in practice this value was often lower; and similar to that achieved independently by patients with the other devices. This reflects the pragmatic nature of TOMADO, making its findings more applicable to the wider NHS. AHI effects have been shown to be proportional to mandibular protrusion.[204–206] Mean (SD) protrusion in this trial was between 52.5% (27.8%) of maximal advancement with the SP2 and 63.4% (22.6%) of maximal advancement with the SP1. These figures are lower than reported in other studies,[69,74,76,83] many of which used an aMAD.[23,52,68,72,75,79,81,84] Nevertheless, although heterogeneity limits comparison, many of these trials did not report greater AHI effects than TOMADO.[23,74,76,83] Furthermore, TOMADO showed no association between protrusion and AHI effects, adding to existing evidence that greater protrusion may be no more effective in milder OSAH. For example, Tegelberg *et al.*[207] compared patients with mild to moderate OSAH who had devices at 50% and 75% maximal protrusion and found no difference in AHI effects. Quality studies comparing aMADs to non-adjustable devices are lacking. A small, non-randomised trial compared an aMAD with a thermoplastic MAD and found a modest difference in AHI favouring the adjustable device.[208] However, the sample size was small and the differing costs of the two devices (paid for by the patients) probably influenced device selection. A retrospective study of 805 patients demonstrated a small but statistically significant difference in AHI between an adjustable and non-adjustable device (7.6 vs. 10.0, respectively), but did not show a significant difference in ESS score or tolerability.[209] This study was also limited by device selection which was non-randomised. Other studies which have featured both adjustable and non-adjustable MADs have reduced the likelihood of finding real-life effect size differences by using similar or identical protrusions for both devices. Therefore, whether or not adjustability improves MAD effectiveness in OSAH remains uncertain and requires rigorous RCT evaluation.

In the meta-analysis and because of the economic decision analysis, all MADs were considered as a single treatment modality. There were too few studies to allow robust subgroup analyses and so we were unable to identify the more modest differences in effects between different MADs. It has been suggested that future meta-analyses distinguish between trials of non-adjustable MADs and those using aMAD.[209,210] From the 2006 Cochrane analysis, considering only trials comparing CPAP with aMADs moved the sleepiness (ESS score) effect size in favour of MADs, but not significantly.[33] We considered performing a similar subgroup analysis when updating the meta-analysis. However, device adjustability could not always

be determined,[80,82] and the potential advantage of titratable advancement was sometimes negated by the use of uniform aMAD protrusion.[83] Classifying trials as fixed MADs and aMADs, in order to perform separate meta-analyses, is not straightforward. For example, one trial with relatively weak treatment effects that has previously been excluded from aMAD reviews[22] used two non-adjustable MADs, but the authors reported near-maximal (80%) jaw protrusion and performed 'pseudotitration' by adapting devices to optimise comfort and benefits. For these reasons we did not include a meta-analysis based on MAD adjustability.

Three separate meta-analyses were conducted comparing MADs with CM, MADs with CPAP and CPAP with CM. A more sophisticated analysis would have been to combine the studies into a network meta-analysis, thereby adding strength to all comparisons and better aligning the studies. However, these analyses rely on the associative law, which was unlikely to be true in this case, given the greater severity of OSAH in populations undergoing trials of CPAP. Furthermore, the heterogeneity observed between studies in *Chapter 3* suggested that combining results within and across different treatments may not be sensible. The likely implication of doing separate meta-analyses is a loss of some precision in the results.

Conservative management encompassed a wide range of control treatments so that their influence on the trial-based treatment effects was difficult to estimate with any precision.

In our systematic review we used the Jadad score as a measure of study quality in order to be consistent with previous reviews.[8,33,51] This is a rather insensitive tool and did not provide substantial insight into the relative quality of different studies. It did, however, provide a broad structure for summarising design features reported in existing clinical trials.

The use of data in the model still reflects the lack of robust sources in some important areas. RTA risk after treatment with MADs is still inferred based on ESS score treatment effects compared with CPAP, rather than using direct data. While the link between OSAH, hypertension and cardiovascular outcomes may be increasingly understood, the treatment effects in the model are still based on short-term BP data rather than long-term CVD outcomes. Given the similarity in ESS score, treatment effect pooled from the meta-analysis, the importance of compliance and determining how prolonged the effects are, is clear but there remains a lack of good data to reflect this for MADs. Only crude sensitivity analyses were able to explore the effect this has on cost-effectiveness.

Conclusions

Implications for service

- CPAP remains the most clinically effective and cost-effective treatment for patients with moderate to severe OSAH based on reduction in AHI. For patients who are intolerant of CPAP, treatment with a MAD is also effective compared with no treatment.
- CPAP and MADs are equally effective treatment options for patients with mild to moderate OSAH and there is little to choose between them in terms of clinical effectiveness and cost-effectiveness, although this is contingent on similar compliance rates.
- Of the three MADs investigated, the semi-bespoke SP2 (or an equivalent MAD) is the most cost-effective treatment in the short term and should be used as the first-choice device, with the custom-made bMAD reserved for patients who have difficulties producing the SP2 mould, whose dental eligibility is more marginal or for whom other obstacles to using the SP2 may be overcome by dental intervention with a bMAD.

Implications for research priorities

- Head-to-head pragmatic clinical effectiveness and cost-effectiveness comparisons of adjustable and non-adjustable MADs, across the entire range of OSAH severity, are still required.
- Head-to-head comparisons of CPAP and MADs in milder OSAH, would reduce the uncertainty surrounding the current guideline stance that CPAP should be reserved as second-line treatment in this patient group.
- There is increasing evidence to suggest that the similar effects of CPAP and MADs on EDS may be as a result of differential adherence to treatment. However, there is limited information on this beyond short-term trials. Medium- to long-term compliance with MADs and CPAP should be monitored and reported. Such work would be strengthened by emerging tools to objectively monitor MAD compliance, which would benefit from further clinical and additional economic evaluation in their own right. Observational studies of HRQoL over time to supplement existing trial data would be useful to understand the treatment outcomes of greatest relevance to patients. In particular, it would be useful to know more about the durability of devices.
- Further data on longer-term risk of CVD and its risk factors would reduce model uncertainty and improve the precision of estimates of clinical effectiveness and cost-effectiveness.

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TOMADO was conceived by **Dr Timothy Quinnell** (Consultant Respiratory and Sleep Disorders Physician, Papworth Hospital NHS Foundation Trust), who had overall responsibility for the study. **Professor Linda Sharples'** Unit (Professor of Statistics and Director of the Comprehensive Health Research Division at the University of Leeds Clinical Trials Research Unit) had overall responsibility for the statistics and research methodology. **Professor Julia Fox-Rushby** (Director of the Health Economics Research Group, Brunel University) had overall responsibility for the health economics. The randomised controlled trial was designed by Dr Quinnell, Professor Sharples and **Rebecca Chadwick** (Clinical Research Manager, Papworth Hospital NHS Foundation Trust).

Mr Malcolm Cameron (Consultant Oral and Maxillofacial Surgeon, Addenbrooke's NHS Foundation Trust) oversaw dental elegibility for the trial and the production and fitting the bMAD and **Professor Mary Morrell** (Professor of Sleep and Respiratory Physiology, Imperial College) contributed to trial management and data interpretation. **Dr Marcus Pittman** (Specialist Registrar, Papworth Hospital NHS Foundation Trust) was responsible for patient recruitment and management during the randomised trial.

Clare East (Clinical Research Assistant, Papworth Hospital NHS Foundation Trust) and **Dr Abigail Clutterbuck-James** (Trial Manager, Papworth Hospital NHS Foundation Trust) obtained the trial data, along with Dr Pittman and Miss Chadwick.

Dr Mike Davies, **Dr Ian Smith** and **Dr Nick Oscroft** (Consultant Respiratory and Sleep Disorders Physicians, Papworth Hospital NHS Foundation Trust) aided trial data collection.

Maxine Bennett (Statistician, Medical Research Council Biostatistics Unit), Professor Sharples and **Jake Jordan** (Health Economist, Brunel University) analysed and interpreted the trial data along with **Matthew Glover** (Health Economist, Brunel University) and Professor Julia Fox-Rushby.

The systematic review of the literature for *Chapter 3* was conducted by Miss Bennett, Mr Glover, Dr Clutterbuck-James and Miss Chadwick and the meta-analysis was conducted and interpreted by Professor Sharples.

The systematic review of the literature for *Chapter 4* and the adaptation of the economic model were conducted by Mr Glover under the supervision of Professor Fox-Rushby.

Professor Sharples created the first draft of the report along with Dr Quinnell, Mr Glover and Professor Fox-Rushby. Dr Clutterbuck-James edited the manuscript and all authors had the opportunity to critically revise it.

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Appendix 1 Epworth Sleepiness Scale

Over the last 4 weeks, how likely were you to fall asleep in the following situations, in contrast to just feeling 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 in the afternoon (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				

Appendix 2 Functional Outcomes of Sleep Questionnaire

Note: in this questionnaire, when the words "sleepy" 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.

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

Please complete the form for how you have been over the **past 4 weeks**.

	I don't do this activity for other reasons	No difficulty	Yes, a little difficulty	Yes, moderate difficulty	Yes, extreme difficulty
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) Do 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 your family or friends in your home because you become sleepy or tired?	☐	☐	☐	☐	☐

	I don't do this activity for other reasons	No difficulty	Yes, a little difficulty	Yes, moderate difficulty	Yes, extreme difficulty
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?	☐	☐	☐	☐	☐

		No	Yes, a little	Yes, moderately	Yes, extremely
Q15) Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	☐	☐	☐	☐	☐

In what way has your relationship been affected?

Free text.

	I don't do this activity for other reasons	No difficulty	Yes, a little difficulty	Yes, moderate difficulty	Yes, extreme difficulty
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 theatre 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?		☐	☐	☐	☐

		Very Low	Low	Medium	High
Q26) How would you rate yourself in your general level of activity?		☐	☐	☐	☐
	I don't engage in sexual activity for other reasons	**No**	**Yes, a little**	**Yes, moderately**	**Yes, extremely**
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 sleepy or tired?	☐	☐	☐	☐	☐

Appendix 3 Sleep Apnoea Quality of Life Index

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 amount	Moderate amount	Moderate to large amount	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)?	☐	☐	☐	☐	☐	☐	☐
How often have you had to use all your energy to accomplish your most important activity (e.g. work, school, childcare, housework)?	☐	☐	☐	☐	☐	☐	☐
How much difficulty have you had finding the energy to do other activities (e.g. exercise, relaxing activities)?	☐	☐	☐	☐	☐	☐	☐
How much difficulty have you had fighting to stay awake?	☐	☐	☐	☐	☐	☐	☐
How much of a problem has it been to be told that your snoring is irritating?	☐	☐	☐	☐	☐	☐	☐
How much of a problem have frequent conflicts or arguments been?	☐	☐	☐	☐	☐	☐	☐
How often have you looked for excuses for being tired?	☐	☐	☐	☐	☐	☐	☐
How often have you not wanted to do things with your family and/or friends?	☐	☐	☐	☐	☐	☐	☐
How often have you felt depressed, down, or hopeless?	☐	☐	☐	☐	☐	☐	☐
How often have you been impatient?	☐	☐	☐	☐	☐	☐	☐
How much of a problem has it been to cope with everyday issues?	☐	☐	☐	☐	☐	☐	☐
How much of a problem have you had with decreased energy?	☐	☐	☐	☐	☐	☐	☐
How much of a problem have you had with fatigue?	☐	☐	☐	☐	☐	☐	☐
How much of a problem have you had waking up feeling unrefreshed?	☐	☐	☐	☐	☐	☐	☐

Appendix 4 Medical outcomes study Short Form questionnaire-36 items

Instructions: this survey asks for views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. If you are unsure about how to answer a question, please give the best answer you can.

GENERAL HEALTH

1. In general, would you say your health is: (Please mark one box).

Excellent ☐
Very good ☐
Good ☐
Fair ☐
Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please mark one box).

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

HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Please mark one box on each line.)

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 half a mile.

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

Walking 100 yards.

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? (Please mark one box on each line.)

Cut down on 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 effort).

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)? (Please mark one box on each line.)

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? (Please mark one box.)

Not at all ☐
Slightly ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

7. How much bodily pain have you had during the past 4 weeks? (Please mark one box.)

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)? (Please mark one box.)

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: (Please mark one box on each line.) . . .

a. Did you feel full of life?

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 low?

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 with family, 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? (Please mark one box on each line.)

a. I seem to get ill more 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 ☐

Appendix 5 European Quality of Life-5 Dimensions 3-level version

Please indicate which statements best describe your health state, **today**, by marking one box in each group.

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 ❑

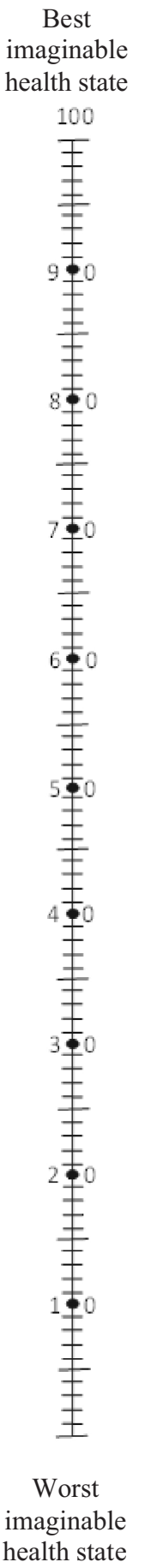
Anxiety/Depression

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.

We 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



Appendix 6 Individual health-care resource use case report form

TOMADO

Participant No: ☐☐☐ Initials: ☐☐☐

Trial Stage: Baseline ☐ Treatment 1 ☐ Treatment 2 ☐ Treatment 3 ☐ Treatment 4 ☐

Health Care Usage

During the past **4 weeks**, has the patient used any health care service? Yes ☐ No ☐

If Yes, how many times:	No. times	No. times related to OSA	
Visited a GP? (not including for repeat prescriptions)	☐	☐	
Been seen at home by a GP?	☐	☐	
Visited a nurse?	☐	☐	
Been seen at home by a nurse?	☐	☐	
Contacted general practice for telephone advice?	☐	☐	
Contacted NHS Direct for telephone advice?	☐	☐	
Contacted the trial helpline at RSSC?	☐	☐	(n/a at baseline)
Had an ambulance called for themselves?	☐	☐	
Visited an Accident and Emergency department?	☐	☐	
Attended an out-patient clinic?	☐	☐	
Been admitted to hospital overnight?	☐	☐	(Not including sleep studies)
Been admitted to hospital overnight, as an emergency?	☐	☐	**Complete details of admission on next page**
Spent the night in hospital?	☐	☐	
Visited a dentist?	☐	☐	
Additional visit to Addenbrooke's for Bespoke MAD?	☐	☐	
Other? (please specify)	☐	☐	
☐			

Trial Stage: Baseline ☐ Treatment 1 ☐ Treatment 2 ☐
Treatment 3 ☐ Treatment 4 ☐

Health Care Usage Continued - Complete if patient admitted to hospital:

Length of stay: ☐☐ days

Reason for admission:
Heart Attack ☐ Stroke ☐
RTA ☐ Other (specify): ☐

Ward type(s):
Cardiac ☐ Surgery - Cardiac ☐
Surgery - General ☐ Surgery - Respiratory ☐
Respiratory Medical ☐ ICU ☐
Other (specify): ☐

Test(s) performed:
MRI ☐ CT Scan ☐
X-ray ☐ Angiogram ☐
Angioplasty ☐ Other (specify): ☐

Appendix 7 Unit costs used and data sources

Resource use item	Mean (2011/12 £)	SD	Source	Notes
MAD				
SP1	£1.62			Pro-rata 4 weeks
SP2	£9.85			Pro-rata 4 weeks
bMAD	£1.95			Pro-rata 4 weeks
Measurement consult (maxillofacial surgeon)	£5.66	£7.42	NHS Ref 144: first attendance	Pro-rata 4 weeks
Fitting consult (maxillofacial surgeon)	£4.72	£7.43	NHS Ref 144: follow-up	Pro-rata 4 weeks
Dentist visit, SP2 moulding	£11.52	£13.77	NHS Ref CZ38Y	Pro-rata 4 weeks
Additional visit to Addenbrooke's Hospital (bMAD)	£4.72	£7.43	NHS Ref 144: follow-up	Pro-rata 4 weeks
Visits				
GP visits	£43.40	£8.68	PSSRU 10.8b	Assumes 14-minute appointment
GP home visits	£28.23	£5.65	PSSRU 10.8b	Assumes 14-minute appointment
Nurse (GP practice) visits	£9.10	£1.82	PSSRU 10.6	Assumes 14-minute appointment
Nurse (specialist community) home visits	£11.67	£2.33	PSSRU 10.4	Assumes 14-minute appointment
Dentist (normal visit)	£105.04	£43.96	NHS Ref: 450	
A&E visit	£64.09	£15.00	NHS Ref: VB11Z	
Outpatient clinical visit	£105.89	£47.08	NHS Ref: average of all outpatient procedures	
Other hospital visit	£105.89	£47.08	NHS Ref: average of all outpatient procedures	
Telephone calls				
GP telephone calls	£22.00	£4.40	PSSRU 10.8b	Assumes 7.1-minute call
NHS Direct calls	£22.00	£4.40	PSSRU 10.8b	Assumes 7.1-minute call
Contacted trial helpline	£22.00	£4.40	PSSRU 10.8b	Assumes 7.1-minute call
Hospital admissions *Heart attack*				
EI	£2251.13	£1073.39	NHS Ref: EB10Z	
Excess bed-days	£312.29	£111.89	NHS Ref: EB10Z	
NEI	£1966.78	£674.38	NHS Ref: EB10Z	
Excess bed-days	£242.46	£67.30	NHS Ref: EB10Z	
RTA	£64.09	£15.00	NHS Ref: VB11Z	
Stroke				
EI	£3302.62	£2855.17	NHS Ref: AA22A/B	
Excess bed-days	£283.34	£82.35	NHS Ref: AA22A/B	

APPENDIX 7

Resource use item	Mean (2011/12 £)	SD	Source	Notes
NEI	£3082.45	£900.66	NHS Ref: AA22A/B	
Excess bed-days	£236.16	£71.92	NHS Ref: AA22A/B	
Diagnostic tests				
MRI	£157.24	£51.20	NHS Ref: average of all MRI codes	
CT	£136.62	£48.84	NHS Ref: average of all CT scan codes	
Radiography	£32.21	£6.44	Auguste *et al.*[60]	
Angiogram	–	–		
Other service use				
Ambulance call-out	£214.02	£53.96	NHS Ref: ASS01/02	
Hospital overnight stay	–	–		
Hospital overnight stay (emergency case)	–	–		
Other classified resource use				
Acupuncture	£80.33	£118.33	NHS Ref: HB63Z used as proxy	
Counsellor session	£60.00	–	PSSRU 2.7	
Echocardiogram	£84.01	£17.34	NHS Ref: RA60A	
Pre-op assessment	£120.71	£35.00	NHS Ref: 100	
Blood test	£2.95	£1.77	NHS Ref: DAP839	
Occupational health session	£60.68	£29.16	NHS Ref: 651	
Ophthalmologist session	£85.12	£19.23	NHS Ref: 130	
Osteopath appointment	£40.70	£13.20	NHS Ref: 650 as proxy	
Physiotherapist appointment	£40.70	£13.20	NHS Ref: 650	
Health trainer session	£40.70	£13.20	NHS Ref: 650 as proxy	
Nasal polyp removal	£132.34	£51.16	NHS Ref: CZ12Y	
Podiatrist session	£41.17	£18.96	NHS Ref: 651	
Minor surgery	£132.34	£51.16	NHS Ref: CZ12Y used as proxy	
Contacted dentist over the telephone	£105.04	£43.96	NHS Ref: 450	
Complete heart block, pacemaker fitted, overnight stay	£1708.17	£901.74	NHS Ref: EA39Z	
Atrial flutter, 3 days' hospital stay	£1360.98	£802.18	NHS Ref: EB07I	
Tonsillitis, overnight hospital stay	£338.62	£159.30	NHS Ref: CZ01Y	
Chest pain, hypertension, day case	£446.00	£156.91	NHS Ref EB04I	

CT, computerised tomography; EI, elective inpatient stay; MRI, magnetic resonance imaging; NEI, non-elective inpatient stay.
NB: PSSRU, Personal Social Service Research Unit, 2011.

Appendix 8 Summary of resource use costs valued in 2011/12 British pounds sterling

Resource use item	Mean unit cost	Baseline ($n = 83$)		No treatment ($n = 78$)		SP1 ($n = 81$)		SP2 ($n = 78$)		bMAD ($n = 77$)	
		Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD
GP visits[a]	£43.40	£11.00	£23.30	£12.20	£26.10	£15.50	£30.20	£16.70	£29.90	£14.70	£39.00
GP home visits[a]	£28.20	£0.30	£3.10	£0.40	£3.20	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Nurse (GP practice) visits[a]	£9.10	£0.00	£0.00	£0.40	£2.30	£0.70	£2.80	£0.20	£1.40	£0.40	£1.80
Nurse (specialist community) home visits[a]	£11.70	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.20	£1.30
GP telephone calls[a]	£22.00	£0.00	£0.00	£0.30	£2.50	£0.00	£0.00	£0.30	£2.50	£0.30	£2.50
NHS Direct calls[a]	£22.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.30	£2.50
Contacted trial helpline[a]	£22.00	£0.00	£0.00	£0.00	£0.00	£0.50	£4.90	£0.30	£2.50	£1.40	£7.40
Ambulance call out[b]	£214.00	£0.00	£0.00	£2.70	£24.20	£2.60	£23.80	£0.00	£0.00	£0.00	£0.00
A&E visit[b]	£64.10	£0.00	£0.00	£0.80	£7.30	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Outpatient clinical visit[b]	£105.90	£51.00	£74.60	£14.90	£44.30	£19.60	£44.60	£10.90	£32.30	£12.40	£45.40
Dentist (normal visit)[b]	£105.00	£8.90	£29.40	£16.20	£38.10	£22.00	£54.40	£16.20	£41.70	£12.30	£34.00
Other											
Acupuncture[b]	£80.30	£0.00	£0.00	£1.00	£9.10	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Minor surgery[c]	£132.30	£0.00	£0.00	£0.00	£0.00	£1.60	£14.70	£0.00	£0.00	£0.00	£0.00
Blood test[b]	£3.00	£0.00	£0.00	£0.30	£2.70	£0.10	£1.30	£0.00	£0.00	£0.00	£0.00
Counsellor session[b]	£60.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.80	£6.80	£0.00	£0.00
Echocardiogram[b]	£84.00	£0.00	£0.00	£0.00	£0.00	£1.00	£9.30	£0.00	£0.00	£0.00	£0.00
Pre-op assessment[b]	£120.70	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£4.60	£23.40	£3.10	£19.30

Resource use item	Mean unit cost	Baseline ($n = 83$)		No treatment ($n = 78$)		SP1 ($n = 81$)		SP2 ($n = 78$)		bMAD ($n = 77$)	
		Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD
Health trainer session[b]	£40.70	£0.00	£0.00	£1.00	£9.20	£0.00	£0.00	£1.00	£9.20	£0.00	£0.00
Occupational health session[b]	£60.70	£0.00	£0.00	£0.00	£0.00	£0.70	£6.70	£0.00	£0.00	£0.00	£0.00
Ophthalmologist session[b]	£85.10	£0.00	£0.00	£0.00	£0.00	£1.10	£9.50	£0.00	£0.00	£0.00	£0.00
Optician[d]	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Osteopath appointment[b]	£40.70	£0.50	£4.50	£2.10	£18.40	£0.00	£0.00	£0.50	£4.60	£0.00	£0.00
Physiotherapist appointment[b]	£40.70	£1.00	£6.30	£2.10	£14.50	£0.50	£4.50	£0.00	£0.00	£1.10	£6.50
Nasal polyp removal[b]	£132.30	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£1.70	£15.10
Podiatrist session[b]	£41.20	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.50	£4.70
Contacted dentist over the telephone[b]	£105.00	£0.00	£0.00	£1.30	£11.90	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Hospital overnight, length of stay[e]	–	–	–	–	–	–	–	–	–	–	–
Heart attack[e]	–	–	–	–	–	–	–	–	–	–	–
RTA requiring medical treatment[f]	£64.10	£0.00	£0.00	£0.80	£7.30	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Stroke[b]	–	–	–	–	–	–	–	–	–	–	–

Resource use item	Mean unit cost	Baseline ($n = 83$)		No treatment ($n = 78$)		SP1 ($n = 81$)		SP2 ($n = 78$)		bMAD ($n = 77$)	
		Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD	Mean cost/participant	SD
Other											
Tonsillitis, overnight hospital stay[b]	£338.60	£0.00	£0.00	£0.00	£0.00	£4.20	£37.60	£0.00	£0.00	£0.00	£0.00
Atrial flutter, 3 days' hospital stay[b]	£1361.00	£0.00	£0.00	£17.40	£154.10	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Complete heart block, pacemaker fitted overnight stay[b]	£1708.20	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£22.20	£194.70
Chest pain, hypertension, day case[b]	£446.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£5.80	£50.80
MRI[b]	£157.20	£0.00	£0.00	£2.00	£17.80	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
CT[b]	£136.60	–	–	–	–	–	–	–	–	–	–
Radiography[g]	£32.20	£0.00	£0.00	£0.00	£0.00	£0.40	£3.60	£0.00	£0.00	£0.40	£3.70
Angioplasty[e]	–	–	–	–	–	–	–	–	–	–	–
Angiogram[e]	–	–	–	–	–	–	–	–	–	–	–
Total	–	£72.70	£80.80	£76.10	£175.10	£70.70	£91.50	£51.50	£67.50	£76.70	£214.80

CT, computerised tomography; MRI, magnetic resonance imaging.
a PSSRU costs 2011.
b NHS Ref cost 2011/12.
c NHS Ref applied cost of nasal polyp removal as proxy.
d No NHS cost for optician visit.
e No events, no unit cost sourced.
f RTA one event, A&E visit only, no treatment NHS ref A&E cost applied.
g Taken from literature (Auguste *et al.*[60]).

