National Institute for Health and Care Excellence

Final

Obstructive sleep apnoea/ hypopnoea syndrome and obesity hypoventilation syndrome in over 16s

Evidence review G: Oral devices

NICE guideline NG202

Intervention evidence review

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Final

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1.1 Review question: What is the clinical and cost effectiveness of different types of oral devices for managing obstructive sleep apnoea/hypopnea syndrome (OSAHS), and COPD-OSAHS overlap syndrome?

1.2 Introduction

Sleep-disordered breathing (including obstructive sleep apnoea, OSAHS) represents a spectrum of conditions, in which the upper airway (pharynx) either partially or completely collapses during sleep, with significant co-morbidity resulting from repeated oxygen dips and sleep deprivation. Most oral devices act to temporarily position the mandible forward to prevent such pharyngeal collapse (during sleep). These devices can either be custom-made for the patient by a dental professional or purchased directly in a ready-made state, with each offering potential advantages and disadvantages. Other oral devices act primarily to advance or stabilise the tongue.

The current review looks at the evidence in support of the role of oral devices in the management of OSAHS, in particular, their effectiveness in OSAHS as either first line treatment or as an alternative treatment for patients unable to tolerate or cope with continuous positive airways pressure (CPAP). Furthermore, the review will explore the evidence for custom-made versus ready-made oral appliances in treating OSAHS, in order to address which design of appliance should be recommended.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Inclusion: People (16 and older) with OSAHS and COPD-OSAHS overlap syndrome Population will be stratified by: • population: OSAHS, COPD-OSAHS overlap syndrome • severity: Mild, moderate, severe (based on AHI/ODI) Studies including a mixed population of disease severity will be extracted under the category that the majority of their participants fall under, with downgrading for indirectness. If studies provide no information on disease severity, they will be extracted in a separate category. Exclusion: • children and young people (under 16)
Intervention	• Any intraoral prostheses -mandibular advancement splints, mandibular advancement devices, mandibular repositioning appliances, dental orthosis, tongue retaining devices or tongue stabilizing devices. Different types of oral devices: • self-customised/self-molded/ready-made/boil and bite • semi-customised/semi-bespoke

	• fully customised/fully bespoke
Comparison	• surgery • other non-surgical intervention (positive airway pressure variants, positional modifiers) • combination therapy (combination of oral devices and any non-surgical/surgical interventions) • no intervention (placebo, inactive control therapy)/ usual care as defined in the studies (including lifestyle advice etc) Types of oral devices: • compare different types of oral devices with each other.
Outcomes	Critical • Generic or disease specific quality of life measures (continuous) • Mortality (dichotomous) Important • sleepiness scores (continuous, e.g. Epworth) • apnoea-Hypopnoea index or respiratory disturbance index (continuous) • oxygen desaturation index (continuous) • CO2 control (continuous) • adverse effects of treatment (rates or dichotomous) • disruption of partner's sleep • driving outcomes (continuous) • neurocognitive outcomes (continuous) • adherence in hours of use (continuous) • patient preference (continuous) • impact on co-existing conditions: • HbA1c for diabetes (continuous) • cardiovascular events for cardiovascular disease (dichotomous) • systolic blood pressure for hypertension (continuous) Outcomes will be separated into short term (latest follow-up to 6 months) and long term (latest follow-up beyond 6 months)
Study design	RCT's Systematic review of RCT's Minimum duration of follow up 1 month Parallel or crossover to be included

1.4 Clinical evidence

1.4.1 Included studies

Oral device is used as a generic term for devices inserted into the mouth to modify the position of the mandible, the tongue, and other structures in the upper airway, for the purpose of relieving snoring or obstructive sleep apnoea.

Oral devices are grouped into two major types: (1) those that make the mandible and the attached tongue protrude; i.e. the mandibular advancement splints (MAS)/mandibular

advancement devices (MAD) (2) those that hold the tongue forward; i.e. the tongue retaining devices, or tongue stabilizing devices.

Mandibular advancement splints can be further classified as: (1) self-customised/self-moulded/readymade/boil and bite: these generally only require and permit a minimal amount of adaption of a thermoplastic material. These are available ready-made over the counter; (2) semi-customised/ semi-bespoke: a semi-bespoke device is formed from a dental impression used by a patient. Patients are provided with an impression kit to mould their device at home and then they send this to the manufacturer so that the device can be made; (3) Fully customised/fully bespoke: a custom-made /MAS fitted by a suitably trained general dental practitioner.