Appendix 9 Adverse event specific tables

Serious adverse events

AE	Dates	Treatment receiving at the time	Classification
Sick sinus syndrome and atrial flutter	25 September 2011–28 September 2011	No treatment	Possibly related to OSA
Hypoglycaemia	13 October 2011–13 October 2011	No treatment	Possibly related to OSA
Complete heart block	3 November 2011–4 November 2011	bMAD	Possibly related to OSA or MAD
Non-specific chest pain	11 February 2012–17 February 2012	bMAD	Possibly related to OSA or MAD

Specific minor adverse events in each category

Adverse event	Adverse events category	Number of events
Achy legs	(1) General adverse events	4
Acid reflux	(1) General adverse events	2
Angina	(1) General adverse events	2
Asthma	(1) General adverse events	2
Asthma episode	(1) General adverse events	1
Bronchitis	(1) General adverse events	2
Cellulitis	(1) General adverse events	1
Chest (6) infection	(1) General adverse events	8
Chest (6) infection/pleuracy	(1) General adverse events	2
Concussion	(1) General adverse events	1
Cramp	(1) General adverse events	3
Cramp (legs)	(1) General adverse events	3
DVT	(1) General adverse events	3
Depression (re-occurring)	(1) General adverse events	1
Diarrhoea	(1) General adverse events	2
Diarrhoea and vomiting	(1) General adverse events	3
Dislocated shoulder	(1) General adverse events	1
Extreme tiredness [viral (6) infection?]	(1) General adverse events	1
Fluid on lungs	(1) General adverse events	1
Fractured wrist	(1) General adverse events	1
Gout	(1) General adverse events	1
Hay fever	(1) General adverse events	2
Hay fever symptoms	(1) General adverse events	1

Adverse event	Adverse events category	Number of events
Head trauma	(1) General adverse events	1
Headache	(1) General adverse events	27
Headache (migraine?)	(1) General adverse events	1
Headaches	(1) General adverse events	4
Hernia operation	(1) General adverse events	1
Hysterectomy	(1) General adverse events	1
Indigestion	(1) General adverse events	3
Infected finger	(1) General adverse events	4
Knee (6) infection	(1) General adverse events	2
Leg pain	(1) General adverse events	5
Nasal polyps	(1) General adverse events	3
Nasal congestion due to polyps	(1) General adverse events	1
Nasal (6) Infection	(1) General adverse events	1
Nausea	(1) General adverse events	2
Neck pain	(1) General adverse events	2
Operation – adenoma (parathyroid)	(1) General adverse events	1
Oral thrush	(1) General adverse events	1
Pacemaker fitted	(1) General adverse events	1
Panic attacks	(1) General adverse events	1
Period pain	(1) General adverse events	1
Shoulder pain	(1) General adverse events	5
Shoulder pain (frozen shoulder)	(1) General adverse events	1
Sore ribs	(1) General adverse events	3
Sore wrist/hand	(1) General adverse events	1
Stomach eramps	(1) General adverse events	1
Stomach ache	(1) General adverse events	1
Stomach ache/nausea	(1) General adverse events	1
Stomach bug	(1) General adverse events	5
Surgery to remove nasal polyps	(1) General adverse events	1
Torn ligaments (in knee)	(1) General adverse events	2
Unwell (exhaustion)	(1) General adverse events	1
Upset stomach	(1) General adverse events	1
Vomiting	(1) General adverse events	1
Wheezing	(1) General adverse events	1
Whiplash	(1) General adverse events	1
Worsening tinnitus	(1) General adverse events	1
Bad taste in mouth	(2) Dryness/Bad taste/Numbness	3
Dry lips	(2) Dryness/Bad taste/Numbness	14
Dry mouth	(2) Dryness/Bad taste/Numbness	65

Adverse event	Adverse events category	Number of events
Dry throat	(2) Dryness/Bad taste/Numbness	3
Dry mouth/throat	(2) Dryness/Bad taste/Numbness	1
Numb lips	(2) Dryness/Bad taste/Numbness	3
Bit lip	(3) Discomfort/Mouth problems	1
Blisters on lip	(3) Discomfort/Mouth problems	1
Blood on device	(3) Discomfort/Mouth problems	1
Broken tooth	(3) Discomfort/Mouth problems	3
Broken tooth crown	(3) Discomfort/Mouth problems	2
Burnt mouth	(3) Discomfort/Mouth problems	2
Change in bite	(3) Discomfort/Mouth problems	10
Change in bite/malocclusion	(3) Discomfort/Mouth problems	1
Clicky jaw	(3) Discomfort/Mouth problems	2
Cold sores	(3) Discomfort/Mouth problems	1
Dental bridge problems	(3) Discomfort/Mouth problems	1
Face/jaw ache	(3) Discomfort/Mouth problems	1
Gum discomfort	(3) Discomfort/Mouth problems	75
Gum sores	(3) Discomfort/Mouth problems	1
Infected milk tooth extraction	(3) Discomfort/Mouth problems	1
Jaw discomfort	(3) Discomfort/Mouth problems	78
Jaw stiffness	(3) Discomfort/Mouth problems	19
Jaw discomfort – left	(3) Discomfort/Mouth problems	1
Jaw discomfort – right	(3) Discomfort/Mouth problems	1
Jaw stiffness (change in bite)	(3) Discomfort/Mouth problems	1
Lip discomfort	(3) Discomfort/Mouth problems	3
Loose tooth	(3) Discomfort/Mouth problems	2
Loose crowns and bridges	(3) Discomfort/Mouth problems	1
Loose teeth	(3) Discomfort/Mouth problems	2
Loose tooth	(3) Discomfort/Mouth problems	2
Malocclusion (tooth moving forward)	(3) Discomfort/Mouth problems	1
Mouth discomfort	(3) Discomfort/Mouth problems	19
Mouth ulcer	(3) Discomfort/Mouth problems	16
Receding gums	(3) Discomfort/Mouth problems	3
Sensitive teeth	(3) Discomfort/Mouth problems	1
Sore throat (due to not wearing device)	(3) Discomfort/Mouth problems	1
Sore upper left palate.	(3) Discomfort/Mouth problems	1
Sore upper right palate.	(3) Discomfort/Mouth problems	1
Teeth moved forward (front top 2)	(3) Discomfort/Mouth problems	1
Tongue discomfort	(3) Discomfort/Mouth problems	8
Tongue ulcer	(3) Discomfort/Mouth problems	1

Adverse event	Adverse events category	Number of events
Tooth discomfort	(3) Discomfort/Mouth problems	128
Tooth discomfort (from clenching teeth)	(3) Discomfort/Mouth problems	4
Tooth discomfort (front crown only)	(3) Discomfort/Mouth problems	1
Tooth discomfort (next to abscessed tooth)	(3) Discomfort/Mouth problems	2
Tooth crown – permanent	(3) Discomfort/Mouth problems	1
Tooth crown – temporary	(3) Discomfort/Mouth problems	1
Tooth crown replacement	(3) Discomfort/Mouth problems	1
Tooth removal	(3) Discomfort/Mouth problems	1
Veneer detachment	(3) Discomfort/Mouth problems	1
Wound healing post wisdom tooth removal	(3) Discomfort/Mouth problems	1
Bleeding gums	(3) Discomfort/Mouth problems	18
Choking	(4) Excessive salivation and choking	2
Choking (due to excessive salivation)	(4) Excessive salivation and choking	1
Excessive Salivation	(4) Excessive salivation and choking	83
Gagging	(4) Excessive salivation and choking	5
Blocked nose	(5) Cold related	14
Cold/sore throat	(5) Cold related	1
Chest and sinus (6) infection	(5) Cold related	1
Common cold	(5) Cold related	39
Cough	(5) Cold related	13
Cough and congestion	(5) Cold related	2
Flu	(5) Cold related	3
Head cold	(5) Cold related	1
Nasal congestion	(5) Cold related	4
Sinus (6) infection	(5) Cold related	1
Sore throat	(5) Cold related	8
Sore throat (and cough)	(5) Cold related	2
Sore nostrils	(5) Cold related	1
Sore throat and ears	(5) Cold related	1
Sore throat and nose	(5) Cold related	1
Throat and upper and lower chest (6) Infection	(5) Cold related	1
Tonsillitis	(5) Cold related	1
Viral (6) infection	(5) Cold related	2
Viral nasal (6) infection	(5) Cold related	1
Infected wisdom tooth	(6) Infection	3
Infected milk tooth	(6) Infection	1
Tooth abscess	(6) Infection	2
Tooth (6) infection	(6) Infection	2

Minor adverse events (classified by an independent sleep physician)

Type of AE	No treatment ($n = 78$)	SP1 ($n = 81$)	SP2 ($n = 78$)	bMAD ($n = 77$)	Total
Possibly related to OSA	3 (3)	1 (1)	3 (3)	1 (1)	8 (5)
Probably related to MAD	22 (16)	179 (66)	143 (59)	184 (75)	528 (85)
Possibly related to OSA or MAD	29 (18)	50 (34)	55 (35)	40 (27)	174 (54)
Probably unrelated	26 (21)	37 (24)	41 (30)	37 (27)	141 (59)
Total	80 (45)	267 (73)	242 (68)	262 (76)	851 (86)

Appendix 10 Differences in European Quality of Life-5 Dimensions 3-level version quality-adjusted life-years for each treatment versus control

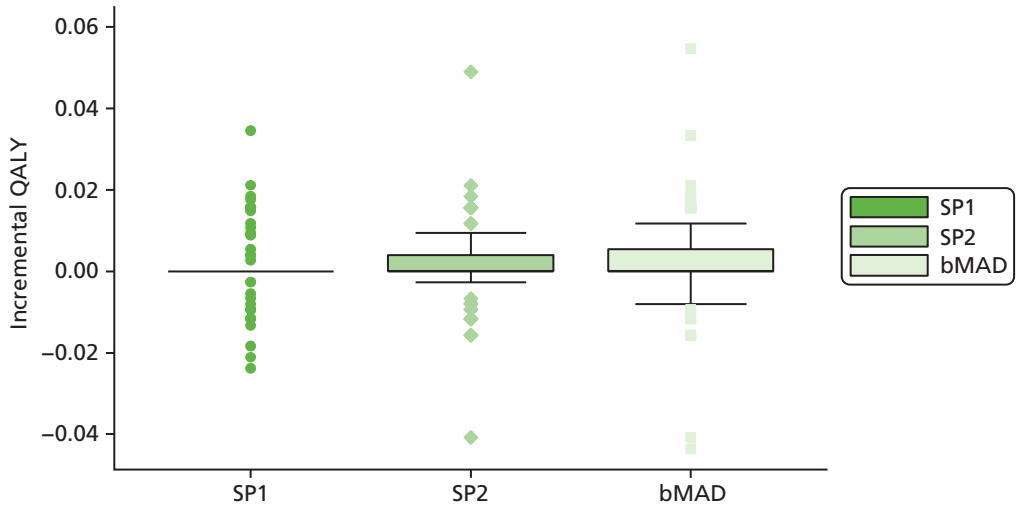


FIGURE 34 Differences in EQ-5D-3L QALYs for each treatment vs. control.

Appendix 11 Differences in quality-adjusted life-years compared with no treatment

QALY valuation	Variable	Coefficient (SE)	*p*-value	Global *p*-value
EQ-5D QALYs	Constant	0.0649 (0.002)	< 0.00	
	Baseline	0.0005 (0.001)	0.69	0.76
	SP1	0.0009 (0.001)	0.37	
	SP2	0.0009 (0.001)	0.47	
	bMAD	0.0018 (0.002)	0.23	
SF-6D QALYs	Constant	0.0527 (0.001)	< 0.00	
	Baseline	−0.0011 (0.001)	0.10	0.00
	SP1	0.00039 (0.001)	0.63	
	SP2	0.0019 (0.001)	0.01	
	bMAD	0.0009 (0.001)	0.31	

Appendix 12 Differences in Short Form questionnaire-6 Dimensions quality-adjusted life-years for each treatment compared with control

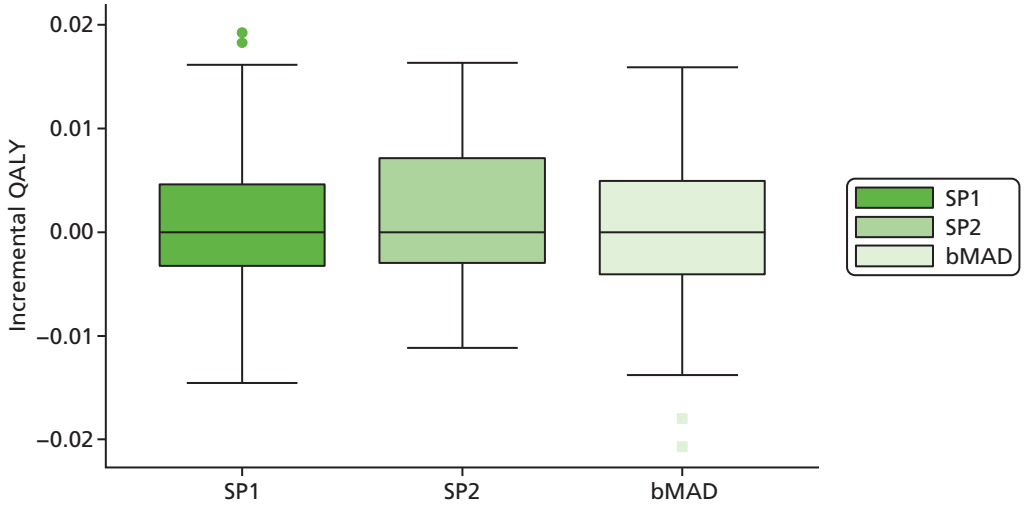


FIGURE 35 Differences in SF-6D QALYs for each treatment vs. control.

Appendix 13 Sensitivity analyses: trial-based economic analysis

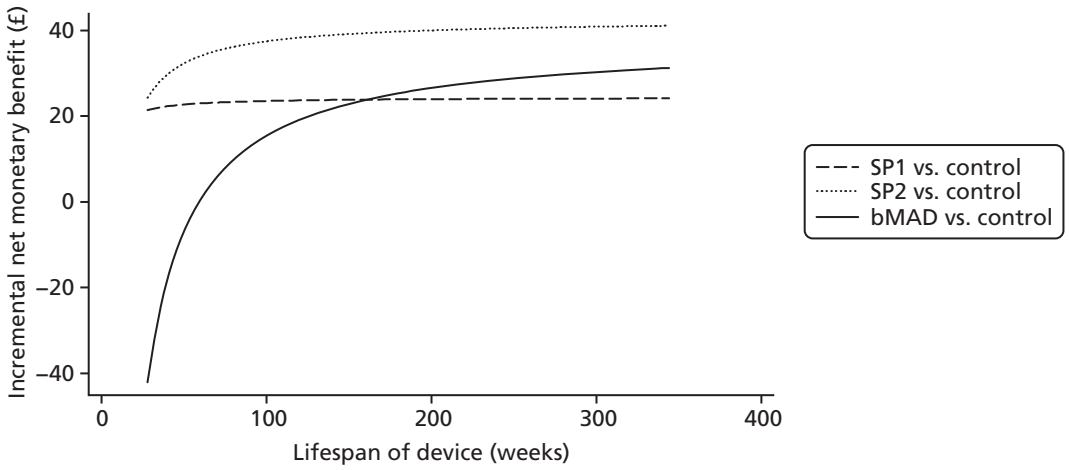


FIGURE 36 Sensitivity analysis: varying lifespan of devices.

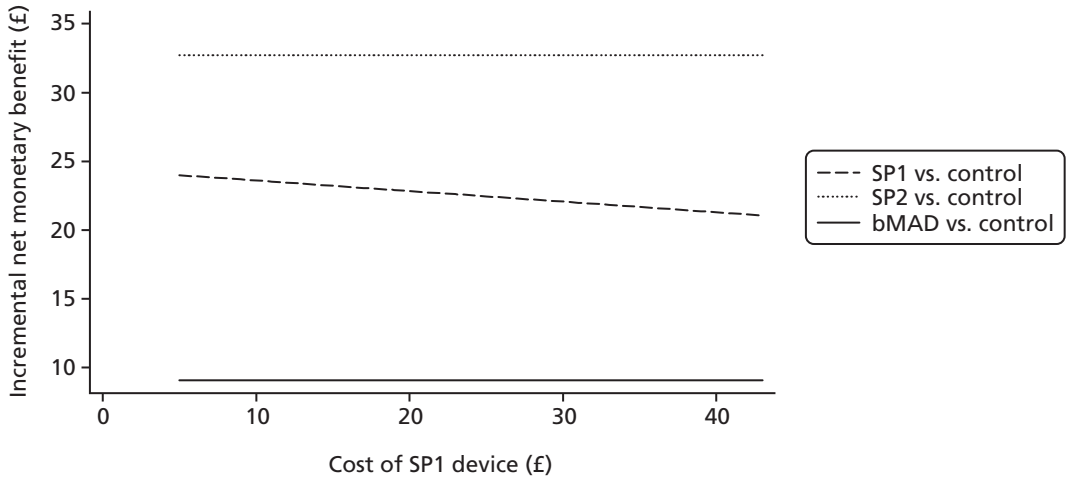


FIGURE 37 Sensitivity analysis: varying cost of SPI.

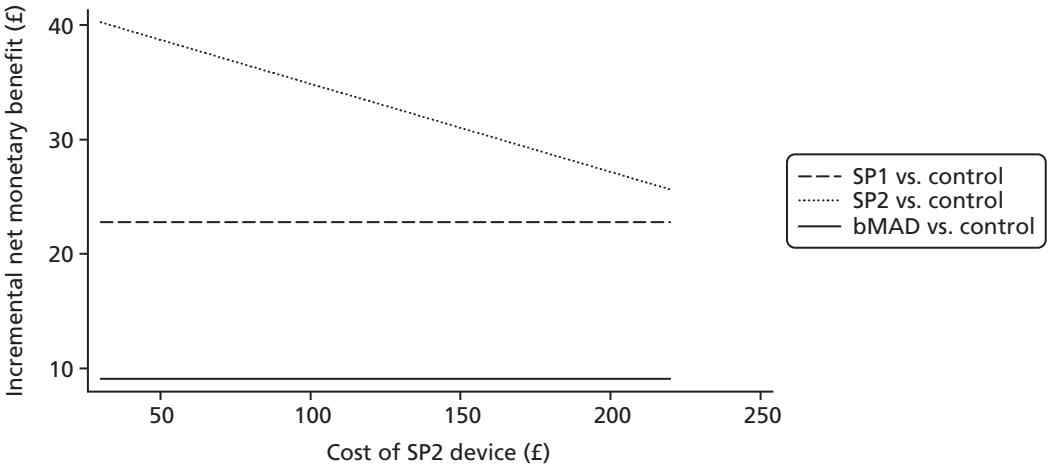


FIGURE 38 Sensitivity analysis: varying cost of SP2.

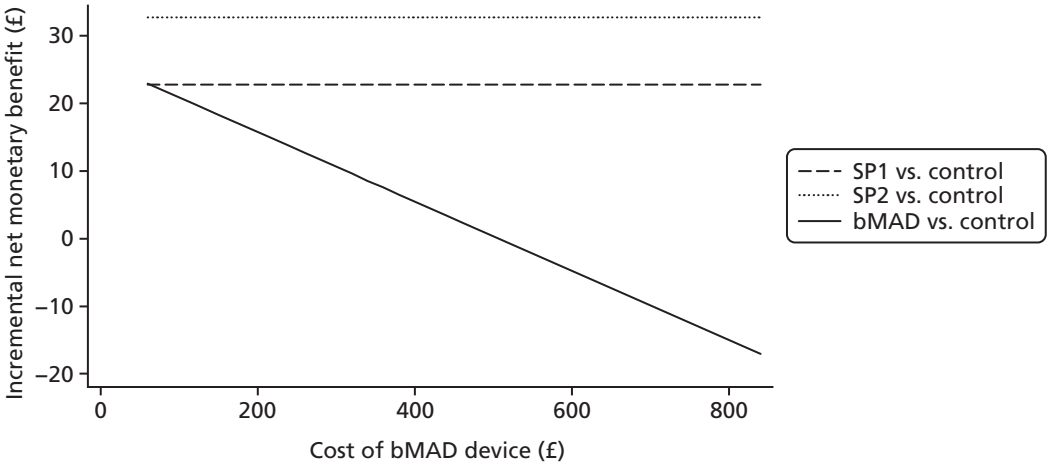


FIGURE 39 Sensitivity analysis: varying cost of bMAD.

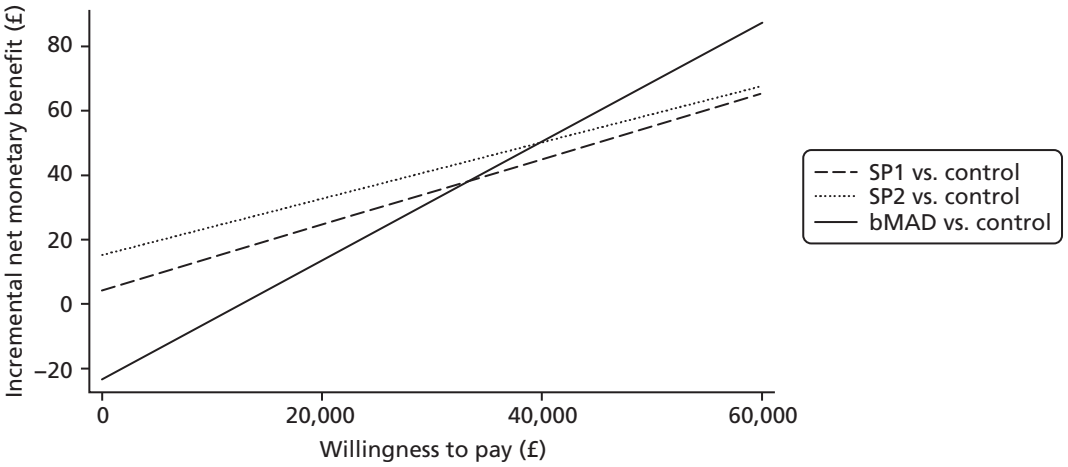


FIGURE 40 Probabalistic sensitivity analysis: net monetary benefit devices vs. control (EQ-5D).

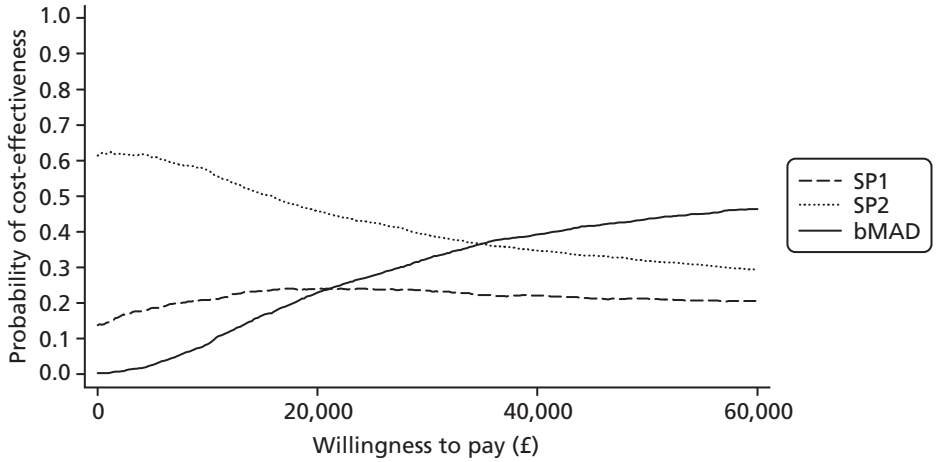


FIGURE 41 Probabalistic sensitivity analysis: CEACs between all devices (EQ-5D).

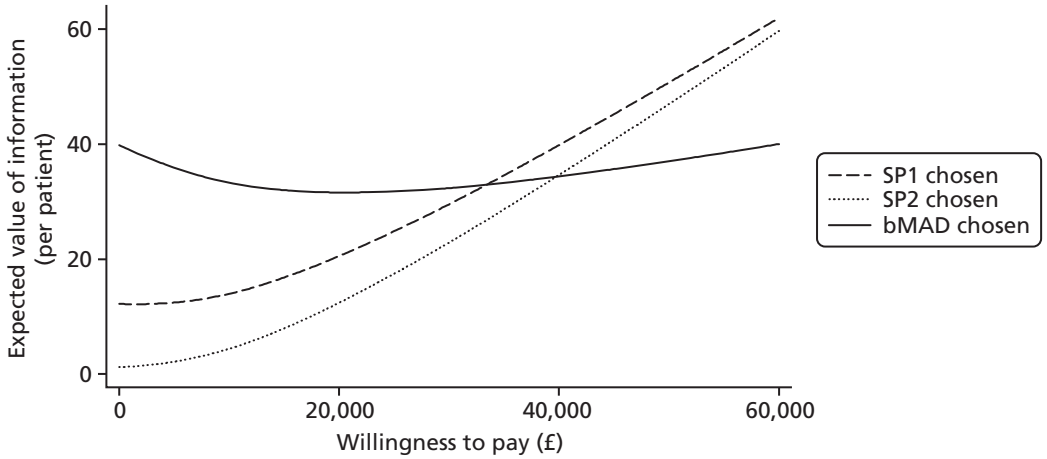


FIGURE 42 Probabalistic sensitivity analysis: expected value of perfect information (EQ-5D).

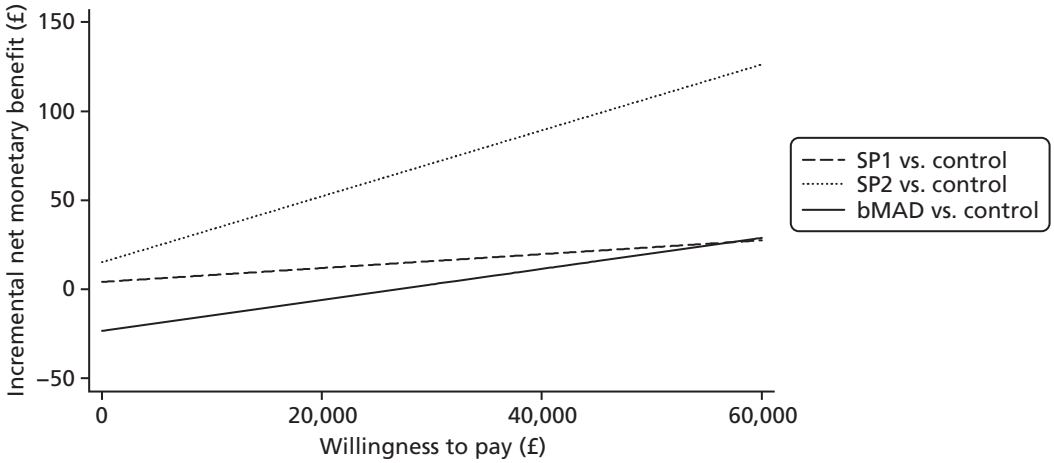


FIGURE 43 Sensitivity analysis: net monetary benefit – device vs. control (SF-6D).

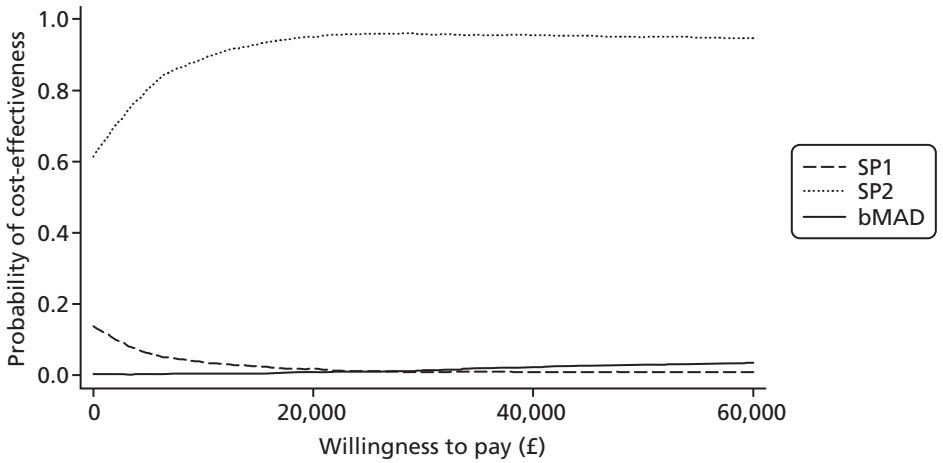


FIGURE 44 Probabalistic sensitivity analysis: CEACs between all devices (SF-6D).

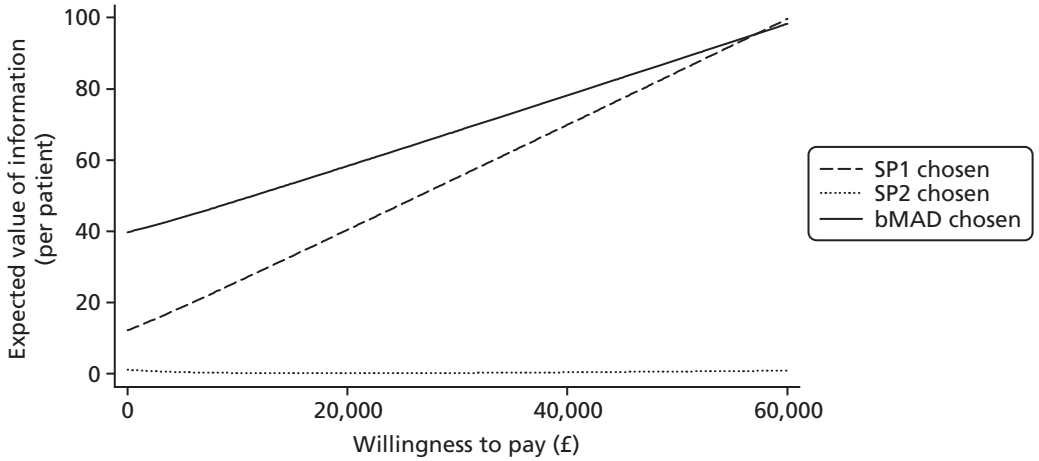


FIGURE 45 Probabalistic sensitivity analysis: expected value of perfect information (SF-6D).

Appendix 14 Search strategies for the systematic review

McDaid *et al.*[8] search strategies and hit count

MEDLINE: 200 hits.

EMBASE: 227 hits.

Web of Knowledge (WoK): 436 hits.

Total unique hits: 565.

EMBASE

1. random*.ti,ab.
2. factorial*.ti,ab.
3. crossover*.ti,ab.
4. "cross over*".ti,ab.
5. placebo*.ti,ab.
6. (double adj blind*).ti,ab.
7. (single adj blind*).ti,ab.
8. assign*.ti,ab.
9. allocat*.ti,ab.
10. volunteer*.ti,ab.
11. CROSSOVER PROCEDURE/
12. DOUBLE BLIND PROCEDURE/
13. RANDOMIZED CONTROLLED TRIAL/
14. SINGLE BLIND PROCEDURE/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp ANIMAL/
17. exp HUMAN/
18. 16 not 17
19. 15 not 18
20. exp Sleep Apnea Syndrome/
21. (sleep* and (apn* or hypop*)).ti,ab.
22. (sleep* adj3 "disorder* breath*").ti,ab.
23. (sleep* adj2 "resp* disorder*").ti,ab.
24. (sahs or shs or osa or osas or osahs).ti,ab.
25. 20 or 21 or 22 or 23 or 24
26. positive end expiratory pressure/
27. (positive* adj3 airway* adj3 pressure*).ti,ab.
28. (cpap or ncpap or apap or bipap).ti,ab.
29. ("c pap" or "bi pap" or "nc pap").ti,ab.
30. autocpap.ti,ab.
31. 26 or 27 or 28 or 29 or 30
32. 19 and 25 and 31
33. limit 32 to yr="2012 –Current"

MEDLINE

1. "randomized controlled trial".pt.
2. "controlled clinical trial".pt.
3. "placebo*".ti,ab.
4. randomly.ti,ab.
5. trial*.ti,ab.
6. groups.ti,ab.
7. CONTROLLED CLINICAL TRIAL/ or RANDOMIZED CONTROLLED TRIAL/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp sleep apnea syndromes/
12. (sleep* adj3 "disorder* breath*").ti,ab.
13. (sleep* and (apn* or hypop*)).ti,ab.
14. (sahs or shs or osa or osas or osahs).ti,ab.
15. exp positive-pressure respiration/
16. (positive* adj3 airway* adj3 pressure*).ti,ab.
17. (cpap or ncpap or apap or bipap).ti,ab.
18. ("c pap" or "bi pap" or "nc pap").ti,ab.
19. autocpap.ti,ab.
20. 15 or 16 or 17 or 18 or 19
21. (sleep* adj2 respirat* disorder*).ti,ab.
22. 11 or 12 or 13 or 14 or 21
23. 10 and 20 and 22
24. limit 23 to yr="2012 -Current"

Web of Knowledge

#15 #13 AND #12 AND #5 Refined by: Publication Years=(2012 OR 2013)

#14 #13 AND #12 AND #5

#13 Topic=(trial* or placebo* or random* or trial* or control* or blind* or crossover or "cross over")

#12 #11 OR #10 OR #9 OR #8 OR #7 OR #6

#11 Topic=(positive* near expirat* near pressure*)

#10 Topic=(positive* near respir* near pressure*)

#9 Topic=(autocpap)

#8 Topic=("c pap" or "bi pap" or "nc pap")

#7 Topic=(cpap or ncpap or apap or bipap)

#6 Topic=(positive* near airway* near pressure*)

#5 #4 OR #3 OR #2 OR #1

#4 Topic=(sleep* near disorder* near breath*)

#3 Topic=(sleep* near respir* near disorder*)

#2 Topic=(sahs or shs or osa or osas or osahs)

#1 Topic=(sleep* and (apn* or hypop*))

Lim *et al.*[51] search strategies and hit count

EMBASE: 144 hits.

MEDLINE: 130 hits.

Web of Science (WoS): 252 hits.

Total 526 hits in EndNote Web.

Unique: 340 hits.

EMBASE

1. random*.ti,ab.
2. factorial*.ti,ab.
3. crossover*.ti,ab.
4. "cross over*".ti,ab.
5. placebo*.ti,ab.
6. (double adj blind*).ti,ab.
7. (single adj blind*).ti,ab.
8. assign*.ti,ab.
9. allocat*.ti,ab.
10. volunteer*.ti,ab.
11. CROSSOVER PROCEDURE/
12. DOUBLE BLIND PROCEDURE/
13. RANDOMIZED CONTROLLED TRIAL/
14. SINGLE BLIND PROCEDURE/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp ANIMAL/
17. exp HUMAN/
18. 16 not 17
19. 15 not 18
20. exp Sleep Apnea Syndrome/
21. (sleep* and (apn* or hypop*)).ti,ab.
22. (sleep* adj3 "disorder* breath*").ti,ab.
23. (sleep* adj2 "resp* disorder*").ti,ab.
24. (sahs or shs or osa or osas or osahs).ti,ab.
25. 20 or 21 or 22 or 23 or 24
26. (oral* or "intra oral*" or intraoral* or dental* or tongue* or mandib* or genioglos*).ti,ab.
27. (jaw* or mouth*).ti,ab.
28. exp orthodontic device/
29. (device* or tool* or splint* or prosthe* or appliance* or advance* or suspen*).ti,ab.
30. (tonsil* or palat* or adenoid* or pharyn* or tooth* or teeth* or gum* or uvul* or maxillo* or face* or facial* or hyoid* or orthodon*).ti,ab.
31. 26 or 27 or 30
32. 29 and 31
33. 28 or 32

34. 19 and 25 and 33
35. 34
36. limit 35 to yr="2008 -Current"

MEDLINE

1. "randomized controlled trial".pt.
2. "controlled clinical trial".pt.
3. "placebo*".ti,ab.
4. randomly.ti,ab.
5. trial*.ti,ab.
6. groups.ti,ab.
7. CONTROLLED CLINICAL TRIAL/ or RANDOMIZED CONTROLLED TRIAL/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. exp sleep apnea syndromes/
12. (sleep* adj3 "disorder* breath*").ti,ab.
13. (sleep* and (apn* or hypop*)).ti,ab.
14. (sahs or shs or osa or osas or osahs).ti,ab.
15. (sleep* adj2 respirat* disorder*).ti,ab.
16. 11 or 12 or 13 or 14 or 15
17. (oral* or "intra oral*" or intraoral* or dental* or tongue* or mandib* or genioglos*).ti,ab.
18. (jaw* or mouth*).ti,ab.
19. (tonsil* or palat* or adenoid* or pharyn* or tooth* or teeth* or gum* or uvul* or maxillo* or face* or facial* or hyoid* or orthodon*).ti,ab.
20. 17 or 18 or 19
21. (device* or tool* or splint* or prosthe* or appliance* or advance* or suspens*).ti,ab.
22. 20 and 21
23. exp Orthodontic Appliances/
24. 22 or 23
25. 10 and 16 and 24
26. 25
27. limit 26 to yr="2008 -Current"

Web of Science

11 #9 AND #6 AND #5 Refined by: Publication Years=(2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2008) (252)

10 #9 AND #6 AND #5 (581)

9 #8 AND #7 (111,128)

8 Topic=(device* or tool* or splint* or prosthe* or appliance* or advance* or suspen*) (2,413,678)

7 Topic=(oral* or "intra oral*" or intraoral* or dental* or tongue* or mandib* or genioglos*) OR Topic=(jaw* or mouth*) OR Topic=(tonsil* or palat* or adenoid* or pharyn* or tooth* or teeth* or gum* or uvul* or maxillo* or face* or facial* or hyoid* or orthodon*) (1,209,904)

6 Topic=(trial* or placebo* or random* or trial* or control* or blind* or crossover or "cross over") (5,046,874)

5 #4 OR #3 OR #2 OR #1 (37,918)

4 Topic=(sleep* near disorder* near breath*) (5428)

3 Topic=(sleep* near respir* near disorder*) (950)

2 Topic=(sahs or shs or osa or osas or osahs) (13,836)

1 Topic=(sleep* and (apn* or hypop*)) (29,814)

York Group's update of McDaid *et al.*[8] search strategies and hit count (PREDICT update searches March 2012)

Searches for systematic reviews and guidelines

Cochrane Database of Systematic Reviews

Searched 28 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 Medical subject heading (MeSH) descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5) (2635)

#7 MeSH descriptor Positive-Pressure Respiration explode all trees (1691)

#8 (cpap or apap or ncpap or autocpap or auto-cpap):ti,ab (1278)

#9 (positive near3 airway near3 pressure):ti,ab (1185)

#10 (#7 OR #8 OR #9) (2538)

#11 (#6 AND #10), from 2006 to 2012 (448)

Of the 448 total results in The Cochrane Library, nine were from Cochrane Database of Systematic Reviews (CDSR) 2006 onwards.

Database of Abstracts of Reviews of Effects

Searched 28 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5) (2635)

#7 MeSH descriptor Positive-Pressure Respiration explode all trees (1691)

#8 (cpap or apap or ncpap or autocpap or auto-cpap):ti,ab (1278)

#9 (positive near3 airway near3 pressure):ti,ab (1185)

#10 (#7 OR #8 OR #9) (2538)

#11 (#6 AND #10), from 2006 to 2012 (448)

Of the 448 total results in The Cochrane Library, 12 were from Database of Abstracts of Reviews of Effects (DARE).

Health Technology Assessment Database

Searched 28 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5) (2635)

#7 MeSH descriptor Positive-Pressure Respiration explode all trees (1691)

#8 (cpap or apap or ncpap or autocpap or auto-cpap):ti,ab (1278)

#9 (positive near3 airway near3 pressure):ti,ab (1185)

#10 (#7 OR #8 OR #9) (2538)

#11 (#6 AND #10), from 2006 to 2012 (448)

Of the 448 total results in The Cochrane Library, seven were from the HTA Database.

Scottish Intercollegiate Guidelines Network

Searched 28 March 2012 via www.sign.ac.uk.

Search strategy

List of guidelines checked – last update to Sleep Apnea Guideline was 2003.

National Guideline Clearinghouse
Searched 28 March 2012 via www.guideline.gov/search/advanced-search.aspx.

Search strategy
apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or sahs or shs or osas or osa

Limited to 2006, 2007, 2008, 2009, 2010 and 2011.

Health Services/Technology Assessment Text
Searched 28 March 2012 via www.ncbi.nlm.nih.gov/books/advanced.

Search strategy
apnea OR apnoea OR hypopnea OR hypopnea OR hypopnea OR hypopnea

Results screened and details of one 2011 Agency for Healthcare Research and Quality guideline added to EndNote library.

Turning Research Into Practice database
Searched 28 March 2012 via www.tripdatabase.com.

Search strategy:
(title:(apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea) AND (cpap or apap or ncpap or autocpap)) from 2006.

Three guideline results screened online – all identified by Clinical Evidence search below so not downloaded.

Clinical Evidence
Searched 28 March 2012 via http://clinicalevidence.bmj.com.

Twelve post-2006 guidelines on sleep apnea identified.

Searches for trials

Database: Ovid MEDLINE(R) in-process and other non-indexed citations and Ovid MEDLINE(R) <1946 to present>
Searched 19 March 2012 via OVID.

Search strategy

1. exp Sleep Apnea Syndromes/ (19,930)
2. (apnea or apnoea).ti,ab. (25,874)
3. (hypopnea or hypopnoea).ti,ab. (4789)
4. (hypoapnea or hypoapnoea).ti,ab. (36)
5. sleep disordered breathing.ti,ab. (2989)
6. (sleep adj2 respirat$ disorder$).ti,ab. (201)
7. sahs.ti,ab. (338)
8. shs.ti,ab. (971)
9. osa.ti,ab. (4692)
10. osas.ti,ab. (2314)
11. osahs.ti,ab. (651)
12. or/1-11 (32,846)
13. exp positive-pressure respiration/ (18,367)

14. (positive adj3 airway adj3 pressure).ti,ab. (5712)
15. (cpap or ncpap or apap or bipap).ti,ab. (5975)
16. (c pap or bi pap or nc pap).ti,ab. (50)
17. autocpap.ti,ab. (19)
18. or/13-17 (21,531)
19. 12 and 18 (5267)
20. limit 19 to yr="2006 - 2012" (2333)
21. randomized controlled trial.pt. (322,037)
22. controlled clinical trial.pt. (83,702)
23. randomized.ab. (237,867)
24. placebo.ab. (133,799)
25. drug therapy.fs. (1,509,972)
26. randomly.ab. (174,912)
27. trial.ab. (245,654)
28. groups.ab. (1,145,620)
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (2,887,984)
30. 20 and 29 (680)
31. limit 30 to english language (620)

Database: EMBASE <1996 to 2012 week 11>

Searched 19 March 2012 via OVID.

Search strategy

1. Sleep Apnea Syndrome/ (23,594)
2. (apnea or apnoea).ti,ab. (24,479)
3. (hypopnea or hypopnoea).ti,ab. (5727)
4. (hypoapnea or hypoapnoea).ti,ab. (42)
5. Sleep Disordered Breathing/ (2654)
6. sleep disordered breathing.ti,ab. (3732)
7. (sleep adj2 respirat$ disorder$).ti,ab. (176)
8. sahs.ti,ab. (355)
9. shs.ti,ab. (1025)
10. osa.ti,ab. (6190)
11. osas.ti,ab. (2811)
12. osahs.ti,ab. (783)
13. or/1-12 (33,560)
14. positive end expiratory pressure/ (19,580)
15. (positive adj3 airway adj3 pressure).ti,ab. (5606)
16. (cpap or ncpap or apap or bipap).ti,ab. (6559)
17. (c pap or bi pap or nc pap).ti,ab. (56)
18. autocpap.ti,ab. (34)
19. or/14-18 (21,932)
20. 13 and 19 (7358)
21. controlled study/ (3,116,507)
22. exp clinical trial/ (719,714)
23. outcomes research/ (65,036)
24. andomized controlled trial/ (250,869)
25. (randomized or randomised or placebo or randomly).ab. (483,327)
26. trial.ti. (89,510)
27. or/21-26 (3,706,892)
28. 20 and 27 (2494)
29. limit 28 to (english language and yr="2006 - 2012") (1381)

Cochrane Central Register of Controlled Trials

Searched 28 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5) (2635)

#7 MeSH descriptor Positive-Pressure Respiration explode all trees (1691)

#8 (cpap or apap or ncpap or autocpap or auto-cpap):ti,ab (1278)

#9 (positive near3 airway near3 pressure):ti,ab (1185)

#10 (#7 OR #8 OR #9) (2538)

#11 (#6 AND #10), from 2006 to 2012 (448)

Of the 448 total results in The Cochrane Library, 395 were from the Cochrane Central Register of Controlled Trials (CENTRAL).

Cumulative Index to Nursing and Allied Health Literature <1981 to present>

Searched 19 March 2012 via EBSCO*host*.

614 results.

Search strategy

S13 (S8 and S12) Limiters – English Language; Published Date from: 20060101-20120331 (614)

S12 (S9 or S10 or S11) (4355)

S11 TI (cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap) or AB(cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap) (930)

S10 TI (positive N3 airway N3 pressure) or AB(positive N3 airway N3 pressure) (1119)

S9 (MH "Positive Pressure Ventilation+") (3987)

S8 (S1 or S2 or S3 or S4 or S5 or S6 or S7) (5843)

S7 TI (sahs or shs or osa or osas or osahs) or AB(sahs or shs or osa or osas or osahs) (1237)

S6 TI (sleep N2 respirat* disorder*) or AB(sleep N2 respirat* disorder*) (36)

S5 TI ("sleep disordered breathing") or AB("sleep disordered breathing") (665)

S4 TI (hypoapnea or hypoapnoea) or AB(hypoapnea or hypoapnoea) (1)

S3 TI (hypopnea or hypopnoea) or AB(hypopnea or hypopnoea) (657)

S2 TI (apnea or apnoea) or AB(apnea or apnoea) (3843)

S1 (MH "Sleep Apnea Syndromes+") (4224)

Science Citation Index <1900 to 21 March 2012>

Searched 22 March 2012 via WoS

1228 results.

2006-2012.

Lemmatisation off.

Search strategy

#14 #12 and #13

#13 TS=(random* or blind* or comparative or comparison or prospective or controlled or trial or crossover or evaluation)

#12 #6 and #11

#11 #7 or #8 or #9 or #10

#10 TS = autocpap

#9 TS = ("c pap" or "nc pap" or "bi pap")

#8 TS = (cpap or ncpap or apap or bipap)

#7 TS = (positive same airway same pressure)

#6 #1 or #2 or #3 or #4 or #5

#5 TS = (sahs or shs or osa or osas or osahs)

#4 TS = "sleep disordered breathing"

#3 TS = (hypoapnea or hypoapnoea)

#2 TS = (hypopnea or hypopnoea)

#1 TS = (apnea or apnoea)

Conference Proceedings Citation Index - Science <1990 to 21 March 2012>

Searched 22 March 2012 via WoS.

388 results.

2006-2012.

Lemmatisation off.

Search strategy

#12 #6 and #11

#11 #7 or #8 or #9 or #10

#10 TS = autocpap

#9 TS = ("c pap" or "nc pap" or "bi pap")

#8 TS = (cpap or ncpap or apap or bipap)

#7 TS = (positive same airway same pressure)

#6 #1 or #2 or #3 or #4 or #5

#5 TS = (sahs or shs or osa or osas or osahs)

#4 TS = "sleep disordered breathing"

#3 TS = (hypoapnea or hypoapnoea)

#2 TS = (hypopnea or hypopnoea)

#1 TS = (apnea or apnoea)

Zetoc conferences <1993 to 22 March 2012>

Searched 22 March 2012 online via www.theses.com/default.asp.

Search strategy

conference: autocpap

conference: bi pap

conference: c pap

conference: nc pap

conference: bipap

conference: apap

conference: ncpap

conference: cpap

conference: positive airway pressure

Search results from 2006 onwards downloaded for each search - total 103 results retrieved.

Index to THESES <1716 to 22 March 2012>
Searched 22 March 2012 online via www.theses.com/default.asp.

Search strategy
((apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or sleep) and (cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap)) OR ((apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or leep) and (positive airway pressure)) OR ((sahs or shs or osa or osas or osahs) and (cpap or ncpap or apap or bipap or c pap or bi pap or nc pap or autocpap)) OR ((sahs or shs or osa or osas or osahs) and (positive airway pressure))

Twenty-two total results retrieved.

Cost-effectiveness searches

Economic evaluations of sleep apnea AND continuous positive airway pressure

NHS Economic Evaluation Database
Searched 28 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5) (2635)

#7 MeSH descriptor Positive-Pressure Respiration explode all trees (1691)

#8 (cpap or apap or ncpap or autocpap or auto-cpap):ti,ab (1278)

#9 (positive near3 airway near3 pressure):ti,ab (1185)

#10 (#7 OR #8 OR #9) (2538)

#11 (#6 AND #10), from 2006 to 2012 (448)

Of the 448 total results in The Cochrane Library, 14 were from NHS Economics Evaluation Database (NHS EED).

EconLit <1961 to February 2012>
Searched 23 March 2012 via OVID

Search strategy

1. (apnea or apnoea).ti,ab.
2. (hypopnea or hypopnoea).ti,ab.
3. (hypoapnea or hypoapnoea).ti,ab.
4. sleep disordered breathing.ti,ab.
5. (sleep adj2 respirat$ disorder$).ti,ab.
6. sahs.ti,ab.
7. shs.ti,ab.
8. osa.ti,ab.
9. osas.ti,ab.
10. osahs.ti,ab.
11. or/1-10
12. (positive adj3 airway adj3 pressure).ti,ab.
13. (cpap or ncpap or apap or bipap).ti,ab.
14. (c pap or bi pap or nc pap).ti,ab.
15. autocpap.ti,ab.
16. or/12-15
17. 11 and 16
18. limit 17 to yr="2006 - 2012"

Nil results found.

Economic evaluations of sleep apnea (any intervention)

EconPapers

Searched 28 March 2012 via http://econpapers.repec.org.

Search strategy

apnea or apnoea or hypopnea or hypopnoea or hypoapnea or hypoapnoea or (sleep AND disorder*)

Limited to working papers.

Seven results scanned – none relevant.

NHS Economic Evaluation Database

Searched 30 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab (612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5), from 2006 to 2012 (1073)

Of the 1073 total results in The Cochrane Library, 25 from NHS EED.

Health Technology Assessment Database

Searched 30 March 2012 via http://onlinelibrary.wiley.com.

Search strategy

#1 MeSH descriptor Sleep Apnea Syndromes explode all trees (1043)

#2 (apnea or apnoea):ti,ab (2393)

#3 (hypopnea or hypopnoea):ti,ab 612)

#4 (hypoapnea or hypoapnoea):ti,ab (2)

#5 (sahs or shs or osas or osa):ti,ab (770)

#6 (#1 OR #2 OR #3 OR #4 OR #5), from 2006 to 2012 (1073)

Of the 1073 total results in The Cochrane Library, 36 were from the HTA Database.

Database: Ovid MEDLINE(R) in-process and other non-indexed citations and Ovid MEDLINE(R) <1946 to present>

Searched 30 March 2012 via OVID.

Search strategy

1. exp Sleep Apnea Syndromes/ (19,973)
2. (apnea or apnoea).ti,ab. (25,964)
3. (hypopnea or hypopnoea).ti,ab. (4820)
4. (hypoapnea or hypoapnoea).ti,ab. (36)
5. sleep disordered breathing.ti,ab. (3003)
6. (sleep adj2 respirat$ disorder$).ti,ab. (201)
7. sahs.ti,ab. (340)
8. shs.ti,ab. (977)
9. osa.ti,ab. (4726)
10. osas.ti,ab. (2328)
11. osahs.ti,ab. (655)
12. or/1-11 (32,955)
13. economics/ (26,193)
14. exp "costs and cost analysis"/ (162,116)
15. economics, dental/ (1836)
16. exp "economics, hospital"/ (17,730)
17. economics, medical/ (8429)
18. economics, nursing/ (3855)
19. economics, pharmaceutical/ (2307)
20. (econom$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab. (380,943)
21. (value adj1 money).ti,ab. (20)
22. budget$.ti,ab. (16,542)
23. or/13-22 (494,267)
24. ((energy or oxygen) adj cost).ti,ab. (2543)
25. (metabolic adj cost).ti,ab. (671)
26. ((energy or oxygen) adj expenditure).ti,ab. (14,406)
27. or/24-26 (16,967)
28. 23 not 27 (490,330)

29. letter.pt. (752,630)
30. editorial.pt. (302,459)
31. historical-article.pt. (280,726)
32. or/29-31 (1,322,522)
33. 28 not 32 (464,959)
34. animals/ (4,889,109)
35. human/ (12,139,643)
36. 34 not (34 and 35) (3,594,930)
37. 33 not 36 (439,079)
38. 12 and 37 (811)
39. limit 38 to (english language and yr="2006 - 2012") (319)

Database: EMBASE <1996 to 2012 week 12>

Searched 30 March 2012 via OVID.

Search strategy

1. Sleep Apnea Syndrome/ (24,439)
2. (apnea or apnoea).ti,ab. (25,475)
3. (hypopnea or hypopnoea).ti,ab. (5996)
4. (hypoapnea or hypoapnoea).ti,ab. (43)
5. sleep Disordered Breathing/ (2644)
6. sleep disordered breathing.ti,ab. (3906)
7. (sleep adj2 respirat$ disorder$).ti,ab. (187)
8. sahs.ti,ab. (365)
9. shs.ti,ab. (1067)
10. osa.ti,ab. (6367)
11. osas.ti,ab. (2902)
12. osahs.ti,ab. (820)
13. or/1-12 (34,818)
14. health-economics/ (13,562)
15. exp economic-evaluation/ (147,865)
16. exp health-care-cost/ (143,430)
17. 14 or 15 or 16 (253,206)
18. (econom$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab. (356,198)
19. (value adj2 money).ti,ab. (872)
20. budget$.ti,ab. (13,757)
21. 18 or 19 or 20 (364,417)
22. 17 or 21 (487,556)
23. letter.pt. (477,438)
24. editorial.pt. (310,953)
25. note.pt. (397,942)
26. 23 or 24 or 25 (1,186,333)
27. 22 not 26 (434,638)
28. (metabolic adj cost).ti,ab. (510)
29. ((energy or oxygen) adj cost).ti,ab. (1653)
30. ((energy or oxygen) adj expenditure).ti,ab. (12,628)
31. 28 or 29 or 30 (14,363)
32. 27 not 31 (431,837)
33. exp animal/ (680,271)
34. exp animal-experiment/ (773,680)
35. nonhuman/ (2,423,637)

36. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (2,170,304)
37. 33 or 34 or 35 or 36 (3,344,387)
38. exp human/ (7,831,966)
39. exp human-experiment/ (168,040)
40. 38 or 39 (7,832,215)
41. 37 not (37 and 40) (2,390,216)
42. 32 not 41 (397,819)
43. 13 and 42 (1267)
44. limit 43 to (english language and yr="2006 - 2012") (700)

TABLE 51 Total results

Source	Results	After deduplication	Custom 4 field
CDSR	20	0	–
DARE	12	1	DARE, 28 March 2012
HTA	7	6	HTA, 28 March 2012
Scottish Intercollegiate Guidelines Network	0	–	–
National Guidelines Clearinghouse	67	Not downloadable	–
Health Services/Technology Assessment Text (HSTAT)	1	1	HSTAT, 28 March 2012
Turning Research Into Practice	3	0	–
Clinical Evidence	12	Not downloadable	–
MEDLINE	620	609	MEDLINE and MEDLINE In-Process, 09 March 2012
EMBASE	1381	896	EMBASE, 19 March 2012
CENTRAL	395	107	CENTRAL, 28 March 2012
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	614	376	CINAHL, 19 March 2012
Science Citation Index	1228	595	Science Citation Index, 22 March 2012
Conference Proceedings Citation Index	388	271	Conference Proceedings Citation Index, 22 March 2012
Zetoc conferences	103	65	Zetoc conference abstracts, 22 March 2012
Index to Theses	7	Not downloadable	–
NHS EED (sleep apnoea AND cpap)	14	1	NHS EED CPAP, 28 March 2012
EconLit	0	–	–
EconPapers	0	–	–
NHS EED (all sleep apnoea)	25	6	NHS EED ALL SLEEP APNOEA, 30 March 2012
HTA (all sleep apnoea)	36	30	HTA ALL SLEEP APNOEA, 30 March 2012
MEDLINE (sleep apnoea cost studies)	319	242	MEDLINE and MEDLINE In-Process ALL SLEEP APNOEA costs, 30 March 2012
EMBASE (sleep apnoea cost studies)	700	354	EMBASE ALL SLEEP APNOEA costs, 30 March 2012
Totals		**3560**	

Cardiovascular disease risk search strategy and summary table

Obstructive sleep apnoea hypopnoea syndrome and cardiovascular risk search terms in Medline (May 2013)

Search strategy

1. (stroke or strokes).ti,ab.
2. (chd or cardiovascular disease).ti,ab.
3. exp heart diseases/ or exp vascular diseases/
4. exp cerebrovascular accident/
5. or/1-4
6. exp sleep apnea syndromes/
7. 5 and 6
8. ep.fs.
9. 7 and 8
10. limit 9 to yr="2007-2013"

TABLE 52 Post-screening articles and reason for exclusion: CVD

Authors	Include or exclude?	Reason for exclusion
Alter (2012)[211]	Exclude	Letter
Parish (2012)[212]	Exclude	Editorial
Bitter (2012)[213]	Exclude	Not CVD risk
Craig (2012)[95]	Exclude	Patient population
Ciccone (2013)[214]	Exclude	Patient population
Sakakibara (2012)[215]	Exclude	Patient population
Mirrakhimov (2012)[216]	Exclude	Letter
Muñoz (2012)[217]	Exclude	Patient population
Loke (2012)[134]	Include	–
Asha'ari (2012)[218]	Exclude	Patient population
Kasai (2012)[163]	Include	–
Thomopoulos (2012)[219]	Exclude	Commentary
Vozoris (2012)[220]	Exclude	Patient population
Hegmann (2012)[221]	Exclude	Not CVD risk
ElKholy (2012)[155]	Include	–
Martínez-Garcia (2012)[162]	Include	–
Saruhara (2012)[222]	Exclude	Abstract only
Wallace (2012)[167]	Include	–
Lee (2011)[223]	Exclude	Patient population
Lavie (2011)[224]	Exclude	Editorial
Cano-Pumarega (2011)[161]	Include	–
Calvin (2011)[225]	Exclude	Patient population
Pedrosa (2011)[154]	Include	–

continued

TABLE 52 Post-screening articles and reason for exclusion: CVD (*continued*)

Authors	Include or exclude?	Reason for exclusion
Monahan (2011)[165]	Include	–
Gopalakrishnan (2011)[226]	Exclude	Abstract only
Mansukhani (2011)[227]	Exclude	Not CVD risk
McKelvie (2011)[228]	Exclude	Guideline
Kokkarinen (2011)[229]	Exclude	Letter
Kohli (2011)[171]	Include	–
Yazdan-Ashoori (2011)[230]	Exclude	Editorial
Bagai (2010)[231]	Exclude	Abstract only
Ramar (2010)[232]	Exclude	Patient population
Lozano (2010)[112]	Exclude	Duplicate from systematic review
Redline (2010)[4]	Include	–
Johnson (2010)[233]	Exclude	Commentary
Calhoun (2010)[166]	Include	–
Selim (2010)[234]	Exclude	Abstract only
Wijkstra (2010)[235]	Exclude	Editorial
Dyken (2009)[168]	Include	–
Budhiraja (2009)[236]	Exclude	Commentary
Young (2009)[133]	Include	–
Kato (2009)[164]	Include	–
Sadatsafavi (2009)[139]	Exclude	Not CVD risk
O'Connor (2009)[159]	Include	–
Portela (2009)[169]	Include	–
Peker (2009)[237]	Exclude	Protocol
Bradley (2009)[5]	Include	–
Al Lawati (2009)[30]	Exclude	Abstract only
Marin (2012)[158]	Include	–
Barbé (2012)[89]	Exclude	Patient population
Parra (2012)[238]	Exclude	Commentary
Monahan (2011)[165]	Exclude	Duplicate
Berg (2008)[239]	Exclude	Not CVD risk
Omelchenko (2008)[240]	Exclude	No abstract
Rola (2008)[241]	Exclude	Patient population
Ali (2008)[242]	Exclude	Abstract only
Koutsourelakis (2008)[243]	Exclude	Not CVD risk
Lavie (2008)[244]	Exclude	Abstract only
Lorenzi-Filho (2008)[245]	Exclude	Editorial
Gottlieb (2008)[246]	Exclude	Progress report
Kapur (2008)[160]	Include	–

TABLE 52 Post-screening articles and reason for exclusion: CVD (*continued*)

Authors	Include or exclude?	Reason for exclusion
Somers (2008)[247]	Exclude	Guideline
Lenfant (2008)[248]	Exclude	Abstract only
Nishibayashi (2008)[153]	Include	–
Baranchuk (2008)[249]	Exclude	Editorial
Rupprecht (2008)[250]	Exclude	Case report
MacDonald (2008)[251]	Exclude	Patient population
Tarasiuk (2008)[9]	Exclude	Not CVD risk
Norman (2008)[252]	Exclude	Patient population
Gonçalves (2007)[156]	Include	–
Foucher (2007)[253]	Exclude	French language
Barthélémy (2007)[254]	Exclude	Patient population
Parati (2007)[172]	Include	–
Cassar (2007)[255]	Exclude	Patient population
Grunstein (2007)[256]	Exclude	Not CVD risk
Redline (2007)[257]	Exclude	Not CVD risk
Olson (2007)[258]	Exclude	Not CVD risk
Caples (2007)[170]	Include	–
Culebras (2007)[259]	Exclude	Abstract only
Lavie (2007)[260]	Include	–
Gami (2007)[261]	Exclude	Patient population

Road traffic accident risk search strategy and summary table

Road traffic accident search terms in MEDLINE (May 2013)

Search strategy

1. exp Sleep Apnea Syndromes/
2. exp Positive-Pressure Respiration/
3. exp Continuous Positive Airway Pressure/
4. 1 and (2 or 3)
5. exp Automobile Driving/
6. exp Accidents/
7. 5 or 6
8. 4 and 7
9. (2008$ or 2009$ or 201$).ep.
10. (2008$ or 2009$ or 201$).ed.
11. 9 or 10

TABLE 53 Post-screening articles and reason for exclusion: RTAs

Authors	Include or exclude?	Reason for exclusion
Filtness (2012)[262]	Exclude	No post treatment observed RTA risk
Filtness (2011)[263]	Exclude	No post treatment observed RTA risk
Hiestand (2011)[264]	Exclude	No post treatment observed RTA risk
Antonopoulos (2011)[179]	Include	–
Vakulin (2011)[265]	Exclude	Patient population
Tregear (2010)[180]	Include	–
Hoffman (2010)[266]	Exclude	No post treatment observed RTA risk
Komada (2009)[267]	Exclude	No post treatment observed RTA risk
Gurubhagavatula (2008)[268]	Exclude	No post treatment observed RTA risk
Guest (2008)[137]	Exclude	No post treatment observed RTA risk
Tan (2008)[140]	Exclude	No post treatment observed RTA risk
Hoekema (2007)[181]	Include	–

Health-related quality-of-life search strategy and summary table

Health-related quality-of-life search terms in MEDLINE (May 2013)

Search strategy

1. exp Sleep Apnea Syndromes/
2. (apnea or apnoea).ti,ab.
3. (hypopnea or hypopnoea).ti,ab.
4. (hypoapnea or hypoapnoea).ti,ab.
5. sleep disordered breathing.ti,ab.
6. (sleep adj2 respirat$disorder$).ti,ab.
7. (sahs or shs or osa or osas or osahs).ti,ab.
8. or/1-7
9. "Quality of Life"/
10. (quality adj2 life).ti,ab.
11. utility.ti,ab.
12. utilities.ti,ab.
13. standard gamble.ti,ab.
14. tto.ti,ab.
15. (time tradeoff or time trade off).ti,ab.
16. (eq or euroqol).ti,ab.
17. osa 18.ti,ab.
18. sf 36.ti,ab.
19. sgrq.ti,ab.
20. respiratory questionnaire.ti,ab.
21. practical sleep scale.ti,ab.
22. sleep scale.ti,ab.
23. scopa.ti,ab.
24. objective daytime sleepiness.ti,ab.
25. oxford sleep resistance.ti,ab.

26. osler test.ti,ab.
27. stai.ti,ab.
28. emotional control scale.ti,ab.
29. cecs.ti,ab.
30. life orientation test.ti,ab.
31. satisfaction with life scale.ti,ab.
32. swls.ti,ab.
33. Calgary sleep apnea quality.ti,ab.
34. (functional outcomes adj2 sleep).ti,ab.
35. osa patient oriented severity.ti,ab.
36. osa 18.ti,ab.
37. cohen$pediatric osa.ti,ab.
38. (comment or letter or editorial).pt.
39. or/9-37
40. 8 and 39
41. 40 not 38
42. limit 41 to yr="2007-2013"
43. limit 42 to english language

TABLE 54 Post-screening articles and reason for exclusion: HRQoL

Authors	Include or exclude?	Reason for exclusion
Chai-Coetzer (2013)[269]	Exclude	No devices compared
Yurtlu (2012)[270]	Exclude	No generic utility measure
Craig (2012)[95]	Exclude	No HRQoL data
Myhill (2012)[271]	Exclude	No HRQoL data
Leger (2012)[272]	Exclude	Review
Weaver (2012)[128]	Exclude	No generic utility measure
Pliska (2012)[273]	Exclude	Abstract only
Van de Heyning (2012)[274]	Exclude	No generic utility measure
Tegelberg (2012)[275]	Exclude	No generic utility measure
Marklund (2012)[203]	Exclude	Review
Pliska (2012)[276]	Exclude	Review
Bulcun (2012)[277]	Exclude	No relevant treatment
Avlonitou (2012)[278]	Exclude	No generic utility measure
Cruz (2012)[279]	Exclude	No generic utility measure
Zhao (2012)[280]	Exclude	No HRQoL data
Medeiros (2012)[281]	Exclude	Patient population
Moroni (2011)[282]	Exclude	No generic utility measure
Cunali (2011)[283]	Exclude	No relevant treatment
Rey de Castro (2011)[284]	Exclude	No generic utility measure
Patidar (2011)[285]	Exclude	Patient population
Ruhle (2011)[286]	Exclude	No relevant treatment
Kushida (2011)[287]	Exclude	No generic utility measure

continued

TABLE 54 Post-screening articles and reason for exclusion: HRQoL (*continued*)

Authors	Include or exclude?	Reason for exclusion
Galetke (2011)[196]	Exclude	No HRQoL data
Pietzsch (2011)[288]	Exclude	No relevant treatment
Jackson (2011)[289]	Exclude	No HRQoL data
Parra (2011)[290]	Exclude	No HRQoL data
Antic (2011)[186]	Include	–
Smolensky (2011)[291]	Exclude	RTA risk review OSA and other sleep-related conditions
Shapiro (2010)[292]	Exclude	No HRQoL data
Skaer (2010)[293]	Exclude	No HRQoL data
Gander (2010)[294]	Exclude	No HRQoL data
Holty (2010)[295]	Exclude	Review
McArdle (2010)[296]	Exclude	No relevant treatment
Chami (2010)[297]	Exclude	No relevant treatment
Drummond (2010)[298]	Exclude	No generic utility measure
Vennelle (2010)[299]	Exclude	No generic utility measure
Schmidlin (2010)[189]	Include	–
Meek (2009)[300]	Exclude	No HRQoL data
Gagnadoux (2009)[24]	Exclude	Duplicate from systematic review
Durán-Cantolla (2009)[301]	Exclude	Review
Silva (2009)[302]	Exclude	No generic utility measure
Ghazal (2009)[194]	Exclude	Duplicate from systematic review
Holmdahl (2009)[303]	Exclude	No generic utility measure
Sadatsafavi (2009)[139]	Exclude	CEA model
Pépin (2009)[304]	Exclude	No HRQoL data
Aguiar (2009)[305]	Exclude	No HRQoL data
Szentkirályi (2009)[306]	Exclude	Review
Smith (2009)[44]	Exclude	No relevant treatments
Tsara (2009)[185]	Include	–
Thickett (2009)[307]	Exclude	No HRQoL data
Martínez-Garcia (2009)[308]	Exclude	No relevant treatments
Vennelle (2010)[299]	Exclude	Duplicate
Schramm (2012)[309]	Exclude	Case report
Larsson (2008)[310]	Exclude	Protocol
Gindre (2008)[195]	Exclude	No generic utility measure
Siccoli (2008)[18]	Exclude	Duplicate from systematic review
Guest (2008)[137]	Exclude	CEA review
Pagel (2008)[311]	Exclude	Abstract
Lojander (2008)[312]	Exclude	No generic utility measure
Jing (2008)[313]	Exclude	Review

TABLE 54 Post-screening articles and reason for exclusion: HRQoL (*continued*)

Authors	Include or exclude?	Reason for exclusion
Petri (2008)[76]	Exclude	No HRQoL data
Gülbay (2008)[314]	Exclude	Patient population
Piper (2008)[315]	Exclude	Patient population
Tan (2008)[140]	Exclude	CEA review
Sanders (2008)[316]	Exclude	Review
Benjamin (2008)[317]	Exclude	No HRQoL data
Stucki (2008)[318]	Exclude	No generic utility measure
Arias (2007)[319]	Exclude	No HRQoL data
Levendowski (2007)[320]	Exclude	No HRQoL data
Fietze (2007)[321]	Exclude	No relevant treatments
Thurnheer (2007)[322]	Exclude	No HRQoL data
Lam (2007)[67]	Exclude	Duplicate from systematic review

CEA, cost-effectiveness analyses.

Compliance search strategy and summary table

Compliance search terms in MEDLINE (November 2013)

Search strategy

1. exp Sleep Apnea Syndromes/
2. compliance.ti,ab.
3. adherence.ti,ab.
4. Continuous Positive Airway Pressure/
5. ("oral device" or "mad" or "mandibular advancement").mp.
6. 2 or 3
7. 4 or 5
8. 1 and 6 and 7
9. limit 8 to (abstracts and english language and "review articles" and humans)
10. (long-term or long$ term or (long adj3 term)).ti,ab.
11. 9 and 10

TABLE 55 Post-screening articles and reason for exclusion: compliance

Authors	Include or exclude?	Reason for exclusion
Schwartz (2013)[323]	Exclude	No measure of continuation of treatment
Broström (2013)[324]	Exclude	< 1 year of follow-up
Brette (2012)[192]	Include	–
Chan (2009)[325]	Exclude	No measure of continuation of treatment
Patel (2012)[326]	Exclude	No measure of continuation of treatment
Woehrle (2011)[327]	Exclude	No measure of continuation of treatment
Vezina (2011)[193]	Include	–
Kushida (2011)[287]	Exclude	< 1 year of follow-up
Galetke (2011)[196]	Include	–
Kato (2011)[328]	Exclude	< 50 patients
Aihara (2010)[329]	Exclude	No measure of continuation of treatment
Kohler (2010)[198]	Include	–
Nguyên (2010)[330]	Exclude	< 1 year of follow-up
Barbé (2010)[331]	Exclude	No measure of continuation of treatment
Giannasi (2009)[332]	Exclude	< 1 year of follow-up
Ghazal (2009)[194]	Include	–
Robinson (2009)[333]	Exclude	< 1 year of follow-up
Ishida (2009)[334]	Exclude	< 1 year of follow-up
Deane (2009)[335]	Exclude	< 50 patients
Thickett (2009)[307]	Exclude	< 1 year of follow-up
Smith (2009)[336]	Exclude	No measure of continuation of treatment
Hoffstein (2007)[199]	Include	–
Sucena (2006)[337]	Exclude	No measure of continuation of treatment
McGown (2010)[338]	Exclude	Patient population
Gindre (2008)[195]	Include	–
Wolkove (2008)[339]	Exclude	Patient population
Jauhar (2008)[340]	Exclude	Patient population
Campos-Rodriguez (2007)[341]	Exclude	No measure of continuation of treatment
Meurice (2007)[342]	Exclude	Patient population
Aloia (2007)[343]	Exclude	< 1 year of follow-up
Chin (2006)[344]	Exclude	< 1 year of follow-up
Marklund (2006)[345]	Exclude	Patient population
Ng (2005)[346]	Exclude	Abstract
Marin (2005)[347]	Exclude	No measure of continuation of treatment
Johnson (2004)[197]	Include	–
Beecroft (2003)[348]	Exclude	< 1 year of follow-up
Walker-Engström (2002)[349]	Exclude	Not at least < 50 patients

Appendix 15 Characteristics of the 71 included studies

Aarab 2011[68]

Methods	Parallel-group RCT Patients randomised to three arms: MAD, nCPAP or placebo
Participants	Sixty-four patients randomised (males = 47, females = 17), of which 57 completed the study Baseline characteristics of MAD group ($n = 20$): mean age: 50.3 years; BMI: 27.1 kg/m^2; AHI: 22.1 events/hour; ESS score: 11.8; neck circumference: 41.7 cm Baseline characteristics of nCPAP group ($n = 18$): mean age: 55.4 years; BMI: 30.7 kg/m^2; AHI: 20.9 events/hour; ESS score: 10.2; neck circumference: 43.6 cm Baseline characteristics of placebo group ($n = 19$): mean age: 51.3 years; BMI: 31.1 kg/m^2; AHI: 20.1 events/hour; ESS score: 10.6; neck circumference: 42.6 cm Baseline characteristics of dropout group ($n = 7$): mean age: 49.3 years; BMI: 27.8 kg/m^2; AHI: 14.8 events/hour; ESS score: 13.7; neck circumference: 41.4 cm Inclusion criteria: age > 18 years, AHI = 5–45 events/hour, ESS score ≥ 10 or at least two of the symptoms suggested by the AASM Task Force (e.g. unrefreshing sleep and daytime fatigue) Exclusion criteria: respiratory/sleep disorder other than OSA, BMI > 40 kg/m^2, medication usage that could influence respiration or sleep, periodic limb movement disorder, previous treatment with CPAP or MAD, reversible morphological upper airway abnormalities (e.g. enlarged tonsils), other medical conditions (e.g. psychiatric disorders), temporomandibular disorders, untreated periodontal problems, dental pain, lack of retention possibilities for an oral appliance
Interventions	MAD or nCPAP or placebo (a thin, hard splint with partial palatal coverage) Study duration: mean of 6 (SD 2) months on treatment Washout: N/A
Outcomes	AHI, ESS score, total sleep time, respiratory arousal index, changes in health perception (SF-36), self-reported compliance, snoring, side effects, evaluation of detecting placebo
Notes	Therapy evaluation data taken from Aarab (2011)[68] – the long-term follow-up paper to this study – control group not included Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Block randomisation in blocks of 6, 12 and 18. Randomly varying the sizes. The randomisation sequence was automatically generated
Allocation concealment?	Yes	Concealed by an independent coworker, who kept a paper copy in a lockable drawer. Sealed opaque envelopes were used to conceal the allocation from the principal investigator
Blinding? All outcomes	Unclear	Participants were blinded to the nature of the assigned therapy (active or control), blinding of the analyst (which outcomes is unclear) was ascertained by assigning codes to data sets and by analysing these sets in random blocks. Unclear if other outcome assessors or the person responsible for participants care were blinded

N/A, not applicable; nCPAP, nasal continuous positive airway pressure.

Andrén 2013[69]

Methods	Parallel RCT Patients randomised to two arms: active MAD vs. control MAD
Participants	Seventy-two patients randomised (males = 57, females = 15), of which 71 completed Baseline characteristics of the active MAD group ($n = 36$): mean age: 57 years; BMI: 30 kg/m^2; AHI: 23 events/hour; ESS score: 11; 24 hour SBP: 136.9 mmHg; 24 hour DBP: 83.8 mmHg Baseline characteristics of the control MAD group ($n = 36$): mean age: 59 years; BMI: 29 kg/m^2; AHI: 24 events/hour; ESS score: 11; 24 hour SBP: 139.3 mmHg; 24 hour DBP: 83.4 mmHg Inclusion criteria: AHI $\geq$ 10 events/hour, systemic hypertension (defined as either: office SBP > 140 mmHg, office DBP > 90 mmHg), not currently being treated with MAD or CPAP, enough teeth to retain a MAD Exclusion criteria: office SBP > 180 mmHg, office DBP > 110 mmHg, BMI > 35 kg/m^2, atrial fibrillation, chronic obstructive lung disease, epilepsy, severe psychiatric disease, maximal protrusion of the mandible < 6 mm, inability to speak or understand Swedish
Interventions	Active MAD or control MAD Study duration: 3 months on either treatment Washout: N/A
Outcomes	BP measurements, AHI, ESS score
Notes	Intention-to-treat analysis Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation was made in blocks of four. Sequence allocation was determined by random number generator
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Patients were informed there were two types of devices to be evaluated but were not informed about which one of the devices they would receive. Unclear whether they were told one of the potential treatments was a control. Outcome assessors were blinded to treatment allocation

N/A, not applicable.

Arias 2005[85]

Methods	Double-blind, randomised placebo-controlled crossover trial of CPAP vs. sham CPAP
Participants	Twenty-seven patients randomised, of which 25 completed (all male) Baseline characteristics of the randomised patients ($n = 27$): mean age: 52 years; BMI: 30.5 kg/m^2; AHI: 44 events/hour; daytime SBP: 126 mmHg; daytime DBP: 79 mmHg Inclusion criteria: male; AHI $\geq$ 10 events/hour; ESS score $\geq$ 10; no current drug or mechanical treatment for OSA Exclusion criteria: unwillingness or inability to perform the testing procedure; obstructive or restrictive lung disease demonstrated on pulmonary function testing; current use of cardioactive drugs; cardiac rhythm disturbances, including sinus bradycardia and sinus tachycardia; known hypertension, or 24-hour mean BP of $\geq$ 135 and/or 85 mmHg; LVEF < 50%; ischaemic or valvular heart disease; hypertrophic, restrictive, or infiltrative cardiomyopathy; pericardial disease or stroke; diabetes mellitus; BMI > 40 kg/m^2 daytime hypoxemia (PaO_2 < 70 mmHg) or hypercapnia ($PaCO_2$ > 45 mmHg) Withdrawal criteria: clinical exacerbation leading to a change in medication; hospital admission for $\geq$ 10 days; average nightly CPAP usage < 3.5 hours
Interventions	CPAP or sham CPAP Study duration: 12 weeks on each treatment Washout: not stated
Outcomes	Echocardiographic parameters, BP recordings, urinary catecholamine levels
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Reported as double blind. Patients were given detailed instructions on using CPAP equipment, but they were not informed of the type of therapy they were receiving. All ECGs were performed by an echocardiographer, unaware of both the subject's group and the patient's treatment assignment at each visit. Not clear if other outcome assessors were blinded

ECG, electrocardiogram; LVEF, left ventricular ejection fraction.

Arias 2006[86]

Methods	Double-blind, randomised placebo-controlled crossover trial of CPAP vs. sham CPAP
Participants	Twenty-three patients randomised (males = 22, females = 1), of which 21 completed the study Baseline characteristics of the randomised patients ($n = 23$): mean age: 51 years; BMI: 30.9 kg/m^2; AHI: 44.1; daytime SBP: 127 mmHg; daytime DBP: 79 mmHg Inclusion criteria: AHI ≥ 10; ESS score ≥ 10; no previous treatment for OSA Exclusion criteria: obstructive or restrictive lung disease demonstrated on pulmonary function testing; connective-tissue or chronic thromboembolic diseases; current cardioactive drugs; cardiac rhythm disturbances, including sinus bradycardia and sinus tachycardia; known hypertension, or 24-hour mean BP of 135 mmHg and/or 85 mmHg or more; LVEF 50%, ischaemic or valvular heart disease, cardiomyopathy, pericardial disease or stroke; diabetes mellitus; BMI > 40 kg/m^2; daytime hypoxaemia or hypercapnia; history of cocaine or appetite-suppressant drug use Withdrawal criteria were: clinical exacerbation leading to a change in medication; hospital admission for ≥ 10 days; and average night CPAP usage < 3.5 hour
Interventions	CPAP or sham CPAP Study duration: 12 weeks on each treatment Washout: no washout
Outcomes	Echocardiographic parameters, BP recordings, urinary catecholamine levels
Notes	Jadad score = 4

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Patients were randomised by one of the investigators, by means of a computer-generated randomisation list using random numbers, to receive either effective CPAP or sham CPAP for two 12-week periods
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Reported as double blind. Not clear if outcome assessors were blinded
All outcomes		

LVEF, left ventricular ejection fraction.

Ballester 1999[87]

Methods	Randomised parallel-group trial of CPAP and CT vs. CT alone
Participants	One hundred and five patients randomised (males = 92, females = 13)
	No withdrawals recorded
	Baseline characteristics of the CPAP + CT group ($n = 68$): mean age: 53 years; BMI: 32 kg/m^2; AHI: 55 events/hour; ESS score: 12.1
	Baseline characteristics of the CT-only group ($n = 37$): mean age: 54 years; BMI: 34 kg/m^2; AHI: 58 events/hour; ESS score: 11.4
	Inclusion criteria: AHI > 15 events/hour plus severe clinical symptoms or AHI > 10 events/hour with mild to moderate clinical symptoms
	Exclusion criteria: severe or unstable CVD or a hazardous job coincident with OSAH (drivers or those who handled dangerous machinery)
Interventions	CPAP and CT (postural advice, avoid sedatives and alcohol, lose weight) vs. CT alone
	Study duration: 12 weeks on treatment
	Washout: N/A
Outcomes	ESS score, associated symptom score, daytime function, Nottingham Health Profile score
Notes	Jadad score = 1

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised. Randomly allocated two patients in the CPAP group for every patient who received only CT. No other information available
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Information not available
All outcomes		

CT, conservative treatment; N/A, not applicable.

Barbé 2001[88]

Methods	Randomised placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Fifty-five patients randomised, of which 54 completed the trial (males = 49, female = 5) Baseline characteristics of the completed CPAP group ($n = 29$): mean age: 54 years; BMI: 29 kg/m^2; AHI: 54 events/hour; ESS score: 7; FOSQ: 102; SF-36 PCS: 49; SF-36 MCS: 51; mean diurnal SBP: 130 mmHg; mean diurnal DBP: 82 mmHg Baseline characteristics of the completed sham CPAP group ($n = 25$): mean age: 52 years; BMI: 29 kg/m^2; AHI: 57 events/hour; ESS score: 7; FOSQ: 107; SF-36 PCS: 48; SF-36 MCS: 50; mean diurnal SBP: 127 mmHg; mean diurnal DBP: 80 mmHg Inclusion criteria: AHI $\geq$ 30 events/hour; ESS score $\leq$ 10; no or mild daytime sleepiness according to the International Classification of Sleep Disorders Exclusion criteria: cognitive deterioration of any cause, chronic underlying disease affecting QoL; severe cardiac disease; < 8 years of formal education; illicit drugs use; excessive alcohol consumption
Interventions	CPAP vs. sham CPAP Study duration: 6 weeks on treatment Washout: N/A
Outcomes	AHI, ESS score, MLST, SF-36, FOSQ, Steer-Clear, PASAT, BP
Notes	Jadad score = 4

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	A computer generated random number list generated with SPSS software (SPSS Inc., Chicago, IL, USA) was used to assign patients
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Information not available
All outcomes		

N/A, not applicable; PASAT, Paced Auditory Serial Addition Test.

Barbé 2012[89]

Methods	Randomised controlled parallel-group trial of CPAP vs. no active intervention
Participants	Seven hundred and twenty-five patients randomised, of whom 723 included in analysis (males = 619, females = 104)
	Baseline characteristics of the control (no active intervention) group ($n = 366$): mean age: 51.8 years; BMI: 31.1 kg/m^2; AHI: 35 events/hour; time with $SaO_2 < 90\%$: 6%; ESS score: 6.5; neck circumference: 42.0 cm; mean SBP: 130.9 mmHg; mean DBP: 79.9 mmHg
	Baseline characteristics of the CPAP group ($n = 357$): mean age: 52.0 years; BMI: 31.3 kg/m^2; AHI: 42 events/hour; time with SaO_2 <90%: 8%; ESS score: 6.5; neck circumference: 42.4 cm; mean SBP: 131.6 mmHg; mean DBP: 80.0 mmHg
	Inclusion criteria: 18–70 years old, AHI ≥ 20 events/hour, no daytime hypersomnolence (i.e. ESS score ≤ 10)
	Exclusion criteria: any physical or psychological incapacity, any previous CVE, chronic disease, drug or alcohol addiction, chronic intake of hypnotics, or refusal to participate in the study
Interventions	Active CPAP or no active intervention
	NOTE: All participants in both arms of the trial received sleep hygiene advice and dietary counselling for weight loss from sleep unit staff. There was no specific weight loss programme, and patients were referred to their GP to monitor weight loss
	Study duration: 3 years on either treatment
	Washout: N/A
Outcomes	Incidence of systemic hypertension in participants who were normotensive at baseline, incidence of CVE among all participants
	BP, ESS score, weight, CPAP adherence
Notes	Non sleepy OSA patients only recruited: ESS score ≤ 10 but AHI ≥ 20 events/hour
	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Eligible patients were randomly assigned in a 1 : 1 ratio to receive CPAP treatment or no active intervention. Randomisation was performed using a computer-generated list of random numbers in the co-ordinating centre and was stratified by centre
Allocation concealment?	Yes	The results were mailed in numbered opaque envelopes. The co-ordinating centre saved a sealed copy of the randomisation list sent to each centre
Blinding?	No	CPAP vs. no intervention compared
All outcomes		

N/A, not applicable.

Barnes 2002[90]

Methods	Randomised placebo-controlled crossover trial of CPAP vs. placebo tablet
Participants	Forty-two randomised (males = 35, females = 7), of which 28 completed the study Baseline characteristics for randomised patients ($n = 42$): mean age: 45.5 years; BMI: 30.2 kg/m^2; AHI: 12.9 events/hour; ESS score: 11.2; FOSQ total score: 0.8; mean diurnal SBP: 132 mmHg; mean diurnal DBP: 84 mmHg Inclusion criteria: AHI 5–30 events/hour; age > 18 years old Exclusion criteria: min. blood O_2 saturation < 75% in REM and 80% in NREM; clinically significant coexisting disease (e.g. diabetes, unstable ischaemic heart disease); sleepiness deemed to be unsafe and requiring urgent treatment, non-fluent in the English language; history of cerebrovascular disease, closed head injury associated with loss of consciousness > 15 minutes in duration, psychiatric illness, or alcohol or drug abuse
Interventions	CPAP vs. oral placebo (lactose tablet) Study duration: 8 weeks per treatment Washout: none
Outcomes	AHI, 4% ODI, ESS score, MLST, FOSQ, SF-36, Steer Clear; preference, BP
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	No	Randomisation was conducted by picking a piece of paper with a treatment order written on it out of a box, and then that piece of paper was placed back in the box
Allocation concealment?	Unclear	No information
Blinding?	No	CPAP compared with placebo tablet (single blinded)
All outcomes		

min., minimum; NREM; non-rapid eye movement; REM, rapid eye movement.

Barnes 2004[23]

Methods	Three–way crossover RCT of CPAP vs. MAD vs. placebo tablet
Participants	One hundred and fourteen patients with mild to moderate OSA (AHI 5–30 events/hour) recruited (males = 91, females = 23), of whom 80 completed all three treatment arms
	Mean age: 47 years; BMI: 31.1 kg/m^2; AHI: 21.3 events/hour; ESS score: 10.7
	Inclusion criteria: AHI 5–30 events/hour
	Exclusion criteria: poor dentition
Interventions	Nasal CPAP vs. MAD vs. placebo tablet
	Study duration: 12 weeks per treatment
	Washout: 2 weeks between treatments
Outcomes	Sleep hypoxemia – AHI, 4% ODI
	Daytime sleepiness – ESS score, MWT
	QoL – FOSQ, SF-36
	Neurobehavioral function and mood – NAB, PASAT 1.2, PVT, BDI
	BP
Notes	Intention-to-treat analysis
	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Yes	Randomisation was conducted by blindly selecting one of six pieces of paper from a box. On each piece of paper were written instructions to follow one of the six possible treatment orders. The paper was then replaced in the box in preparation for the next patient randomisation
Blinding?	No	MAD and CPAP compared with placebo tablet (single blinded)
All outcomes		

BDI, Beck Depression Inventory; NAB, Neuropsychological Assessment Battery; PASAT, Paced Auditory Serial Addition Test; PVT, psychomotor vigilance task.

Becker 2003[91]

Methods	Randomised placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Sixty patients randomised, of which 32 completed the trial (males = 29, females = 3) Baseline characteristics of the completed CPAP group ($n = 16$): mean age: 54.4 years; BMI: 33.3 kg/m^2; AHI: 62.5 events/hour; ESS score: 14.4; mean SBP: 135.9 mmHg; mean DBP: 83.4 mmHg Baseline characteristics of the completed subtherapeutic CPAP group ($n = 16$): mean age: 52.3 years; BMI: 33.5 kg/m^2; AHI: 65.0 events/hour; ESS score: 14.1; mean SBP: 136.2 mmHg; mean DBP: 81.1 mmHg Inclusion criteria: AHI $\geq$ 5 events/hour, ESS score $\geq$ 10 Exclusion criteria: predominantly central sleep apnoea; respiratory failure; heart failure (NYHA class III or IV); myocardial infarction 3 months before the study; relevant cardiac arrhythmia (second- and third-degree heart block or premature ventricular contractions in Lown classes IV or V); professional drivers
Interventions	Therapeutic CPAP vs. sham (subtherapeutic) CPAP Study duration: 9 weeks on average Washout: N/A
Outcomes	AHI, ESS score, BP, sleep parameters
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Yes	Randomisation was performed on the telephone by a person who was otherwise not involved in the study
Blinding? All outcomes	No	Not double blind. Used a single-blind study design because a method for applying therapeutic and subtherapeutic nCPAP in a double-blind fashion was not available

N/A, not applicable; NYHA, New York Heart Association.

Blanco 2005[70]

Methods	Randomised parallel-group trial of MAD vs. control MAD Method of allocation unclear
Participants	Twenty-four patients with mixed severity OSA (AHI ≥ 10 events/hour) recruited, of whom 15 completed the study (only data from these 15 presented) (males = 13, females = 2) Mean age: 53.5 years; BMI: 28.3 kg/m^2; AHI: 24.0–33.8 events/hour; ESS score: 14.7–16.3 Inclusion criteria: AHI ≥ 10 events/hour; two OSA symptoms Exclusion criteria: age > 75 years; BMI > 40 kg/m^2; poor dentition, TMJ problems
Interventions	MAD vs. control MAD without advancement Study duration: 12 weeks on treatment
Outcomes	Sleep – AHI Symptoms – ESS score, snoring scale QoL – FOSQ, SF-36
Notes	Indication that it was per-protocol analysis Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	Presentation of control intervention different; information on whether or not it was described as being an alternative treatment to intervention not available

TMJ, temporomandibular joint.

Campos-Rodriguez 2006[92]

Methods	Randomised placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Seventy-two patients randomised, of whom 68 completed the trial (males = 41, females = 27) Baseline characteristics of the completed CPAP group ($n = 34$): mean age: 55.3 years; BMI: 35.7 kg/m^2; AHI: 58.3 events/hour; ESS score: 15.0; mean 24 our SBP: 131.9 mmHg; mean 24-hour DBP: 78.4 mmHg Baseline characteristics of the completed sham CPAP group ($n = 34$): mean age: 58.0 years; BMI: 33.8 kg/m^2; AHI: 59.5 events/hour; ESS score: 13.6; mean 24-hour SBP: 130.4 mmHg; mean 24 hour DBP: 77.6 mmHg Inclusion criteria: aged between 30 and 70 years; AHI $\geq$ 10 events/hour; previous diagnosis of systemic arterial hypertension with treatment of hypertension with at least one drug for at least 3 months previous to the inclusion in the study Exclusion criteria: > 30% central sleep apnoea; respiratory failure; heart failure (NYHA class III or IV); ischaemic heart disease; cardiac arrhythmia; neoplastic or systemic diseases; secondary hypertension; professional drivers
Interventions	Therapeutic CPAP vs. sham (subtherapeutic) CPAP Study duration: 4 weeks on average Washout: N/A
Outcomes	AHI, ESS score, BP
Notes	Jadad score = 4

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Yes	Patients were randomly assigned to either therapeutic or subtherapeutic CPAP groups using a series of pre-sealed envelopes
Blinding? All outcomes	Yes	Patients were naive to CPAP and did not know if they were prescribed an effective or subtherapeutic pressure. The research faculty who assigned patients to treatment groups did not take part in the outcome assessments, and the nurse who fitted the monitors did not know the treatment group of the patients. Investigators that assessed the study outcome were unaware of the randomisation status, making the study double blind

N/A, not applicable; NYHA, New York Heart Association.

Chakravorty 2002[93]

Methods	Randomised parallel-group trial of CPAP vs. lifestyle intervention (conservative measurement)
Participants	Seventy-one patients randomised, of whom 53 completed the trial (sex not reported) Baseline characteristics of the completed CPAP group ($n = 32$): mean age: 49 years; BMI: 40 kg/m^2; AHI: 55 events/hour; ESS score: 16.0; neck circumference: 50 cm; EuroQol thermometer: 59 Baseline characteristics of the completed lifestyle intervention group ($n = 21$): mean age: 52 years; BMI: 32.3 kg/m^2; AHI: 35 events/hour; ESS score: 14; neck circumference: 45 cm; EuroQol thermometer: 68 Inclusion criteria: AHI $\geq$ 15 events/hour Exclusion criteria: neuromuscular disorders, hypothyroidism and associated respiratory diseases
Interventions	CPAP vs. lifestyle intervention (verbal advice, leaflet of strategies for sleep hygiene, stopping smoking, reducing alcohol intake, controlling stress, verbal and written advice in ideal body weight, weight reduction and exercise) Study duration: 3 months Washout: N/A
Outcomes	AHI, ESS score, EuroQol
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised. No other information
Allocation concealment?	Unclear	No information
Blinding?	Unclear	No information
All outcomes		

N/A, not applicable.

Coughlin 2007[94]

Methods	Randomised controlled crossover trial of CPAP vs. sham CPAP
Participants	Thirty-five patients randomised, 34 patients analysed (all male) Baseline characteristics of the analysed patients ($n = 34$): mean age: 49.0 years; BMI: 36.1 kg/m^2; RDI apnoea: 39.7; ESS score: 13.8; neck circumference: 48.0 cm Inclusion criteria: untreated male patients with OSAH Exclusion criteria: other medical conditions; on medication; abnormality on baseline ECG; evidence of diabetes (fasting blood glucose ≥ 7.1 mmol/l); renal, liver or cardiac disease; symptoms of peripheral neuropathy or a waking DBP and SBP ≥ 110 mmHg and ≥ 180 mmHg, respectively; or BP requiring treatment
Interventions	CPAP vs. sham CPAP Study duration: 6 weeks on each treatment Washout: none
Outcomes	ESS score, waking BP, metabolic variables (e.g. fasting glucose)
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation used a computer-generated sequence of random numbers
Allocation concealment?	Yes	Investigators were blinded to treatment allocation so were unaware of the order of treatment group assignment
Blinding? All outcomes	Yes	CPAP was provided by a technician unconnected with the study, so that both subject and investigators were blinded to treatment allocation

ECG, electrocardiogram.

Craig 2012[95]

Methods	Randomised controlled parallel-group trial of CPAP vs. standard care
Participants	Three hundred and ninety-one patients randomised (males = 305, females = 86), 341 included in ESS score analysis Baseline characteristics of the control (standard care) group ($n = 196$): mean age: 57.6 years; BMI: 32.5 kg/m^2; ODI: 9.4; ESS score: 8.0; neck circumference: 43.0 cm; mean SBP: 129.6 mmHg; mean DBP: 81.3 mmHg Baseline characteristics of the CPAP group ($n = 195$): mean age: 57.9 years; BMI: 32.2 kg/m^2; ODI: 10.2; ESS score: 7.9; neck circumference: 42.5 cm; mean SBP: 129.7 mmHg; mean DBP: 81.3 mmHg Inclusion criteria: aged 45–75 years, OSA on the diagnostic sleep study, with > 7.5 per hour oxygen desaturation index (ODI) of > 4%, insufficient daytime OSA symptoms to warrant CPAP therapy but ESS score could be above the conventional upper normal limit of 9 when this was not accompanied by patient concerns Exclusion criteria: ventilatory failure, Cheyne–Stokes breathing, previous exposure to CPAP, SBP > 180 mmHg or DBP > 110 mmHg on three successive measurements during the eligibility assessment, a HGV or public service vehicle driver's licence, previous sleep-related accident Disability precluding either informed consent or compliance with the protocol
Interventions	CPAP vs. standard care. The standard care group had an identical planned visit schedule to the CPAP group. Both groups were asked to continue on their normal medication and not given any specific advice regarding diet and exercise. MAD without advancement Study duration: 6 months on either treatment
Outcomes	ESS score, composite vascular risk end point, BP, lipids, glucose metabolism, obesity measures, vascular events, sleep apnoea severity (ODI), health status: SF-36, SAQLI, EQ-5D
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation was carried out by telephoning the MRC CTU, using minimisation with a random element of 80%; the minimisation factors were OSA severity (ODI, above or below 20/hour), risk score (above or below 40) and participating centre
Allocation concealment?	Unclear	Information not available
Blinding?	No	CPAP vs. standard care compared
All outcomes		

HGV, heavy goods vehicle; MRC CTU, Medical Research Council Clinical Trials Unit.

Diaferia 2013[96]

Methods	Randomised parallel-group trial Four arms: CPAP vs. ST vs. placebo (sham ST) vs. combination (CPAP + ST)
Participants	One hundred and forty patients randomised, 100 completed and included in analysis Baseline characteristics of the placebo group ($n = 24$): mean age: 42.9 years; BMI: 28.6 kg/m^2; AHI: 27.8 events/hour; ESS score: 12.8; neck circumference: 41.9 cm Baseline characteristics of the ST group ($n = 27$): mean age: 45.2 years; BMI: 25.0 kg/m^2; AHI: 28.0 events/hour; ESS score: 13.7; neck circumference: 41.6 cm Baseline characteristics of the CPAP group ($n = 27$): mean age: 46.4 years; BMI: 28.7 kg/m^2; AHI: 34.4 events/hour; ESS score: 12.0; neck circumference: 41.9 cm Baseline characteristics of the combination group ($n = 22$): mean age: 47.5 years; BMI: 27.9 kg/m^2; AHI: 30.4 events/hour; ESS score: 12.0; neck circumference: 42.4 cm Inclusion criteria: OSA based on clinical and polysomnographic criteria independently of severity, male, age 25–65 years, BMI < 35 kg/m^2 Exclusion criteria: lower levels of education attainment; presence of other sleep disorders or previous treatment for OSA; severe or decompensated clinical or psychiatric diseases; use of alcohol, stimulants or sedatives; craniofacial or upper airway anatomic alterations; grade III or IV palatine tonsils, grade II or III septal deviation, evident micrognathia
Interventions	CPAP vs. ST vs. placebo (sham ST) vs. combination (CPAP + ST) Study duration: 3 months on treatment
Outcomes	QoL questionnaires (FOSQ, WHOQoL and SF-36), ESS score, polysomnography, ST assessment
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	CPAP vs. ST compared
All outcomes		

ST, speech therapy; WHOQoL, World Health Organization Quality of Life.

Drager 2006[97]

Methods	Randomised parallel-group trial of CPAP vs. no treatment
Participants	Sixteen patients randomised (sex not disclosed)
	Baseline characteristics of the CPAP group ($n = 8$): mean age: 45 years; BMI: 31 kg/m^2; AHI: 54 events/hour; SBP: 118 mmHg
	Baseline characteristics of the no-treatment group ($n = 8$): mean age: 47; BMI: 30 kg/m^2; AHI: 65 events/hour; SBP: 125 mmHg
	Inclusion criteria: normotensive patients; AHI > 30 events/hour; untreated OSA
	Exclusion criteria: no information
Interventions	CPAP vs. no treatment
	Study duration: 3 months
Outcomes	Arterial stiffness, BP, cholesterol level, heart rate
Notes	Jadad score = 2
	Conference abstract – insufficient outcome data available

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	No information given but was CPAP vs. no treatment so patients would not have been blinded

Drager 2007[98]

Methods	Randomised parallel-group trial of CPAP vs. no treatment
Participants	Twenty-four patients randomised and completed the trial (all male)
	Baseline characteristics of the control group ($n = 12$): mean age: 47 years; BMI: 29.7 kg/m^2; AHI: 62 events/hour; ESS score: 13; SBP: 122 mmHg; DBP: 66 mmHg
	Baseline characteristics of the CPAP group ($n = 12$): mean age: 44 years; BMI: 29.9 kg/m^2; AHI: 56 events/hour; ESS score: 14; SBP: 123 mmHg; DBP: 73 mmHg
	Inclusion criteria: male; sleep study within 1 month showing severe OSA (AHI > 30 events/hour) and naive to treatment
	Exclusion criteria: age > 60 years; BMI > 35 kg/m^2; diabetes mellitus, hypertension, cerebrovascular disease, valvular heart disease, renal failure; current or past smoking history; chronic use of any medication
Interventions	CPAP vs. no treatment
	Study duration: 4 months
Outcomes	Carotid intima–media thickness, vascular parameters (arterial stiffness, carotid intima–media thickness and carotid diameter), 24-hour BP, cholesterol, catecholamines and C-reactive protein, ESS score
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Computer-generated list of random numbers
Allocation concealment?	Unclear	Information not available
Blinding?	No	CPAP vs. no treatment
All outcomes		

Duran 2002[71]

Methods	Randomised, crossover trial	
	Method of allocation not clear	
Participants	Forty-four participants recruited, 38 participants completed the study (four women)	
	Mean age: 46.5 years; BMI: 27.7 kg/m^2; AHI: 15.3 events/hour	
	Inclusion criteria: mild OSA (AHI > 5 events/hour) and snoring	
Interventions	MAD vs. MAD in centric occlusion	
	Study duration: unclear	
	Study preceded by a 12–18 week acclimatisation period	
Outcomes	AHI, symptoms, tolerability	
Notes		
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Presentation of control intervention different; information on whether or not it was described as being an alternative treatment to intervention not available
All outcomes		

Durán-Cantolla 2010[99]

Methods	Randomised parallel-group trial Two arms: CPAP vs. sham CPAP
Participants	Three hundred and forty patients randomised (males = 277, females = 63) and 272 completed the trial Baseline characteristics of the CPAP group ($n = 169$): mean age: 53.2 years; BMI: 31.9 kg/m^2; AHI: 44.5 events/hour; lowest SaO_2: 79.9%; ESS score: 10.3; SBP: 131.1 mmHg; DBP: 82.5 mmHg Baseline characteristics of the control (sham CPAP) group ($n = 171$): mean age: 51.7 years; BMI: 31.9 kg/m^2; AHI: 42.5 events/hour; lowest SaO_2: 80.1%; ESS score: 9.8; SBP: 128.8 mmHg; DBP: 81.8 mmHg Inclusion criteria: aged 18–75 years, recent diagnosis of hypertension, untreated hypertension, habitual snorers Exclusion criteria: secondary systemic hypertension, BP > 80/110 mmHg, cognitive deterioration, professional drivers, handled dangerous machinery, worked shifts, pregnancy, life threatening OSA or severe chronic disease, previous OSA treatment or patients for whom CPAP treatment was not appropriate, antihypertensive, psychotropic, stimulatory, antidepressant or illicit drug users, excessive alcohol intake
Interventions	CPAP vs. sham CPAP Study duration: 12 weeks
Outcomes	BP, ESS score, EuroQol
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	An external health research unit generated the allocation sequence, using a computerised randomisation procedure
Allocation concealment?	Yes	When an eligible patient was identified, the clinician sent the patient's identification information by e-mail, and the group assignation to either optimal therapeutic CPAP or sham CPAP was returned within 24 hours
Blinding? All outcomes	Yes	Patients and outcome assessors blinded to treatment allocation

Engleman 1996[100]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. oral tablet	
Participants	Sixteen patients randomised, 13 patients completed (males = 11, females = 2)	
	Mean age: 51 years; BMI: 36 kg/m^2; AHI: 49 events/hour	
	Inclusion criteria: AHI ≥ 5 events/hour; at least two symptoms of sleep apnoea/hypopnoea syndrome	
	Exclusion criteria: not stated	
Interventions	CPAP vs. oral placebo tablet	
	Study duration: between 3–5 weeks per treatment	
	Washout: none	
Outcomes	24-hour ambulatory BP	
Notes	Jadad score = 2	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	CPAP and oral tablet compared so not double blind. No information about assessors

Engleman 1997[101]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. oral tablet
Participants	18 patients randomised, 16 patients completed (males = 12, females = 4) Baseline characteristics of the completed patients ($n = 16$): mean age: 52 years; BMI: 29.8 kg/m^2; AHI: 11 events/hour; ESS score: 14 (ESS score data from nine patients only) Inclusion criteria: AHI 5.0–14.9 events/hour; at least two symptoms of sleep apnoea/hypopnoea syndrome Exclusion criteria: co-existing neurological or sleep disorders; residence outside a 50-mile radius from the laboratory
Interventions	CPAP vs. oral placebo tablet (ranitidine 300 mg homologue, Glaxo, Greenford, UK, in a dose of two tablets at bedtime) Study duration: 4 weeks per treatment Washout: none
Outcomes	Sleepiness (e.g. MSLT, ESS score), cognitive function, psychiatric morbidity (e.g. HADS), CPAP compliance
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	CPAP and oral tablet compared so not double blind. No information about assessors

HADS, Hospital Anxiety and Depression Scale.

Engleman 1998[102]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. oral tablet
Participants	Twenty-three patients randomised (males = 21, females = 2), 22 patients analysed
	Baseline characteristics of the randomised patients ($n = 23$): mean age: 47 years; BMI: 30 kg/m^2; AHI: 43 events/hour; ESS score: 12 (ESS score data from 22 patients only)
	Inclusion criteria: AHI ≥ 15 events/hour; at least two symptoms of sleep apnoea/hypopnoea syndrome
	Exclusion criteria: lung disease; neurological disorders; co-existing sleep disorders; residence outside a 50-mile radius from the Scottish National Sleep Centre
Interventions	CPAP vs. oral placebo tablet (Glaxo, UK)
	Study duration: 4 weeks per treatment
	Washout: none
Outcomes	ESS score, AHI, MSLT, cognitive function, psychiatric wellbeing, preference
Notes	Jadad score = 2
	Intention-to-treat analysis

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	Described as single blind. CPAP and oral tablet compared. No further information
All outcomes		

Engleman 1999[103]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. oral tablet
Participants	Thirty-seven patients randomised, 34 patients completed (males = 21, females = 13)
	Baseline characteristics of completed patients ($n = 34$): mean age: 44 years; BMI: 30 kg/m^2; AHI: 10 events/hour; ESS score: 13
	Inclusion criteria: at least two symptoms of sleep apnoea/hypopnoea syndrome, including: AHI 5.0–14.9 events/hour; ESS score ≥ 8
	Exclusion criteria: lung disease; neurological disorders; co-existing sleep disorders; residence outside a 50-mile radius from the laboratory; shift workers
Interventions	CPAP vs. oral placebo tablet (Glaxo, Greenford, UK)
	Study duration: 4 weeks per treatment
	Washout: none
Outcomes	ESS score, SF-36, MSLT, cognitive function, psychiatric well-being, preference
Notes	Jadad score = 2
	Intention-to-treat analysis
	Full study following on from a pilot study

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	Not double blind as CPAP and oral tablet compared. No further information

Engleman 2002[22]

Methods	Two–way crossover randomised trial Patient randomisation stratified by severity of OSA (AHI ≥ 15 events/hour or < 15 events/hour) using balanced blocks of four. Patients then randomised to two arms: CPAP and one of two MADs
Participants	Fifty-one patients with mixed severity OSA (AHI ≥ 5 events/hour) recruited, of which 48 completed both treatment arms (males = 36, females = 12) Mean age: 46 years; BMI: 28–31 kg/m^2; AHI: 31 events/hour; ESS score: 14 Inclusion criteria: AHI ≥ 5 events/hour and ≥ two symptoms including sleepiness Exclusion criteria: poor dentition, co-existing sleep disorder, medical conditions, shift work or residency > 50 miles from Edinburgh
Interventions	CPAP vs. one of two MADs (occlusal or non-occlusal coverage) Study duration: 8 weeks per treatment Washout: not mentioned
Outcomes	Treatment effectiveness – AHI Treatment use – acceptability, satisfaction, preference Symptoms and sleepiness – ESS score, MWT, FOSQ, daytime sleep Well-being – FOSQ, SF-36, HADS Cognitive performance – PASAT 2, Trailmaking B, SteerClear, performance IQ decrement score
Notes	Intention-to-treat analysis Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD and CPAP compared
All outcomes		

HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient.

Faccenda 2001[104]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. oral tablet
Participants	Seventy-one patients randomised, 68 patients analysed (males = 55, females = 13)
	Baseline characteristics of analysed patients ($n = 68$): median age: 50 years; BMI: 30 kg/m^2; AHI: 35; ESS score: 15; neck circumference: 40 cm
	Inclusion criteria: at least two symptoms of sleep apnoea/hypopnoea syndrome; AHI $\geq$ 15
	Exclusion criteria: sleepiness when driving; residence outside a 50-mile radius from the laboratory; shift workers; diabetes; BP changing drugs
Interventions	CPAP vs. oral placebo tablet (Glaxo, UK)
	Study duration: 4 weeks per treatment
	Washout: none
Outcomes	ESS score, AHI, BP, FOSQ
Notes	Jadad score = 2
	Intention-to-treat analysis
	Median baseline values not mean

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Patient was randomised using a balanced block design
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	Not double blind as CPAP and oral tablet compared. All data were manually checked for artefact by an observer who was blinded to the treatment status of the patient

Ferguson 1996[78]

Methods	Two–way crossover randomised trial
	Patients randomised to two arms: nCPAP and MAD
Participants	Twenty-seven patients with mild to moderate OSA (AHI 15–50) recruited (males = 24, females = 3), of which 25 completed both treatment arms
	Mean age: 46.2 years; BMI: 30.4 kg/m^2; AHI: 24.5 events/hour
	Inclusion criteria: AHI 15–50 events/hour
	Exclusion criteria: poor dentition or residency outside the metropolitan Vancouver area
Interventions	nCPAP vs. MAD
	Study duration: 16 weeks per treatment
	Washout: 2 weeks between treatments
	2 week wash in before randomisation
Outcomes	Treatment effectiveness – AHI, AI, TST, desaturations < 90%, min. SaO_2, sleep efficiency, arousals
	Treatment use – satisfaction, preference
	Symptoms and sleepiness – in-house questionnaires
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD and CPAP compared
All outcomes		

AI, Apnoea Index; min; mimimum; nCPAP, nasal continuous positive airway pressure; TST, total sleep time.

Ferguson 1997[79]

Methods	Two–way crossover randomised trial
	Patients randomised to two arms: nCPAP and MAD
Participants	Twenty-four patients with mild to moderate OSA (AHI 15–55 events/hour) recruited (males = 19, females = 5), of which 20 completed both treatment arms
	Mean age: 44.0 years; BMI: 32.0 kg/m^2; AHI: 26.8 events/hour; ESS score: 10.7
	Inclusion criteria: AHI 15–55 events/hour
	Exclusion criteria: poor dentition or residency outside the metropolitan Vancouver area
Interventions	nCPAP vs. MAD
	Study duration: 16 weeks per treatment
	Washout: 2 weeks between treatments
	2 week wash in before randomisation
Outcomes	Treatment effectiveness – AHI, AI, TST, desaturations < 90%, min. SaO_2, sleep latency, NREM, REM, arousals
	Treatment use – compliance and preference
	Symptoms and sleepiness – ESS score, in-house questionnaires
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD and CPAP compared
All outcomes		

AI, Apnoea Index; min., minimum; nCPAP, nasal continuous positive airway pressure; NREM, non-rapid eye movement; REM, rapid eye movement; TST, total sleep time.

Fleetham 1998[80]

Methods	Randomised, prospective, unblended parallel-group study comparing MAD with nCPAP
Participants	One hundred and one patients (AHI > 10 events/hour) recruited and randomised. Fifty-one to receive nCPAP, 50 to receive MAD (males = 96, females = 5) Mean baseline values for nCPAP group: age: 49.0 years, BMI: 32.0 kg/m^2; AHI: 37.6 events/hour; min. SaO_2: 75.8; ESS score: 12.8; SAQLI: 4.2 Mean baseline values for MAD group: age: 46.2 years, BMI: 31.4 kg/m^2; AHI: 38.7 events/hour; min. SaO_2: 73.6; ESS score: 11.1; SAQLI: 4.2 Inclusion criteria = AHI > 10
Interventions	nCPAP or MAD Study duration: 3 months
Outcomes	AHI, min. SaO_2, ESS score, SAQLI
Notes	Jadad score = 1

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, no other information available
Allocation concealment?	Unclear	Information not available
Blinding?	No	OA and CPAP compared
All outcomes		

min., minimum; nCPAP, nasal continuous positive airway pressure; OA, oral appliance.

Gagnadoux 2009[24]

Methods	Randomised crossover trial Two arms: MAD vs. CPAP
Participants	Fifty-nine patients randomised (males = 46, females = 13) and 56 completed the trial Baseline characteristics of the 59 randomised patients: mean age: 50.3 years; BMI: 26.7 kg/m^2; AHI: 34.2 events/hour; ESS score: 10.6 Inclusion criteria: 18–70 years with newly diagnosed OSAH; AHI 10–60 events/hour and two more symptoms of OSAH including: snoring, witnessed apnoea or complaint of daytime sleepiness Exclusion criteria: previous treatment for OSAH, BMI $\geq$ 35 kg/m^2, coexisting sleep disorder other than OSAH, inadequate dental structure, TMJ disease contraindicating MAD treatment as assessed by dentist, unstable medical illness, severe sleepiness which may constitute risk to self or others
Interventions	MAD vs. CPAP Study duration: 8 weeks on each treatment Washout period = 1 week
Outcomes	AHI, ESS score, OSLER test, HRQoL (Nottingham health profile); trial making A and B cognitive tests for attention and concentration
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	CPAP vs. MAD compared
All outcomes		

OSLER, Oxford Sleep Resistance; TMJ, temporomandibular joint.

Gotsopoulos 2002[72]

Methods	Two–way crossover randomised trial Patients randomised to two arms: MAD and control MAD
Participants	Eighty-five patients recruited, 73 patients with OSA (RDI $\geq$ 10) randomised (males = 59, females = 14) Mean age: 48 years; BMI: 29.0 kg/m^2; RDI: 27.1; ESS score: 11 Inclusion criteria: RDI $\geq$ 10, > 20 years old, able to protrude mandible by at least 3 mm Exclusion criteria: predominant CSA, conflicting medications/psychiatric disease, poor dentition or exaggerated gag reflex
Interventions	MAD vs. control MAD without advancement Study duration: 4 weeks per treatment Washout: 1 week between treatments Patients had 8 $\pm$ 4 weeks (range 2–22 weeks) to adjust to MAD advancement before a 1-week washout before randomisation and subsequent treatment allocation
Outcomes	Treatment effectiveness – RDI, min. SaO_2, TST, sleep efficiency, arousal index, snoring frequency and intensity Treatment use – compliance and satisfaction Symptoms and sleepiness – ESS score, in-house questionnaires, MSLT
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Sequence allocation determined by a random number generator
Allocation concealment?	Yes	Investigators unaware as to order of treatment group assignment
Blinding? All outcomes	Unclear	Two treatments not identical in presentation but control treatment described as an alternative treatment to participants (single blind)

CSA, central sleep apnoea; min., minimum; TST, total sleep time.

Haensel 2007[105]

Methods	Randomised parallel-group trial Two arms: CPAP vs. sham CPAP
Participants	Fifty patients randomised and completed the trial (males = 40, females = 10) Baseline characteristics of the CPAP group ($n = 25$): mean age: 48.2 years; BMI: 33.1 kg/m^2; AHI: 63.6 events/hour; mean SaO_2: 92.9 Baseline characteristics of the sham CPAP group ($n = 25$): mean age: 49.0 years; BMI: 33.7 kg/m^2; AHI: 58.4 events/hour; mean SaO_2: 92.8 Inclusion criteria: history of snoring and daytime sleepiness, age 30–65 years, weight 100–200% of body weight per Metropolitan Life Insurance tables, AHI ≥ 15 events/hour on PSG Exclusion criteria: history of heart, liver or renal disease, diabetes, psychosis, narcolepsy, current alcohol or drug abuse, severe asthma or cerebrovascular disease, a history of depression, BP > 170/105 SaO_2 mmHg, patients who were taking antihypertensive medication had their medication tapered slowly in 2–3 steps for 3 weeks before admission
Interventions	CPAP vs. sham CPAP Study duration: 2 weeks on treatment
Outcomes	AHI, O_2 saturation < 90%, mean O_2 saturation, total sleep time, sleep efficiency, POMS
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	Yes	Study described as double blind
All outcomes		

POMS, profile of mood states; PSG, polysomnogram.

Hans 1997[73]

Methods	Randomised parallel-group trial of OA vs. minimally active (placebo) OA Then seven of those on placebo crossed over to OA
Participants	Twenty-four adult volunteers (RDI < 30) recruited, of which 18 completed (males = 83%, females = 17%) Mean age: 51.9 years Active OA group (A) means: BMI: 29.5 kg/m^2; RDI: 35.6; ESS score: 12.0 Placebo OA group (B) means: BMI: 29.4 kg/m^2; RDI: 36.5; ESS score: 13.0 Inclusion criteria: RDI < 30 Exclusion criteria: systemic diseases apart from OSAS, pregnancy, prisoners, minors, chronic illnesses, mental disability, RDI > 30 with pathophysiological symptoms, edentulism, previous corrective surgery for snoring of OSA, non-OSAS sleep disorders (e.g. PLM), CNS disease, psychiatric disease, alcoholism, severe obstructive or restrictive lung diseases, unstable ischaemic heart disease, pulmonary oedema, poorly controlled hypertension, use of sedative/hypnotic medication, shift workers
Interventions	Participants were randomised to either active oral appliance or minimally active oral appliance
Outcomes	RDI, ESS score
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Presentation of control intervention different; information on whether or not it was described as being an alternative treatment to intervention not available

CNS, central nervous system; OA, oral appliance; PLM, periodic limb movement.

Henke 2001[106]

Methods	Randomised, placebo-controlled partial crossover trial of CPAP vs. sham CPAP
Participants	Forty-five patients randomised (males = 25, females = 20), of which 39 patients completed the entire study Baseline characteristics of randomised patients in the CPAP group ($n = 27$): mean age: 50.2 years; BMI: 42.7 kg/m^2; AHI: 62.1 events/hour; ESS score: 16.4 Baseline characteristics of randomised patients in the sham CPAP/CPAP group ($n = 18$): mean age: 50.6 years; BMI: 42.2 kg/m^2; AHI: 68.1 events/hour; ESS score: 16.0 Inclusion criteria: AHI > 10 events/hour + daytime sleepiness or AHI > 20 events/hour ± daytime sleepiness Exclusion criteria: previous treatment for sleep apnoea/hypopnoea syndrome; oxygen saturation < 85% for > 50% of the sleep time; clinical signs of right-sided congestive heart failure; claustrophobia or nasal obstruction preventing use of nasal CPAP
Interventions	Sham-CPAP group received treatment for 15 days then crossed over and received CPAP for rest of treatment period. CPAP received treatment for entire period Study duration: 6 weeks per treatment group Washout: none
Outcomes	ESS score, AHI, ODI, Steer Clear
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Described as double blind. Neither subjects nor staff who had contact with the subjects or their records knew the group to which the subjects belonged. At study entry, the subjects were informed that during the course of the study they may or may not be receiving effective treatment but that every subject would receive effective treatment for at least part of the study

Hoekema 2008[81]

Methods	Randomised parallel-group trial Two arms: CPAP vs. MAD
Participants	One hundred and three patients randomised (males = 92, females = 11), of which 99 completed the trial Baseline characteristics of the MAD group ($n = 51$): age: 48.8 years; BMI: 32.3 kg/m^2; neck circumference: 43.8 cm; AHI: 39.4 events/hour; ESS score: 12.9; FOSQ total score: 13.7; SBP: 150.8 mmHg; DBP: 93.1 mmHg Baseline characteristics of the CPAP group ($n = 52$): age: 49.4 years; BMI: 33.3 kg/m^2; neck circumference: 44.5 cm; AHI: 40.3 events/hour; ESS score: 14.2; FOSQ total score: 13.9; SBP: 151.5 mmHg; DBP: 91.6 mmHg Inclusion criteria: age > 20 years, diagnosis of OSA on PSG Exclusion criteria: Medical and psychological exclusion criteria: Previous treatment for OSA (CPAP, oral appliance therapy or uvulopalatopharyngoplasty); reversible morphological airway abnormalities (compromised nasal passage, enlarged tonsils or adenoids, upper-airway or pulmonary neoplasm, or upper-airway soft tissue or craniofacial abnormality); endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma); reported or documented history of severe cardiac or pulmonary disease (daytime respiratory insufficiency, severe COPD (Tiffeneau index < 40%), heart failure, coronary disease or severe cardiac arrhythmias); moderate or severe PLMD (PLM index > 25); psychological conditions precluding informed consent (mental retardation or psychiatric disorder; e.g. depression or schizophrenia) Dental criteria for exclusion: Extensive periodontal disease or tooth decay; active TMJ disease (including severe bruxism); restrictions in mouth opening (< 25 mm) or advancement of the mandible (< 5 mm); partial or complete edentulism (< 8 teeth in upper or lower jaw)
Interventions	CPAP vs. MAD Study duration: 8 weeks on treatment
Outcomes	AHI, ESS score, FOSQ, SF-36, hospital anxiety and depression scale, treatment usage and satisfaction
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	The clinical epidemiologist for the study made computer-generated randomisation sequences, balancing for disease severity. The randomisation sequences were used for selecting random permuted blocks with lengths of 2, 4, and 6 numbers
Allocation concealment?	Yes	The randomisation sequences were concealed and administered by Department of Oral and Maxillofacial Surgery staff. After each person's serial number and diagnosis of disease severity were provided, the treatment was disclosed. Each serial number could be provided only once
Blinding?	No	CPAP vs. MAD compared
All outcomes		

COPD, chronic obstructive pulmonary disease; PLM, periodic limb movement; PLMD, periodic limb movement disorder; PSG, polysomnogram; TMJ, temporomandibular joint.

Hoyos 2012[107]

Methods	Randomised parallel-group trial of CPAP vs. sham CPAP
Participants	Sixty-five patients randomised (all male), of which 46 completed trial Baseline characteristics of the CPAP group ($n = 34$): age: 51.0 years; BMI: 31.6 kg/m^2; AHI: 38.5 events/hour; ESS score: 10.0; 3% ODI: 32.0 Baseline characteristics of the control (sham CPAP) group ($n = 31$): age: 46.4 years; BMI: 31.0 kg/m^2; AHI: 41.5 events/hour; ESS score: 10.2; 3% ODI: 34.9 Inclusion criteria: adults ≥ 18 years, male, AHI ≥ 20 events/hour and 3% ODI ≥ 15 on PSG Exclusion criteria: type II diabetes mellitus; previously used CPAP; min. O_2 saturation < 65%, AHI > 80 events/hour, requiring immediate CPAP as a result of excessive sleepiness in relation to the subject's occupation; uncontrolled concurrent medical, drug abuse or psychiatric illness; contraindication to CPAP therapy; irregular sleep patterns such as shift workers; participation in another clinical trial in the previous 30 days
Interventions	CPAP vs. sham CPAP Study duration: 12 weeks on treatment
Outcomes	AHI, ESS score, metabolic outcomes
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	A computer program produced randomised permuted blocks with a block size of four. Participants were assigned to real or sham CPAP in a 1 : 1 ratio
Allocation concealment?	Yes	At baseline each participant was assigned a unique number in sequential, ascending, chronological order which corresponded to the treatment allocation
Blinding? All outcomes	Yes	Participants and study investigators were blinded to treatment allocation

min., minimum; PSG, polysomnogram.

Hui 2006[108]

Methods	Randomised parallel-group trial of CPAP vs. sham CPAP	
Participants	Fifty-six patients randomised (males = 43, female = 13), of which 46 completed trial Baseline characteristics of randomised patients ($n = 56$): mean age: 50.8 years; BMI: 27.2 kg/m^2; AHI: 31.2 events/hour; ESS score: 11.1; neck circumference: 38.5 cm; 24-hour SBP: 123.7 mmHg; 24-hour DBP: 80.9 mmHg Inclusion criteria: AHI $\geq$ 5 events/hour + excessive daytime sleepiness or two of the following symptoms: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue and impaired concentration Exclusion criteria: problems staying awake during driving; professional drivers; shift workers; recent myocardial infarction; unstable angina; underlying malignancy	
Interventions	CPAP vs. sham CPAP (subtherapeutic low-pressure CPAP) Study duration: 3 months on treatment	
Outcomes	ESS score, BP (change in mean 24-hour arterial BP, changes in SBP and DBP, changes in mean BP awake and asleep, and relationship between BP change and baseline hypertensive status and CPAP compliance over 3 months)	
Notes	Jadad score = 5	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Patients were randomised into two groups to receive nasal therapeutic or subtherapeutic CPAP in a balanced block design
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Yes	Although the two different treatment arms were explained in the patient information, the CPAP-naive patients were not aware of whether or not they received therapeutic or subtherapeutic CPAP during the study period The investigator responsible for randomisation of patients to the different treatment arms did not participate in outcome assessments which were conducted by a different team of investigators who were not aware of the randomisation status of the patients

Jenkinson 1999[109]

Methods	Randomised parallel-group trial of CPAP vs. sham CPAP
Participants	One hundred and seven patients randomised, of which 101 completed the trial (all male) Baseline characteristics of completed CPAP group ($n = 52$): median age: 50 years; BMI: 35.1 kg/m^2; 4% SaO_2 (dips/hour): 32.9; ESS score: 16.0; neck circumference: 44.5 cm; SF-36 MCS: 44.8; SF-36 PCS: 43.7 Baseline characteristics of completed sham CPAP group ($n = 49$): median age: 48 years; BMI: 35.0 kg/m^2; 4% SaO_2 (dips/hour): 28.5; ESS score: 17.0; neck circumference: 45.7 cm; SF-36 MCS: 43.5; SF-36 PCS: 42.6 Inclusion criteria: male; aged 30–75 years; ESS score ≥ 10; ≥ 10 dips per hour of $> 4\%$ in arterial oxygen saturation Exclusion criteria: requiring urgent CPAP because of associated respiratory failure or because of imminent job loss; mental disability preventing informed consent
Interventions	CPAP vs. sham CPAP (subtherapeutic low pressure CPAP) Study duration: 1 month on treatment
Outcomes	ESS score, MWT, daytime saturation, SF-36
Notes	Jadad score = 4 Median values given not mean values

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised. Other information not available
Allocation concealment?	Yes	Patients were randomly assigned their treatment by use of a series of opaque sealed envelope prepared in advance of the trial
Blinding? All outcomes	Yes	Described as double blind. Patients and outcome assessors not aware of treatment allocation

Johnston 2002[74]

Methods	Randomised, placebo-controlled cross-over trial of OA vs. 'placebo' appliance	
Participants	Twenty-one participants recruited (males = 17; females = 4), of which 20 participants completed the study	
	Baseline characteristics for the 20 patients who completed the trial: mean age: 55.1 years; BMI: 31.63 kg/m^2; AHI: 31.93 events/hour, ODI: 30.69, ESS score: 13.90	
	Inclusion criteria: ≥ 10 desaturations (≥ 4% drop in SpO_2) per hour	
	Exclusion criteria: concurrent pulmonary disease; edentulous patients and those with inadequate number of sound teeth to support a MAA	
Interventions	MAA vs. placebo device	
	Study duration: 4–6 weeks	
	No washout period	
Outcomes	AHI, ODI, ESS score, partner-evaluated snoring scale, tolerability and compliance	
Notes	Jadad score = 2	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	No information available
Blinding?	No	Information not available
All outcomes		

MAA, mandibular advancement appliance; OA, oral appliance.

Kaneko 2003[110]

Methods	Randomised controlled parallel-group trial of CPAP + medical therapy vs. medical therapy alone
Participants	Twenty-four patients randomised, all completed (males = 21, females = 3) Baseline characteristics of patients in the CPAP group ($n = 12$): mean age: 55.9 years; BMI: 30.4 kg/m^2; total AHI: 37.1 events/hour; obstructive AHI: 30.3 events/hour; ESS score: 6.8; SBP: 126 mmHg; DBP: 62 mmHg Baseline characteristics of patients in the control group ($n = 12$): mean age: 55.2 years; BMI: 32.3 kg/m^2; total AHI: 45.2 events/hour; obstructive AHI: 34.8 events/hour; ESS score: 5.7; SBP: 128 mmHg; DBP: 60 mmHg Inclusion criteria: history of heart failure because of ischaemic or non-ischaemic dilated cardiomyopathy for at least 6 months; a LVEF of $\leq 45\%$ at rest; assignment to NYHA functional class II, III, or IV; the absence, within the previous 3 months, of exacerbations of heart failure while on stable, optimal pharmacologic therapy at the highest tolerated doses; and AHI ≥ 20 events/hour of which $\geq 50\%$ were obstructive Exclusion criteria: primary valvular heart disease; presence of an implanted cardiac pacemaker; unstable angina, myocardial infarction or cardiac surgery within the previous 3 months
Interventions	CPAP + optimal drug therapy vs. optimal drug therapy alone Study duration: 1 month on treatment
Outcomes	AHI, BP and cardiovascular outcomes
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised but no information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes – partial	Patients were aware of their treatment assignments. Cardiovascular outcome measurements were obtained by persons blinded to treatment assignment. Unclear whether or not polysomnographic outcome assessor blinded

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Kushida 2012[25]

Methods	Parallel-group, randomised, double-blind, sham-controlled trial Two arms: CPAP vs. sham CPAP
Participants	One thousand one hundred and five patients randomised, 1098 analysed (baseline data reported for 1098) (males = 719, females = 379) Baseline characteristics of the CPAP group ($n = 556$): age: 52.2 years; BMI: 32.4 kg/m^2; AHI: 39.7; ESS score: 10.07; min. O_2 saturation: 81.0 Baseline characteristics of the control (sham CPAP) group ($n = 542$): age: 50.8 years; BMI: 32.1 kg/m^2; AHI: 40.6; ESS score: 10.09; min. O_2 saturation: 80.8 Inclusion criteria: diagnosis of OSA with AHI ≥ 10; age ≥ 18 years Exclusion criteria: prior OSA treatment with CPAP or surgery; anyone in the household with current/past CPAP use; sleepiness-related automobile accident within past year; O_2 saturation $< 75\%$ for $> 10\%$ of the diagnostic PSG total sleep time; conditions (including known neurocognitive impairment), disorders, medications or substances that could potentially affect neurocognitive function and/or alertness
Interventions	CPAP vs. sham CPAP Study duration: 6 months on treatment
Outcomes	ESS score; maintenance of wakefulness test and neurocognitive measures
Notes	ESS score only, AHI measured at baseline and through trial but post-treatment values not reported, just says, 'a significant difference was detected in AHI between active vs. sham CPAP groups at 2 months ($P < 0.0001$) and 6 months ($P < 0.0001$)' Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	The Data Coordinating Centre used a computerised permuted block design to randomise 1105 participants to active vs. sham CPAP. Randomisation was stratified by gender, race (white vs. non-white) and OSA severity (mild, AHI = 10.0–15.0; moderate, 15.1–30.0; severe, > 30). A biased coin (7 : 3) was implemented for blocks of 30 when the difference in percentage randomised to active vs. sham at a given site was > 7%
Allocation concealment?	Yes	The Data Coordinating Centre passed allocation on to trial personnel so investigators were unaware to order of treatment group assignment
Blinding? All outcomes	Yes	Participants and study investigators were blinded to treatment allocation

min., minimum; PSG, polysomnogram.

Lam 2007[67]

Methods	Randomised parallel-group trial Patients randomised to either CM, or CM with CPAP or CM with OA therapy
Participants	One hundred and one patients with OSA randomised (CM = 33, CPAP = 34, OA = 34) (males = 79, females = 22), of which 91 patients completed the study Mean AHI = 21.4 events/hour Inclusion criteria: AHI ≥ 5–40 events/hour; ESS score > 9 for those with AHI 5–20 events/hour Exclusion criteria: excessive sleepiness, unstable medical diseases, coexisting sleep disorders, upper airway surgery, pregnancy
Interventions	CM vs. CM + OA vs. CM + CPAP Study duration: 10 weeks
Outcomes	Sleep parameters – AHI; arousal index, min. O_2 saturation BP – morning and evening Daytime sleepiness – ESS score HRQoL – SF-36, SAQLI Treatment adherence – self reported and CPAP internal memory Treatment-related side effects – self reported
Notes	Post-treatment changes were analysed based on both intention-to-treat and per-protocol principles Conservative measures as a control group was not considered by Lim *et al.*[51] but has been included in this review Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	The randomisation list was generated by the Statistical Analysis System
Allocation concealment?	Unclear	Information not available
Blinding?	No	CM vs. OA vs. CPAP compared
All outcomes		

min, minimum; OA, oral appliance.

Lee 2012[111]

Methods	Parallel-group, randomised, double-blind, sham-controlled trial Two arms: CPAP vs. sham CPAP
Participants	Seventy-one patients randomised, 56 analysed (baseline data reported for 56) (males = 47, females = 9) Baseline characteristics of the CPAP group ($n = 26$): age: 48.3 years; BMI: 29.8 kg/m^2; AHI: 36.7 events/hour; min. O_2 saturation 79.8 Baseline characteristics of the control (sham CPAP) group ($n = 30$): age: 48.2 years; BMI: 28.6 kg/m^2; AHI: 31.3 events/hour; min. O_2 saturation 79.8 Inclusion criteria: newly diagnosed OSA with AHI $\geq$ 10 events/hour Exclusion criteria: history of major medical illnesses (other than OSA and hypertension); current psychiatric diagnosis; receiving psychotropic, sedative or hypnotic medication; pregnancy; previous treatment for OSA
Interventions	CPAP vs. sham CPAP Study duration: 3 weeks on treatment
Outcomes	The POMS Depression scale; multiple measures of depression (CES-D, BSI Depression) and anxiety (POMS Tension, BSI Anxiety), AHI
Notes	No ESS score. Sleep outcomes were not listed as secondary outcomes but were measured Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Eligible subjects with AHI $\geq$ 10 were randomised in a 1 : 1 allocation ratio to receive either CPAP or placebo in a double-blind fashion. A permuted block design was used with a block size of 10. The randomisation list was generated by the study statistician
Allocation concealment?	Yes	The randomisation list was generated by the study statistician. The principal investigator and staff responsible for obtaining study outcomes were blinded to the treatment assignment therefore one presumes they would not have known what sequence was due next
Blinding? All outcomes	Yes	Participants and study investigators were blinded to treatment allocation

BSI, Brief Symptom Inventory; CES-D, Centre for Epidemiologic Studies – Depression; POMS, Profile of Mood States.

Lozano 2010[112]

Methods	Parallel-group, randomised controlled trial Two arms: CPAP + hypertension treatment vs. conventional pharmacological treatment alone
Participants	Seventy-five patients randomised, 64 analysed (baseline data reported for 64) (males = 44; females = 20) Baseline characteristics of the conventional treatment group ($n = 35$): age: 59.2 years; BMI: 31.5 kg/m^2; AHI: 46.78 events/hour; ESS score: 5.94; consulting room SBP: 151.3 mmHg; consulting room DBP: 87.9 mmHg Baseline characteristics of the CPAP treatment group ($n = 29$): age: 59.2 years; BMI: 30 kg/m^2; AHI: 59.79 events/hour; ESS score: 6.39; consulting room SBP: 157.6 mmHg; consulting room DBP: 90.2 mmHg Inclusion criteria: age 18–80 years; diagnosis of resistant hypertension (BP values measured in the consulting room as equal to or higher than 140/90 mmHg on at least three different occasions, despite treatment with three or more drugs at adequate doses, including a diuretic) Exclusion criteria: upper airway malformations; a history of poor treatment compliance; secondary causes of hypertension, including renal insufficiency (creatinine > 1.5 mg/dl); shift workers
Interventions	CPAP + hypertension treatment vs. conventional pharmacological treatment alone Study duration: 3 months
Outcomes	Change in mean 24-hour SBP and DBP at 3 months, ESS score, treatment compliance
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Unclear	Information not available
Blinding?	No	CPAP + conventional therapy vs. conventional therapy alone compared
All outcomes		

Mansfield 2004[113]

Methods	Randomised parallel-group trial of CPAP vs. no treatment
Participants	Fifty-five patients randomised (males = 52, females = 3), of which 40 completed Baseline characteristics of the randomised CPAP group ($n = 28$): mean age: 57.2 years; BMI: 33.5 kg/m^2; AHI: 28.3 events/hour; ESS score: 10.7; BP mean: 99 mmHg Baseline characteristics of the randomised control group ($n = 27$): mean age: 57.5 years; BMI: 34.6 kg/m^2; AHI: 28.1 events/hour; ESS score: 9.2; BP mean: 107 mmHg Inclusion criteria: aged 18–80 years, diagnosis of symptomatic, stable and optimally treated CHF; AHI > 5 events/hour; symptoms of snoring and one or more of excessive daytime sleepiness, witnessed apnoeas or nocturnal choking Exclusion criteria: significant central sleep apnoea (> 20% events central in type), clinical evidence of neurological disease, renal disease with serum creatinine higher than 150 mmol/l or spirometric confirmation of pulmonary disease with forced expiratory ratio of less than 70%; valvular heart disease
Interventions	CPAP vs. no treatment Study duration: 3 months on treatment
Outcomes	AHI, ESS score, min. SpO_2, BMI, BP, LVEF, overnight urinary noradrenaline excretion and QoL
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Single blinded. No placebo so the participants could not be blinded to treatment. Objective measurements were analysed by scientists blinded to the patients' treatment status

CHF, congestive heart failure; LVEF, left ventricular ejection fraction; min. minimum.

Marshall 2005[114]

Methods	Randomised controlled crossover trial of CPAP vs. sham CPAP
Participants	Thirty-one patients randomised, 29 patients analysed (males = 22, females = 7) Baseline characteristics of the completed patients ($n = 29$): mean age: 50.5 years; BMI: 31.5 kg/m^2; AHI: 21.6 events/hour; ESS score: 12.5, FOSQ total: 12.6 Inclusion criteria: aged ≥ 18 years; English speaking; CPAP naive; AHI: 5–30 events/hour; habitual snoring or nocturnal choking; and at least one daytime sleepiness symptom (daytime/evening napping, sleepiness while driving, never or rarely awakening refreshed) or ESS score > 8 Exclusion criteria: history of extreme somnolence requiring immediate treatment; shift worker; chronic sleep restriction (average total sleep time ≤ 6 hours/night); current sedative, antidepressant, psychotropic or stimulant use; alcohol intake of > 3 standard units/24 hours or caffeine dependency; upper airway surgery since the diagnostic sleep study; any clinically significant co-existing disease or additional sleep disorders
Interventions	Humidified CPAP vs. humidified sham CPAP Study duration: 3 weeks on each treatment Washout: 2 weeks
Outcomes	AHI, ESS score, FOSQ, SF-36, MWT, HADS, PVT, treatment compliance and preference
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	No	Simple coin flipping
Allocation concealment?	No	Treatment allocation sequence was not predetermined and was achieved by the duty polysomnographic technician blindly drawing a slip of paper without replacement from an urn after testing on the first day had been completed
Blinding? All outcomes	Yes	Study described as blinded. Patients were blinded to treatment and were informed that the study was 'testing two different pressures of humidified CPAP'. The investigator responsible for daytime study data collection was also blinded to treatment allocation

HADS, Hospital Anxiety and Depression Scale; PVT, psychomotor vigilance task.

Mehta 2001[75]

Methods	Randomised controlled cross-over trial of MAD vs. control oral plate Participants blinded as to likely superior efficacy of the double-plate appliance over the single plate
Participants	Twenty-eight participants recruited (males = 22, women = 6), of which 24 participants completed the study (males = 19, females = 5) Baseline characteristics for the 24 patients who completed the trial: mean age: 48 years; BMI: 29.4 kg/m^2; AHI: 27 events/hour; min. SaO_2: 85; ESS score: 10.1 Inclusion criteria: at least 2 symptoms of OSA and AHI ≥ 10 events/hour Exclusion criteria: periodontal disease, edentulism, exaggerated gag reflex, regular use of sedatives
Interventions	Participants randomised to three periods (ABB/BAA) of control plate (A) or MAD (B) after an acclimatisation period (mean acclimatisation period = 19.7 weeks, range: 5–40 weeks) Study duration: 3 weeks (1 week per period with no washout) No washout period (only 1 week washout between pre-treatment acclimatisation and start of first treatment period)
Outcomes	AHI, min. SaO_2, snoring frequency, mean snoring intensity, maximum snoring intensity, total sleep time, REM, NREM, total sleep time spent supine, arousal index, sleep efficiency
Notes	ESS score recorded pre- and post-acclimatisation period but not after the treatment periods Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Information not available
All outcomes		

min, minimum; NREM, non-rapid eye movement; REM, rapid eye movement.

Monasterio 2001[115]

Methods	Randomised controlled parallel-group trial of CPAP plus CT vs. CT alone
Participants	One hundred and forty-two patients randomised, 125 patients analysed (males = 86%)
	Baseline characteristics of the completed patients in the CPAP group ($n = 66$): mean age: 53 years; BMI: 29.4 kg/m^2; AHI: 20 events/hour; ESS score: 12.1; FOSQ: 101; SBP: 126 mmHg; DBP: 81 mmHg
	Baseline characteristics of the completed patients in the CT-alone group ($n = 59$): mean age: 54 years; BMI: 29.5 kg/m^2; AHI: 21 events/hour; ESS score: 13.2; FOSQ: 100; SBP: 132 mmHg; DBP: 84 mmHg
	Inclusion criteria: AHI: 10–30 events/hour; absence of severe daytime sleepiness
	Exclusion criteria: apnoea index > 20; hazardous jobs (drivers or those who handle dangerous machinery); notable CVD; conditions affecting cognitive or QoL evaluation; severe neurological or psychiatric disease, severe chronic disease; illiteracy
Interventions	CPAP + CT (weight loss programme following a home diet, if BMI > 27 kg/m^2; avoidance of sedatives and alcohol consumption; avoidance of supine position during sleep; and adequate hours of sleep every night) vs. CT alone
	Study duration: 6 months on treatment
Outcomes	AHI; ESS score; MSLT; SAHS symptoms; cognitive function; FOSQ; Nottingham Health Profile
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation was performed with a computer-generated allocation schedule restricted by centre
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Patients were aware of treatment as they were different in presentation (CPAP + CT vs. CT). Unclear if all outcome assessors were blinded. Cognitive function assessed by a trained psychologist who was blinded. Staff entering and analysing data were blinded to treatment group

CT, conservative treatment; SAHS, sleep apnoea–hypopnea syndrome.

Montserrat 2001[116]

Methods	Randomised controlled partial crossover trial of CPAP vs. sham CPAP
Participants	Forty-eight patients randomised, 45 patients competed (male: 91%)
	Baseline characteristics of completed patients in the CPAP group ($n = 23$): mean age: 55.65 years; BMI: 30.31 kg/m^2; AHI: 50.52; ESS score: 16.13; FOSQ: 84.45; SF-36 physical component: 46.53; SF-36 mental component: 48.21; neck circumference: 42.52 cm
	Baseline characteristics of the completed patients in the sham CPAP group ($n = 22$): mean age: 52.59 years; BMI: 33.73 kg/m^2; AHI: 57.14; ESS score: 16.86; FOSQ: 86.16; SF-36 physical component: 45.54; SF-36 mental component: 48.73; neck circumference: 43.72 cm
	Inclusion criteria: excessive daytime somnolence and an AHI > 10
	Exclusion criteria: severe or unstable CVD; a hazardous job coincidentally with SAHS (professional drivers or handling dangerous machinery)
Interventions	CPAP vs. sham CPAP
	Study duration: CPAP group had a 6-week study period using the intervention; sham CPAP group trialled 6 weeks on sham CPAP then 6 weeks on optimal CPAP
	Washout: 10 days
Outcomes	ESS score, FOSQ, SF-36, questionnaire of symptoms related to SAHS, body weight, hours of CPAP use
Notes	Jadad score = 3
	All patients included in the study were encouraged to follow conservative measures (a diet and sleep hygiene regimen) regardless of the treatment group assigned

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	A block-randomised assignment was used. Randomisation was performed with a computer-generated allocation schedule that had a block size of 12 patients in accordance with severity
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Described as double blind but no information available
All outcomes		

Norman 2006[117]

Methods	Randomised controlled parallel-group trial of CPAP vs. sham CPAP vs. nocturnal oxygen + sham CPAP	
Participants	Forty-six patients randomised, and no reported withdrawals (male = 37, female = 9)	
	Baseline characteristics of patients in the CPAP group ($n = 18$): mean age: 49.7 years; BMI: 31.5 kg/m^2; AHI: 66.1 events/hour; ESS score: 12.0; SBP: 135.1 mmHg; DBP: 79.6 mmHg	
	Baseline characteristics of patients in the sham CPAP group ($n = 15$): mean age: 49.3 years; BMI: 29.9 kg/m^2; AHI: 53.9 events/hour; ESS score: 12.0; SBP: 122.5 mmHg; DBP: 75.6 mmHg	
	Baseline characteristics of patients in the oxygen group ($n = 13$): mean age: 44.2 years; BMI: 29.5 kg/m^2; AHI: 60.7 events/hour; ESS score: 12.2; SBP: 132.5 mmHg; DBP: 76.0 mmHg	
	Inclusion criteria: aged 25–65 years; AHI ≥ 20 events/hour; within 100% to 170% of ideal body weight	
	Exclusion criteria: major illnesses other than hypertension; previous CPAP therapy; pharyngeal surgery for OSA	
Interventions	CPAP vs. sham CPAP vs. supplemented oxygen + sham CPAP	
	Study duration: 2 weeks on treatment	
Outcomes	AHI, BP, other polysomnographic outcomes	
Notes	Jadad score = 2	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised but no further information
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Described as double blind but no information available
All outcomes		

Olson 2002[82]

Methods	Randomised crossover study, comparing MAD with nCPAP
Participants	Twenty-four patients included Sex: unknown Baseline AHI: 8.1–36.9 events/hour Inclusion criteria = AHI > 15, or apnoea index > 5, or AHI > 5 events/hour and arousal index > 15 Exclusion criteria: poor dentition, TMJ pin, previous treatment with MAD or nCPAP
Interventions	nCPAP or MAD Study duration: 6 week treatment period on MAD or CPAP Washout period: 2 weeks
Outcomes	Total sleep time, sleep efficiency,% REM sleep, AHI, arousal index, SAQLI
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD vs. nCPAP compared
All outcomes		

nCPAP, nasal continuous positive airway pressure; REM, rapid eye movement; TMJ, temporomandibular joint.

Pepperell 2002[34]

Methods	Randomised controlled parallel trial of CPAP vs. subtherapeutic CPAP
Participants	One hundred and eighteen participants randomised (all male), of which 104 participants completed the study Baseline characteristics for CPAP group ($n = 59$): mean age: 50.1 years; BMI: 34.6 kg/m^2; oxygen desaturation dips > 4%: 38.0; ESS score: 16.3; neck circumference: 44.5 cm; SBP: 132.5 mmHg; DBP: 85.1 mmHg Baseline characteristics for subtherapeutic CPAP group ($n = 59$): mean age: 51.0 years; BMI: 35.3 kg/m^2; oxygen desaturation dips > 4%: 35.9; ESS score: 16.0; neck circumference: 45.7 cm; SBP: 134.9 mmHg; DBP: 85.1 mmHg Inclusion criteria: male; aged 30–75 years; ESS score > 9; > 10 oxygen desaturation dips (> 4%) Exclusion criteria: required urgent CPAP therapy; imminent job loss because of sleepiness; unable to give informed consent
Interventions	Therapeutic CPAP vs. subtherapeutic CPAP Study duration: 4 weeks
Outcomes	BP, ESS score, severity of sleep apnoea
Notes	Jadad score = 4

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised. No other information available
Allocation concealment?	Yes	Pre-sealed and numbered opaque envelopes
Blinding? All outcomes	Yes	Described as double blind. Neither patients nor outcome assessors were aware of treatment allocation

Petri 2008[76]

Methods	Randomised controlled parallel trial of MAD vs. non-advanced MAD (sham) vs. no treatment
Participants	Ninety-three participants recruited (males = 76, females = 17), of which 81 participants completed the study (males = 66, females = 15)
	Baseline characteristics for MAD group ($n = 27$): mean age: 50 years; BMI: 30.7 kg/m^2; AHI: 39.1 events/hour; ESS score: 11.7
	Baseline characteristics for sham MAD group ($n = 25$): mean age: 50 years; BMI: 31.3 kg/m^2; AHI: 32.6 events/hour; ESS score: 10.8
	Baseline characteristics for no-treatment group ($n = 29$): mean age: 49 years; BMI: 31.3 kg/m^2; AHI: 34.3 events/hour; ESS score: 10.7
	Baseline characteristics for not completing group ($n = 12$): mean age: 46 years; BMI: 32.9 kg/m^2; AHI: 29.9 events/hour; ESS score: 10.1
	Inclusion criteria: AHI > 5 events/hour on diagnostic PSG; age > 20 years; sufficient set of teeth to hold a splint; written informed consent
	Exclusion criteria: severe somatic or psychiatric disease; periodontal disease; temporomandibular dysfunction; pregnancy
Interventions	Participants randomised to one of three arms:
	MAD (advanced the mandible to the most protrusive position without discomfort) vs. sham MAD (MAD with no advancement holding mandible in the occulsal position) vs. no treatment
	Study duration: 4 weeks
	Washout period: N/A
Outcomes	AHI, ESS score and QoL (SF-36)
Notes	Both intention-to-treat and per-protocol analyses conducted, with sensitivity analyses
	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Allocation was computer generated, minimisation methods were used, stratifying by sex and AHI > 30 and < 30
Allocation concealment?	Yes	Central telephone randomisation by a trials unit
Blinding? All outcomes	Yes	MAD vs. sham MAD comparisons were blinded. The no-treatment arm was not blinded. Sleep studies were scored by a single investigator blinded to the three treatment groups

N/A, not applicable; PSG, polysomnogram.

Phillips 2011[118]

Methods	Randomised controlled crossover trial of CPAP vs. sham CPAP
Participants	Thirty-eight participants randomised (males = 35, females = 3), of which 29 participants completed the study Baseline characteristics for all randomised patients ($n = 38$): mean age: 49 years; BMI: 32.1 kg/m^2; AHI: 41.2 events/hour; ESS score: 11.2; FOSQ: 15.2 Inclusion criteria: AHI ≥ 25 events/hour and/or a significant component of hypoxia (ODI ≥ 20 per hour; desaturation ≥ 3% of baseline) on PSG; age > 21 years Exclusion criteria: BMI > 35 kg/m^2; fasting TAGs ≥ 4 mmol/l, use of fibrate medication, previous CPAP use, uncontrolled type II diabetes, and any clinically significant comorbidity (e.g. cardiovascular, pulmonary, renal or psychiatric disease)
Interventions	Participants randomised to one of two arms: CPAP vs. sham CPAP Study duration: 8 weeks per treatment Washout period: 4 weeks
Outcomes	AHI, ESS score, FOSQ
Notes	Both intention-to-treat and per-protocol analyses conducted Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Computer program used to produce the random treatment sequence using random block sizes of 2, 4 and 6
Allocation concealment?	Yes	Randomised treatment sequences stored in sequentially numbered opaque envelopes. The project manager was responsible for the allocation consignment and had no contact with any patient before or during the trial
Blinding? All outcomes	Yes	Outcome assessors blinded. Treatment allocation only known by the project manager and trial physician – neither of whom saw the patients during the trial (unless involved in withdrawing a patient) Attempted to blind patients by telling them they were testing two CPAP machines that 'deliver pressurised air in a different way'. Patients were informed that the low-pressure machine was a placebo during a post-study debriefing interview

PSG, polysomnogram; TAGs, triglycerides.

Phillips 2013[52]

Methods	Randomised controlled crossover trial of CPAP vs. MAD
Participants	One hundred and twenty-six participants randomised (males = 102, females = 24), of which 108 participants completed the study Baseline characteristics for all randomised patients ($n = 126$): mean age: 49.5 years; BMI: 29.5 kg/m^2; AHI: 25.6 events/hour; ESS score: 9.1; neck circumference: 40.5 cm; mean SBP: 123.7 mmHg; mean DBP: 80.6 mmHg; FOSQ: 16.3 Inclusion criteria: AHI >10 events/hour; age ≥ 20 years; ≥ two symptoms of OSA (snoring, fragmented sleep, witnessed apnoeas, or daytime sleepiness); willingness to use both treatments Exclusion criteria: previous OSA treatment or a need for immediate treatment; central sleep apnoea; a coexisting sleep disorder; regular use of sedatives or narcotics; pre-existing lung or psychiatric disease; and any contraindication for oral appliance therapy (e.g. periodontal disease or insufficient dentition)
Interventions	Participants were randomised to both the treatment acclimatisation and treatment arm orders (MAD = M; CPAP = C) thus the following treatment sequences were generated: MCMC, MCCM, CMMC and CMCM Study duration: 4–8 weeks on acclimatisation per treatment; 4 weeks per treatment Washout period: occurred but duration not stated
Outcomes	AHI, ESS score, BP and arterial stiffness, FOSQ, SF-36, the AusEd driving simulator. Treatment side effects, compliance and preference
Notes	Intention-to-treat analysis Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Each randomisation sequence was generated by a computer program using random permuted blocks
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Patients not blinded as two devices different in presentation. Not stated whether or not outcome assessors were blinded

TOMADO 2014[77]

Methods	Randomised controlled crossover trial of three MADs vs. no treatment
Participants	Ninety participants randomised (males = 72; females = 18), of which 74 participants completed the study Baseline characteristics for all randomised patients ($n = 90$): mean age: 50.9 years; BMI: 30.6 kg/m^2; AHI: 13.8 events/hour; ESS score: 11.9 Inclusion criteria: AHI 5 to < 30 events/hour; age ≥ 18 years; ESS score ≥ 9 Exclusion criteria: predominantly central sleep apnoea; coexistent sleep disorder; poor sleep hygiene; psychiatric disorder or drug treatment likely to impact symptoms or assessment of MAD effectiveness; CVD or disabling sleepiness requiring immediate CPAP; significant periodontal disease or tooth decay; partial or complete edentulism or presence of fixed orthodontic devices; mandibular joint pain or disease; severe bruxism; restricted mouth opening or mandibular advancement; respiratory failure; previous MAD treatment; pregnancy; or inability to give informed consent
Interventions	Participants received four different treatments in random order: 1. SP1: a thermoplastic 'boil and bite' MAD 2. SP2: semibespoke MAD, from a dental impression mould used by the patient 3. bMAD: fitted and manufactured by a hospital maxillofacial team 4. No-treatment period Study duration: 2 weeks' acclimatisation and 4 weeks' treatment per device; 4 weeks on no-treatment period Washout period: 1 week following each active treatment period
Outcomes	AHI, ESS score, rPSG indices (4% ODI, mean, minimum and time < 90% of nocturnal SpO_2) and BP FOSQ, SAQLI, SF-36 and EQ-5D Health-care usage, driving and RTA data Treatment compliance, satisfaction and preference AEs
Notes	Intention-to-treat analysis Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Patients were randomised using two Williams' Latin squares designs with allocations generated by randomisation software utilising permuted blocks of eight
Allocation concealment?	Yes	The trial team contacted the R&D department at the hospital by telephone to receive the randomisation sequence
Blinding? All outcomes	No	Patients not blinded as devices different in presentation. Polysomnographer was blinded to treatment allocation

rPSG, respiratory polysomnogram.

Randerath 2002[83]

Methods	Randomised crossover study Patients randomised to either CPAP or MAD
Participants	Twenty participants with mild to moderate OSA randomised to CPAP ($n = 8$) or MAD ($n = 12$) (males = 16, females = 4), do not know how many completed Baseline characteristics of the 20 completed patients: mean age: 56.5 years, BMI: 31.2 kg/m^2; AHI: 17.5 events/hour Inclusion criteria: AHI = 5–30 events/hour in two diagnostic PSGs and clinical symptoms of OSAS Exclusion criteria: AHI > 30 events/hour, TMJ disorders, bruxism, gaps in teeth preventing device fitting
Interventions	Participants underwent one night PSG with both treatment modes, followed by 6 weeks treatment with either OA or CPAP in random order. Participants then crossed over to the other treatment Study duration: 12 weeks No washout period
Outcomes	AHI; snoring (epochs/hour); SaO_2 (%); TST (minutes); wake after sleep onset; sleep stage 1, 2, 3, 4; REM sleep; arousals per hour; respiration-induced arousals, per hour of TST
Notes	Jadad score = 1

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD vs. CPAP compared
All outcomes		

min., minimum; PSG, polysomnogram; REM, rapid eye movement; TMJ, temporomandibular joint; TST, total sleep time.

Redline 1998[119]

Methods	Randomised controlled parallel trial of CPAP + CT vs. CT alone
Participants	One hundred and eleven participants randomised, of which 97 participants completed the study (males = 50; females = 47) Baseline characteristics for CPAP group ($n = 51$): mean age: 48.1 years; BMI: 33.4 kg/m^2; RDI: 14.6; ESS score: 10.4 Baseline characteristics for CT group ($n = 46$): mean age: 49.2 years; BMI: 32.0 kg/m^2; RDI: 11.8; ESS score: 10.6 Inclusion criteria: age 25–65 years; RDI 5–30; absence of (subjective) pathological sleepiness (did not fall asleep driving or in other potentially dangerous situations); absence of a sleep disorder other than SDB (narcolepsy); insomnia, defined as regularly sleeping < 6 hours per night; regular use of hypnotics; sleep insufficiency, defined as sleeping > 2 hours more on non-work than on work days; or a history of periodic leg movements Exclusion criteria: presence of underlying conditions that could interfere with neuropsychological test performance or with adherence to the study protocol, including severe or unstable medical disease (myocardial infarction or congestive heart failure documented with the previous 3 months, uncontrolled diabetes or thyroid disorder, cirrhosis or recently diagnosed cancer); neurological disease, history of stroke, seizure disorder or head trauma with loss of consciousness for > 6 hours or associated with memory impairment; alcohol abuse (a history of ≥ 5 alcoholic drinks/day for > 6 years) or drug abuse (current drug use or heavy past use leading to tolerance or dependency); regular use of medications that impair the sensorium (e.g. benzodiazepines); and < 8 years of schooling
Interventions	CPAP + CT vs. CT alone (subjects in both treatment arms received counselling about sleep posture and hygiene). Subjects with BMI > 29 kg/m^2 referred to a dietitian for weight-reduction counselling, and subjects with symptoms of nasal congestion were provided with a nasal steroid spray (Becanase nasal spray). Additionally, subjects in the CT arm of the study were given a supply of mechanical nasal dilators and those in the CPAP arm were provided with a CPAP machine. Mechanical nasal dilators were used as a component of treatment in the control arm of the study Study duration: 8 weeks
Outcomes	Polysomnographic parameters and daytime test battery: mood (POMS, PANAS); well-being and functional status (SF-36) and measures of sleepiness (MSLT and ESS score)
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Subjects were randomised through the use of a computerised program based on random-number assignments
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Treatments different in appearance. Other information not available

CT, conservative treatment; PANAS, Positive and Negative Affect Scale; POMS, Profile of Mood States; SDB, sleep-disordered breathing.

Robinson 2006[120]

Methods	Randomised, placebo-controlled crossover trial of CPAP vs. sham CPAP	
Participants	Thirty-five participants randomised (males = 31, females = 4), of which 32 participants completed the study Baseline characteristics for randomised patients ($n = 35$): mean age: 54 years; BMI: 33.2 kg/m^2; dips in oxygen saturation of > 4%: 28.1; ESS score: 5.3, neck circumference: 43.9 cm Baseline 24-hour BP in the CPAP group: SBP: 140.3 mmHg; DBP: 85.3 mmHg Baseline 24-hour BP in the placebo group: SBP: 143.0 mmHg; DBP: 86.7 mmHg Inclusion criteria: aged > 18 years; > 10 dips in oxygen saturation > 4%; no daytime hypersomnolence (ESS score < 10); hypertension (either taking antihypertensive drugs, or a BP > 140/90 mmHg on 24-hour ambulatory BP monitoring) Exclusion criteria: respiratory failure; declined to participate; or unable to give informed consent	
Interventions	CPAP vs. sham CPAP Study duration: 1 month on each treatment Washout: 2 weeks	
Outcomes	Oxygen saturation, ESS score, 24-hour BP	
Notes	Jadad score = 4	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Yes	Randomisation was by a series of pre-sealed and numbered opaque envelopes
Blinding? All outcomes	Yes	Sham-placebo CPAP identical to therapeutic CPAP. Patients were not aware which treatment they had received, and the nurse who assigned the patients to each treatment arm did not take part in outcome assessments. The investigators who assessed the study outcomes were not involved in randomisation or patient CPAP set-up

Sharma 2011[121]

Methods	Double-blind, placebo-controlled crossover group trial of CPAP vs. sham CPAP
Participants	Ninety participants randomised, for which 86 participants analysed (males = 77; females = 9) Baseline characteristics for CPAP first patients ($n = 43$): mean age: 45 years; BMI: 33.8 kg/m^2; AHI: 47.9 events/hour, ESS score: 14.8. mean SBP: 133.2 mmHg; mean DBP: 89.1 mmHg Baseline characteristics for sham CPAP first patients ($n = 43$): mean age: 45 years; BMI: 31.8 kg/m^2; AHI: 47.8 events/hour, ESS score: 14.1; mean SBP: 131.1 mmHg; mean DBP: 87.8 mmHg Inclusion criteria: AHI ≥ 15 events/hour; ESS score > 10; CPAP naive; not on treatment for hypertension, diabetes mellitus or dyslipidaemia Exclusion criteria: 1. Patients, if diabetic, were excluded if any one of the following was present: (a) proliferative diabetic retinopathy (b) nephropathy (serum creatinine > 1.8 mg/dl) (c) clinically manifest neuropathy defined as absent ankle jerks (d) severe hyperglycaemia (FBS > 200 mg/dl) 2. Patients, if hypertensive, were excluded if any one of the following was present: (a) symptomatic coronary artery disease (b) symptomatic peripheral vascular disease (c) past history of cerebrovascular accident (d) known case of aortic aneurysm or left ventricular dysfunction (e) nephropathy (serum creatinine > 1.8 mg/dl) (f) marked elevation in BP (BP > 180/110 mmHg on two occasions) 3. Comorbid illnesses like hypothyroidism, chronic renal failure, coronary artery disease or left ventricular dysfunction 4. Patients with chronic inflammatory diseases or malignancies 5. Patients requiring long-term corticosteroids or other drugs affecting metabolic syndrome constituents
Interventions	Participants received either CPAP followed by sham CPAP or vice versa Study duration: 3 months on each treatment Washout period: 1 month
Outcomes	Reduction in the frequency of the metabolic syndrome, ESS score, anthropometric variables, BP, fat content and resting insulin and glucose levels
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	The randomisation sequence was generated by a statistician not otherwise involved in the study, by means of a computer-generated random-number table. An unrestricted randomisation scheme was followed
Allocation concealment?	Yes	The randomisation numbers were contained in serially numbered, sealed, opaque envelopes kept by office staff not involved in outcome measurements
Blinding? All outcomes	Yes	Participants and outcome assessors blinded to two treatments similar in presentation

FBS, fasting blood sugar.

Siccoli 2008[18]

Methods	Double-blind placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	One hundred and two participants randomised (all men), of which 99 participants analysed Baseline characteristics for sham CPAP patients ($n = 51$): mean age: 48.7 years; BMI: 34.5 kg/m^2; ESS score: 15.2; neck circumference: 44.6 cm; oxygen saturation dips > 4%: 42.7 Baseline characteristics for CPAP patients ($n = 51$): mean age: 48.1 years; BMI: 35.8 kg/m^2; ESS score: 15.8; neck circumference: 45.1 cm; oxygen saturation dips > 4%: 41.9 Inclusion criteria: males; aged 20–75 years; ESS score ≥ 10; ODI > 10/hour Exclusion criteria: urgent CPAP therapy required because of respiratory failure, driving or job-related issues
Interventions	Participants received either CPAP or sham CPAP Study duration: 1 month on treatment Washout period: N/A
Outcomes	ESS score, QoL measures (SF-36/SF-12 and SAQLI), bed partner's QoL and rating of patient's response to CPAP
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	A sleep nurse (not involved in outcome assessments) randomly assigned patients to the two groups. No further information
Allocation concealment?	Unclear	No information
Blinding?	Yes	Participants and outcome assessors blinded to two treatments similar in presentation
All outcomes		

N/A, not applicable.

Simpson 2012[122]

Methods	Double-blind sham-controlled parallel-group trial of CPAP vs. sham CPAP	
Participants	Forty-six participants at baseline (all male), of which 36 participants had results (CPAP $n = 20$; sham $n = 16$)	
	Baseline characteristics for all randomised patients ($n = 90$): mean age: 49 years; BMI: 31.5; AHI: 37.6 events/hour	
	Inclusion criteria: moderate to severe OSA; CPAP naive, men, without diabetes mellitus	
	Exclusion criteria: not stated	
Interventions	Participants received either CPAP or sham CPAP	
	Study duration: 12 weeks on treatment	
	Washout period: N/A	
Outcomes	AHI, markers of endothelial cell dysfunction and levels of circulating progenitor cells	
Notes	Jadad score = 2	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding?	Unclear	Information not available
All outcomes		

N/A, not applicable.

Skinner 2004[123]

Methods	Randomised controlled crossover trial of CPAP vs. cervicomandibular collar
Participants	Ten participants randomised and completed (males = 8, females = 2)
	Baseline characteristics ($n = 10$): mean age: 48.6 years; BMI: 34.1 kg/m^2; AHI: 29.4 events/hour; ESS score: 13.2; neck circumference: 42.6 cm; FOSQ: 12.2; SF-36 PCS: 45.3; SF-36 MCS: 43.8
	Inclusion criteria: mild to moderate sleep OSA (AHI 10–60 events/hour)
	Exclusion criteria: medical history of cardiovascular, neurological or psychological disorders affecting sleep; coexisting sleep disorders; known cervical or temporomandibular joint dysfunction and/or pain
Interventions	CPAP vs. cervicomandibular support collar
	Study duration: 1 month on each treatment
	Washout: none
Outcomes	Sleep parameters including AHI; ESS score, SF-36; FOSQ; Scottish National Sleep Laboratory symptom questionnaire; cephalometric outcomes
Notes	Jadad score = 2
	Intention-to-treat analysis

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	No information available
Blinding?	Unclear	No information available
All outcomes		

Skinner 2008[124]

Methods	Randomised controlled crossover group trial of CPAP vs. TASB
Participants	Twenty participants randomised and analysed (sex unknown) Baseline characteristics for randomised patients ($n = 20$): mean age: 55.9 years; BMI: 30.7 kg/m^2; AHI: 22.7 events/hour, ESS score: 13.6; FOSQ: 11.1; SF-36 PCS: 45.9; SF-36 MCS: 42.4; mean neck circumference: 41.9 cm Inclusion criteria: AHI > 5 events/hour; > 50 minutes spent in the supine position during baseline study; time spent in the supine position amounted to 10–90% of total study time; AHI in the supine position was greater or equal to twice the AHI in other positions; maximum AHI = 10 events/hour in all other positions Exclusion criteria: other conditions affecting sleep; known thoracic pathology; previous intervention for OSA
Interventions	Participants received either CPAP followed by TASB or vice versa Study duration: 1 month on each treatment Washout period: 1 week
Outcomes	AHI Total study time lying supine Other measures collected were: ESS score; FOSQ; SF-36; and anthropometric measures
Notes	Jadad score = 1

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Participants were randomly assigned to receive TASB or CPAP for the first month followed by a 1-week washout. No further information given
Allocation concealment?	Unclear	No information
Blinding?	Unclear	No mention of blinding
All outcomes		

TASB, thoracic anti-supine band.

Spicuzza 2006[125]

Methods	Randomised parallel trial of CPAP vs. sham CPAP	
Participants	Twenty-five participants recruited (males = 20, females = 5). Assume all completed as no withdrawals reported	
	Baseline characteristics for CPAP group ($n = 15$): mean age: 55.9 years; BMI: 31.1 kg/m^2; AHI: 55.3 events/hour; SBP: 145.4 mmHg; DBP: 87.9 mmHg	
	Baseline characteristics for the sham CPAP group ($n = 10$): mean age: 55.1 years; BMI: 33.5 kg/m^2; AHI: 59.2 events/hour; SBP: 149.5 mmHg; DBP: 85.0 mmHg	
	Inclusion criteria: moderate to severe OSA	
	Exclusion criteria: presence of hypertension and/or other CVDs, diabetes, thyroid disorders, chronic obstructive/restrictive lung diseases or chronic respiratory failure and smokers	
Interventions	CPAP vs. sham CPAP	
	Study duration: 1 month on treatment	
Outcomes	Ventilatory response, AHI	
Notes	Jadad score = 2	
Risk of bias		
Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	States that patients were randomly assigned but no other information available
Allocation concealment?	Unclear	No information available
Blinding? All outcomes	Yes	The study was double blind, as neither patients nor the staff in contact with them knew which group the patient was assigned

Tan 2002[84]

Methods	Randomised crossover study Patients randomised to either CPAP or MAD
Participants	Forty-six subjects assessed, 24 participants recruited and took part in at least one arm (males = 20, females = 4), of which 21 completed Baseline characteristics of the 24 recruited patients: mean age: 50.9 years; BMI: 31.9 kg/m^2; AHI: 22.2 events/hour; ESS score: 13.4; O_2 desaturation: 7.1; arousals/hour: 19.3 Inclusion criteria: age > 18 years, mild to moderate OSA (AHI < 50 events/hour) Exclusion criteria: inadequate dentition for the MAD, TMJ dysfunction, medical contraindications, unavailability to attend sleep clinics and laboratory, heart disease, COPD, use of hypnotics, epilepsy, arterial O_2 saturation < 60% during initial sleep study, unable to understand study because of language difficulties
Interventions	Participants underwent 2 months of CPAP and MAD in random order Study duration: 4 months Washout period = 2 weeks
Outcomes	AHI, O_2 desaturation, ESS score, general symptoms, daytime somnolence score, partner's assessment, duration of apnoeas, arousals/hour, sleep efficiency, REM sleep
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Described as randomised, other information not available
Allocation concealment?	Unclear	Information not available
Blinding?	No	MAD vs. CPAP compared
All outcomes		

COPD; chronic obstructive pulmonary disease; REM, rapid eye movement; TMJ, temporomandibular joint.

Tomfohr 2011[126]

Methods	Double-blind sham-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Seventy-one participants randomised (all male); 59 participants analysed (males = 51, females = 8) Baseline characteristics for sham CPAP patients ($n = 30$): mean age: 48.30 years; BMI: 28.47 kg/m^2; AHI: 31.67 events/hour; ESS score: 10.93 Baseline characteristics for CPAP patients ($n = 29$): mean age: 48.14 years; BMI: 30.57 kg/m^2; AHI: 38.64 events/hour; ESS score: 9.26 Inclusion criteria: moderate to severe OSA; CPAP naive, men, without diabetes mellitus Exclusion criteria: history of heart, liver or renal disease; diabetes; psychosis; narcolepsy; current alcohol or drug abuse; severe asthma; or cerebrovascular disease or were taking prescription medications; pregnancy; patients taking hypertensive medications were withdrawn from their medications and followed during a 1-week washout period while being monitored by a study physician. If BP remained consistently below 170/105 mmHg, subjects were entered into the study
Interventions	Participants received either CPAP or sham CPAP Study duration: 3 weeks on treatment Washout period: N/A
Outcomes	MFSI-SF, fatigue and vigour subscales on the POMS-SF and ESS score. AHI not a listed outcome but was reported
Notes	Jadad score = 2

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	The placebo–CPAP system was a modified version of the sham CPAP. Proper equipment use and setup was ensured by telephone calls and home visits by a sleep technician who was not involved in outcome assessments. Questionnaires were administered by a research co-ordinator who was blinded to treatment condition

MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; N/A, not applicable; POMS-SF, Profile Mood of States-Short Form.

von Känel 2006[127]

Methods	Double-blind, placebo-controlled parallel-group trial of CPAP vs. sham CPAP vs. supplemental oxygen
Participants	Forty-four participants randomised and analysed (males = 35; females = 9) Baseline characteristics for CPAP patients ($n = 18$): mean age: 47.1 years; BMI: 31.3 kg/m^2; AHI: 66.6 events/hour; SBP: 135.1 mmHg; DBP: 79.3 mmHg Baseline characteristics for oxygen patients ($n = 16$): mean age: 46.1 years; BMI: 30.4 kg/m^2; AHI: 61.0 events/hour; SBP: 130.6 mmHg; DBP: 77.9 mmHg Baseline characteristics for sham CPAP patients ($n = 10$): mean age: 48.4 years; BMI: 30.8 kg/m^2; AHI: 59.1 events/hour; SBP: 128.9 mmHg; DBP: 80.0 mmHg Inclusion criteria: AHI: > 15 events/hour; aged 30–65 years; < 15 periodic limb movements/hour of sleep, weight between 1 and 2 times ideal body weight as determined from Metropolitan Life tables Exclusion criteria: congestive heart failure, symptomatic obstructive pulmonary, coronary, cerebrovascular disease, history of life threatening arrhythmias, cardiomyopathy, history of narcolepsy, current alcohol or drug abuse, psychosis, previous surgery for treatment of OSA or regular use of medications
Interventions	Participants received either CPAP or sham CPAP or supplemental oxygen Study duration: 2 weeks Washout period: N/A
Outcomes	Haemostasis factors, AHI
Notes	Jadad score = 3

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Unclear	Patients were randomised by random number allocation to one of three treatment groups
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Yes	Patients were randomised to one of three treatment groups in a double-blind fashion. In essence, investigators and co-ordinators, recruiters and those who analysed the data were blinded to the patients' treatment. Only the polysomnography technician, by necessity, was unblinded to the randomisation. CPAP equipment for the three treatment arms was identical in appearance

N/A, not applicable.

Weaver 2012[128]

Methods	Double-blind placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Two hundred and eighty-one participants randomised. Two hundred and thirty-nine randomised and exposed (males = 140, females = 99). Two hundred and twenty-three participants analysed Baseline characteristics for CPAP patients randomised and exposed ($n = 121$): mean age: 49.5 years; BMI: 33.2 kg/m^2; AHI: 12.8 events/hour; ESS score: 15.21; FOSQ: 13.91; SF-36 PCS: 41.81; SF-36 MCS: 42.92; SBP: 124.5 mmHg; DBP: 76.2 mmHg Baseline characteristics for sham CPAP patients randomised and exposed ($n = 118$): mean age: 51.7 years; BMI: 34.2 kg/m^2; AHI: 12.5 events/hour; ESS score: 15.21; FOSQ: 14.41; SF-36 PCS: 42.26; SF-36 MCS: 46.04; SBP: 124.4 mmHg; DBP: 74.8 mmHg Inclusion criteria: AHI: 5–30 events/hour; ESS score > 10; CPAP naive Exclusion criteria: an unstable medical condition in the past 3 months; below fifth grade reading level; history of other sleep disorder; current pregnancy; substance abuse; sleepiness-related driving accident; or sleepiness sensitive occupation
Interventions	Participants received either CPAP or sham CPAP Study duration: 8 weeks Washout period: N/A
Outcomes	FOSQ, SF-36, ESS score, objective sleepiness (measured by the PVT), POMS (17), mean 48-hour ambulatory BP, AHI
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation was performed by computer centrally for each site by the Data Coordinating Centre at the University of Pennsylvania. For enrolled participants, a computer-generated randomisation number was obtained by the research co-ordinator
Allocation concealment?	Yes	A computer-generated randomisation number was obtained by the research co-ordinator and communicated to the PSG technologist who matched it with a sealed envelope kept in a locked box, containing the treatment allocation. The appropriate device was then selected by the PSG technologist who distributed it to the research co-ordinator for distribution in a sealed black bag
Blinding?	Yes	PSG and CPAP set-ups based on the assigned intervention. Treatments were identical in presentation
All outcomes		

N/A, not applicable; POMS, Profile of Mood States; PSG, polysomnogram; PVT, psychomotor vigilance task.

Weinstock 2012[129]

Methods	Double-blind randomised controlled crossover group trial of CPAP vs. sham CPAP
Participants	Fifty participants randomised (males = 21, female = 29), 49 participants completed
	Baseline characteristics for CPAP first randomised patients ($n = 25$): mean age: 54 years; BMI: 39 kg/m^2; AHI: 44 events/hour
	Baseline characteristics for sham CPAP first randomised patients ($n = 25$): mean age: 53 years; BMI: 38 kg/m^2; AHI: 32 events/hour
	Inclusion criteria: AHI ≥ 15 events/hour; 18–75 years old; evidence of IGT
	Exclusion criteria: current use of oral hypoglycaemic medications or insulin; overt diabetes; use of supplemental oxygen; primary sleep disorder other than SDB; severe chronic insomnia or circadian rhythm disorder with < 4 hours of sleep per night; unstable medical conditions (e.g. new-onset or changing angina, myocardial infarction, or congestive heart failure exacerbation documented within the previous 3 months, uncontrolled hypertension, etc.); daytime sleepiness with reports of sleepiness while driving or otherwise in situations which would present a risk for the subject or public; alcohol abuse; pregnancy
Interventions	Participants received either CPAP or sham CPAP
	Study duration: 8 weeks on each treatment
	Washout period: 1 month
Outcomes	Normalisation of impaired glucose tolerance, metabolic indices and AHI
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Sequence order (CPAP/sham CPAP; or sham CPAP/CPAP) was determined by a computerised program that generated random numbers
Allocation concealment?	Unclear	No information
Blinding?	Yes	Participants and outcome assessors blinded to treatment
All outcomes		

IGT, impaired glucose tolerance; SDB, sleep-disordered breathing.

West 2007[130]

Methods	Double-blind placebo-controlled parallel-group trial of CPAP vs. sham CPAP
Participants	Forty-two participants randomised, 40 analysed (all male)
	Baseline characteristics for CPAP patients randomised ($n = 20$): mean age: 57.8 years; BMI: 36.6 kg/m^2; oxygen saturation dips > 4%/hour: 33.1; ESS score: 14.7; SAQLI: 4.3; neck circumference: 46.2 cm
	Baseline characteristics for sham CPAP patients randomised ($n = 22$): mean age: 54.5 years; BMI: 36.8 kg/m^2; oxygen saturation dips > 4%/hour: 39.1; ESS score: 13.6; SAQLI: 4.4; neck circumference: 47 cm
	Inclusion criteria: male; age 18–75 years; established type II diabetes; ESS score > 9; > 10 oxygen saturation dips of > 4% per hour on overnight sleep study; due to start CPAP
	Exclusion criteria: urgent CPAP required because of respiratory failure or to prevent job loss as a result of excessive daytime sleepiness; unstable diabetes (requiring an escalation in treatment)
Interventions	Participants received either CPAP or sham CPAP
	Study duration: 3 months
	Washout period: N/A
Outcomes	Change in glycosylated haemoglobin (HbA_{1c}); changes in insulin sensitivity. Sleepiness (ESS score, SAQLI, MWT) assessed to confirm response to active CPAP compared with placebo but not mentioned as outcomes
Notes	Jadad score = 5

Risk of bias

Item	*Authors' judgement*	*Description*
Adequate sequence generation?	Yes	Randomisation was by means of a balanced computer program (MINIM version 1.5, Evans S)
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Yes	The nurses involved in the randomisation, CPAP initiation and ongoing CPAP care were separate from the study investigators. Study described as double blind. Participants blinded to treatment as the two treatments were identical in presentation

N/A, not applicable.

Appendix 16 Characteristics of the 56 excluded studies

Author	Appropriate intervention[a]	Relevant comparator[b]	Appropriate study design[c]	Appropriate patient group[d]	Appropriate outcome measures[e]	List applicable outcome measures[f]	Duplicate data/study[g]	Data extraction possible[h]	Specific reason(s) for exclusion
Aarab (2011)[350]	Yes	Yes	Yes	Yes	Yes	AHI, EDS	Yes	Yes	Follow-up study data to Aarab (2011)[68] (respiration, included)
Almeida (2013)[351]	Yes	Yes	No	No	Yes	AHI, ESS score, SAQLI	No	Yes	Non-RCT, recruited patients on CPAP
Ayers (2013)[352]	Yes	Yes	Yes	No	Yes	AHI, ESS	No	Yes	Recruited patients on CPAP withdrawal vs. continuation study
Barbé (2010)[331]	Yes	Yes	Yes	Yes	Yes	ESS score, BP	Yes	Yes	Partial results from Barbé (2012)[89] (included)
Berlowitz (2013)[353]	No	No	No	No	No	None	Yes	No	Non-RCT – commentary on Kushida (2012)[25] (included)
Bishop (2010)[354]	Yes	No	Yes	Yes	Yes	RDI, ESS score, SAQLI	No	No	MAD vs. MAD
Blau (2012)[355]	Yes	No	Yes	Yes	Yes	AHI, ESS score	No	Yes	CPAP vs. auto bilevel pressure relief-positive airway pressure study
Buchner (2007)[356]	Yes	Yes	No	Yes	Yes	AHI	No	Yes	Non-RCT
Craig (2010)[357]	Yes	Yes	Yes	Yes	Yes	ESS score	Yes	Yes	Preliminary results from Craig (2012)[95] (included)
Cross (2008)[358]	Yes	Yes	Yes	Yes	No	BP	No	Yes	AHI and ESS score not measured after treatment
Dal-Fabbro (2009)[359]	Yes	Yes	Yes	Yes	Yes	Respiratory sleep parameters; ESS score, SF-36	No	No	AHI and ESS score values not reported after treatment
Deane (2009)[335]	Yes	No	Yes	Yes	Yes	AHI, ESS score	No	Yes	MAD vs. TSD. Treatment period 1 week only
Deleanu (2012)[360]	Yes	No	No	No	Yes	ESS score	No	Yes	Non-RCT, studied CPAP pressures in hypertension vs. resistant hypertension patients

Author	Appropriate intervention[a]	Relevant comparator[b]	Appropriate study design[c]	Appropriate patient group[d]	Appropriate outcome measures[e]	List applicable outcome measures[f]	Duplicate data/study[g]	Data extraction possible[h]	Specific reason(s) for exclusion
Doff (2010)[361]	Yes	Yes	Yes	Yes	No	None	Yes	No	Long-term follow-up of Hoekema (2008)[81] (included) but no ESS score/AHI reported
Doff (2012)[362]	Yes	Yes	Yes	Yes	No	None	Yes	No	Long-term follow-up of Hoekema (2008)[81] (included) but no ESS score/AHI reported
Doff (2013)[363]	Yes	Yes	Yes	Yes	No	None	Yes	No	Long-term follow-up of Hoekema (2008)[81] (included) but no ESS score/AHI reported
Drager (2010)	Yes	?	?	?	?	?	Yes?	No	Suspected duplicate study of Drager (2011)[364] (excluded). Unable to find
Drager (2011)[364]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score, BP	No	No	AHI and ESS score values not reported after control treatment
Fleury (2010)[365]	No	No	No	No	No	None	No	No	Non-RCT
Garbuio (2009)[366]	Yes	Yes	Yes	Yes	Yes	PSG parameters, EDS	No	No	Abstract only with no information to extract
Gauthier (2009)[367]	Yes	No	Yes	Yes	Yes	RDI, ESS score, FOSQ	No	Yes	MAD vs. MAD
Gauthier (2010)[368]	Yes	No	Yes	Yes	Yes	RDI, ESS score, FOSQ	Yes	No	MAD vs. MAD. Abstract of Gauthier (2011)[370] (excluded)
Gauthier (2010)[369]	Yes	No	Yes	Yes	Yes	RDI, ESS score, FOSQ	Yes	No	MAD vs. MAD. Abstract of Gauthier (2011)[370] (excluded)
Gauthier (2011)[370]	Yes	No	Yes	Yes	Yes	RDI, ESS score, FOSQ, BP	Yes	Yes	MAD vs. MAD. Long-term follow-up of Gauthier (2009)[367] (excluded)
Ghazal (2009)[194]	Yes	No	Yes	Yes	Yes	AHI, ESS score, SF-36	No	Yes	MAD vs. MAD
Hall (2012)[371]	Yes	Yes	Yes	No	No	BP	No	No	BP only reported in patients with OSA and heart failure – abstract only

Author	Appropriate intervention[a]	Relevant comparator[b]	Appropriate study design[c]	Appropriate patient group[d]	Appropriate outcome measures[e]	List applicable outcome measures[f]	Duplicate data/study[g]	Data extraction possible[h]	Specific reason(s) for exclusion
Heeley (2012)[372]	Yes	Yes	Yes	No	Yes	ESS score	No	No	Preliminary trial report. Patients with OSA and prior stroke/CVD – abstract only
Hoekema (2008)[373]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score	Yes	Yes	Patient subset of Hoekema (2008)[81] (included)
Hoyos (2011)[374]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score	Yes	No	Abstract of Hoyos (2012)[107] (included)
Hoyos (2012)[375]	Yes	Yes	Yes	Yes	Yes	AHI	Yes	No	Abstract of Hoyos (2012)[107] (included)
Kohler (2009)[376]	Yes	Yes	Yes	Yes	Yes	ESS score	Yes	No	Duplicate data from Siccoli (2008)[18] (included)
Kohler (2011)[377]	Yes	Yes	Yes	No	Yes	AHI, ESS score, BP	Yes	Yes	Recruited patients on CPAP – withdrawal vs. continuation study. Link with Rossi (2012)[389] (excluded)
McEwen (2012)[378]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score	Yes	Yes	Patient subset of Philips (2011)[118] (included) and repeat of Phillips (2012)[382] (excluded) AHI data
Mello-Fujita (2012)[379]	Yes	Yes	Yes	Yes	Yes	ESS score, BP	Unclear	No	Abstract only – insufficient data to extract. Possible link with Rizzi (2010)[388] (excluded)
Oliveira (2012)[380]	Yes	Yes	Yes	Yes	No	BP	No	No	AHI only measured at baseline and on CPAP titration night, not following a treatment period
Permut (2010)[381]	Yes	No	Yes	Yes	Yes	AHI	No	Yes	Positional device vs. CPAP for one night only
Phillips (2012)[382]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score	Yes	Yes	Patient subset of Philips (2011)[118] (AJRRCM, included)
Phillips (2011)[383]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score, FOSQ, SF-36; BP	Yes	Yes	Abstract of Phillips (2013)[52] (included)

Author	Appropriate intervention[a]	Relevant comparator[b]	Appropriate study design[c]	Appropriate patient group[d]	Appropriate outcome measures[e]	List applicable outcome measures[f]	Duplicate data/study[g]	Data extraction possible[h]	Specific reason(s) for exclusion
Phillips (2011)[384]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score, FOSQ, SF-36, BP	Yes	Yes	Abstract of Phillips (2013)[52] (included)
Portier (2010)[385]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score, quality of sleep	No	No	Abstract only – insufficient data to extract
Prilipko (2012)[386]	Yes	Yes	Yes	Yes	No	None	No	No	AHI and ESS score measured at baseline only
Prudon (2012)[387]	Yes	Yes	Yes	Yes	No	None	Yes	No	Abstract only. Used samples from West (2007)[130] (included)
Rizzi (2010)[388]	Yes	Yes	Yes	Yes	No	BP	Unclear	Yes	Abstract only – no ESS score/ AHI outcomes. Possible link with Mello-Fujita (2012)[379] (excluded)
Rossi (2012)[389]	Yes	Yes	Yes	No	Yes	AHI, ESS score	Yes	Yes	Recruited patients on CPAP – withdrawal vs. continuation study. Sleep data from Kohler (2011)[377] (excluded)
Sari (2011)[390]	Yes	No	Unclear	Yes	Yes	AHI, ESS score	No	Yes	MAD vs. MAD
Seehra (2013)[391]	Yes	No	No	No	No	None	No	No	Non-RCT – technical note
Sivam (2012)[392]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score	Yes	Yes	Patient subset from Philips (2011)[118] (included)
Sutherland (2011)[393]	Yes	No	Yes	No	No	None	No	No	Compared optimal CPAP pressures in MAD responders vs. MAD non-responders
Sutherland (2012)[394]	Yes	Yes	Yes	Yes	No	None	No	No	Abstract only – no ESS score/ AHI outcomes
Takaesu (2012)[395]	Yes	Yes	Yes	No	Yes	AHI, BP	No	Yes	Patients with panic disorder and OSA
Toukh (2012)[396]	Yes	Yes	Yes	No	Yes	AHI	No	Yes	Patients had used CPAP prior to study

Author	Appropriate intervention[a]	Relevant comparator[b]	Appropriate study design[c]	Appropriate patient group[d]	Appropriate outcome measures[e]	List applicable outcome measures[f]	Duplicate data/study[g]	Data extraction possible[h]	Specific reason(s) for exclusion
Trzepizur (2009)[397]	Yes	Yes	Yes	Yes	Yes	AHI, ESS score, BP	Yes	Yes	Substudy of Gagnadoux (2009)[24] (included)
Turnbull (2012)[398]	Yes	Yes	Yes	Yes	No	None	Yes	No	Follow-up on vascular events and accidents from Craig (2012)[95] (included)
Vicini (2010)[399]	Yes	No	Yes	Yes	Yes	AHI, ESS score	No	Yes	APAP vs. surgery
von Känel (2013)[400]	Yes	Yes	Yes	Yes	Yes	AHI	No	No	Insufficient data to extract
West (2009)[401]	Yes	Yes	Yes	Yes	Yes	ESS score	Yes	Yes	Duplicate data from West (2007)[130] (included)

TSD, tongue stabilising device.

a Does the study look at CPAP/APAP and/or MAD?

b Does the study have relevant comparators, i.e. placebo/sham treatment/no treatment/MAD (if CPAP intervention)/CPAP (if MAD intervention) and does the intervention and the comparator last ≥ 2 weeks?

c Is the study a RCT?

d Does the study include participants with OSAH, 16 years old, who do not specifically relate to a population with brain disease, heart failure, chronic airways disease or psychological disorders, who are not already on treatment with CPAP or MAD?

e Does the study look at subjective daytime sleepiness (ESS score, AHI or RDI)?

f Applicable outcome measures include: subjective daytime sleepiness (ESS score), excessive daytime somnolence (EDS), AHI or RDI, SF-36, (EQ-5D-3L), sleep-related QoL (FOSQ, SAQLI, BP)?

g Have the data been published elsewhere, i.e. duplicated from the same study in another paper or are they from a subgroup of patients in another paper?

h Are the outcome data suitable for extraction?

Appendix 17 Study protocol

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

Chief Investigator: Dr T Quinnell

Co-Investigators: Smith IE[1], Shneerson JM[1], Davies MG[1], Sharples L[2], Morrell M[3], Glover M[4], Jackson S[1] & Chadwick R[1]

Institution: [1] **Papworth Hospital**

[2] **Medical Research Council Biostatistics Unit, Cambridge**

[3] **National Heart & Lung Institute, Imperial College London**

[4] **Health Economics Research Group, Brunel University**

Investigation Sites: Papworth Hospital NHS Trust

Collaborator: Mr M Cameron, Maxillofacial Lab, Addenbrooke's Hospital.

Protocol Identification Number: P01415

Date of Protocol: 19th Sept. 2012

Protocol Version Number: 4.0

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'

CONTENTS

SIGNATURE PAGE

Trial Sponsor (Papworth Hospital NHS Trust)

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

Study Identification Number: P01415

HTA Reference No: 08/110/03

REC Reference: 10/H0308/4

Approved by the following:

Name:

Signature:

Date:

Chief Investigator Name: Dr T Quinnell

Signature

Date:

	Version	Date	Amendment	Date approved
Current Version	**4.0**	**19 September, 2012**	**SA03**	**16 October, 2012**
Previous Version	**3.0**	**01 June, 2012**	**SA02**	**26 June, 2012**
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 Amended (in SA02) to 96 (maximum)
Study Design	Crossover Randomised 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
SpO2	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.

Our main objectives are to determine:

1) Are MADs more effective than no treatment?

2) 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 acclimatisation 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.

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, EQ-5D, 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. Participants who do not initially respond will be contacted once by phone and once by letter to request they 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 ≥ 4 hrs per night and ≥ 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.

Table 4. Outcome Measures Collection

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, EQ-5D and SAQLI Tolerability Side effects, withdrawals and adherence BMI Bite measurement

3.10 VISIT SCHEDULE AND ASSESSMENTS

Visits should be scheduled and performed according to Table 5.

Table 5. Assessment Schedule

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								(×)	(×)

4. Economioc 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.

5.1 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.

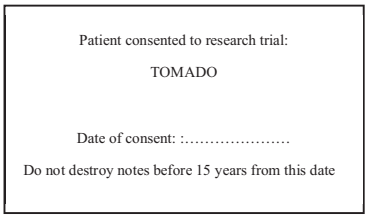
The investigator/clinical research assistant will maintain source documents (patient's hospital case notes) for each patient in the study, consisting of all demographic and medical information, including respiratory sleep study results. A copy of the consent form and patient information sheet will also 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.

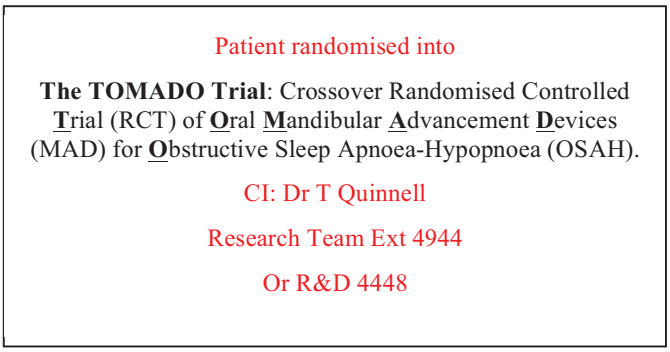
5.2 Labeling of Source Documentation

The patients' hospital case notes 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:



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



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

7. Statistical 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.

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 (SA02): 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.

14. Protocol References

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Appendix 18 Summary of protocol changes

During the course of the trial, three substantial amendments to the protocol were submitted to, and subsequently approved by, the Research Ethics Committee (REC).

Substantial amendment 1, dated 6 December 2010 and reviewed 20 December 2010 included:

- Change of investigator at Addenbrooke's maxillofacial laboratory.
- Clarification of inclusion and exclusion criteria.
- Sections on degree of protrusion and randomisation added to the study plan.
- Clarification of timelines.
- Outcome measures updated.
- Strengths and limitations added as a response to peer-review comments.
- Clarification of adverse event reporting.
- Updating of patient information sheet and patient diaries.

Substantial amendment 2, dated 1 June 2012 and reviewed 26 June 2012 included:

- Increasing number of participants randomised from 90 to a maximum of 96.
- Longer-term follow-up at 1 year and 2 years post-trial completion.
- Extension of current trial end date.
- Minor changes throughout protocol for clarification purposes.

Substantial amendment 3, dated 19 September 2012 and reviewed 16 October 2012 included:

- Removal of a contact from the protocol.
- Change to FOSQ questionnaire.
- Change to sponsor contact.
- Change to follow-up questionnaire.

A fourth substantial amendment was approved by the REC, but the amendment applied to the follow-up questionnaire alone and not the protocol. Substantial amendment 4, dated 1 May 2013 and reviewed 27 May 2013 included:

- Adding an extra question to the follow-up up questionnaire.

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