There are two main categories of custom-made oral appliance; the adjustable or titratable, and the non-adjustable or monoblocks. The adjustable appliances allow for different mandibular protrusions at increment of 0.1 mm to 1 mm, depending on the manufacturer.

Oral devices compared to other interventions/no intervention

OSAHS

Twenty one studies (twenty seven papers) were included in the review; [2-4, 9, 16, 41-43, 54, 61, 62, 78-80, 93, 121, 132, 146, 164, 167, 175, 181, 185, 190, 203, 224, 225] these are summarised in table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 2Table 6).

Thirteen studies compared oral devices (mandibular advancement splints) with CPAP in a moderate severity population, one study compared oral devices (mandibular advancement splints) with a placebo in a mild severity population, ten studies compared oral devices (mandibular advancement splints) with a placebo in a moderate severity population and one study compared oral devices (mandibular advancement splints) with surgery in a moderate severity population. There was no evidence for CPAP versus oral devices or oral devices versus surgery in a mild severity population.

All included studies used a mandibular advancement splint. The majority of the studies employed fully bespoke titratable devices fitted by dentists. Two studies[41, 121] used fully bespoke devices which were non titratable. One study[203] used a semi-bespoke device for the first 10 patients and a fully bespoke device for the remaining patients due to patient complaints; both of these devices were titratable. One study[175] compared three different mandibular advancement splints; a thermoplastic ‘boil and bite’ ready-made device, a semi-bespoke device formed from a dental impression mould self-fitted by the patient and a custom-custom-made mandibular advancement device professionally fitted by specialists.

Three studies compared an oral device (mandibular advancement splint) with no active treatment (advice and education only) and 8 studies compared an oral device (mandibular advancement splint) with a placebo device. Placebo devices varied between the studies, but the majority reported a device similar to the oral device (mandibular advancement splint) used with an acrylic plate covering the palate but without the mandibular advancement.

There was no evidence available for tongue retaining/tongue stabilising devices.

Studies were stratified based on the AHI/ODI severity of the population. When a mixed severity population was included, the severity of the majority of the population was used by taking the mean AHI of the patients included and the study was downgraded for indirectness.

COPD-OSAHS overlap syndrome

There was no evidence available for COPD-OSAHS overlap syndrome.

Different types of oral devices compared to each other

OSAHS

Three papers were included in this review comparing different types of oral devices with each other. These papers are summarised below. (Table 3).

All included studies used a mandibular advancement splint. One paper[175] included three comparisons: a ready-made 'boil and bite' mandibular advancement splint, a semi-bespoke mandibular advancement splint formed from a dental impression mould self-fitted by the patient, and a custom-made mandibular advancement splint professionally fitted by specialists all compared to each other. Another paper[108] compared a ready-made heat moulded mandibular advancement splint with a fully custom-made titratable mandibular advancement splint. The final paper[164] compared a semi-bespoke heat moulded titratable mandibular advancement splint with a fully custom-made titratable mandibular advancement splint.

Studies were stratified based on the AHI/ODI severity of the population. Two studies included in this review were of mild severity populations, while one was in a moderate severity population. When a mixed severity population was included the severity of the majority of the population was used by taking the mean AHI of the patients included and the study was downgraded for indirectness.

There was no evidence for moderate and severe populations.

There was no evidence available for driving outcomes, neurocognitive outcomes, impact on co-existing conditions (HbA1 for diabetes, cardiovascular events for cardiovascular disease, systolic blood pressure)

COPD-OSAHS overlap syndrome

There was no evidence available for COPD-OSAHS overlap syndrome.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D: D, forest plots in Appendix E, and GRADE tables in Appendix F.

See the excluded studies list in Appendix I.

1.4.2 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review- oral devices compared to other interventions/no interventions - OSAHS

Study	Intervention and comparison	Population	Outcomes	Comments
Aarab 2011[2] Aarab 2011[3] Aarab 2017[4] Nikolopoulou 2020[152] RCT Netherlands	**Oral devices** - individually fabricated MAD with an adjustable protrusive mandibular position at constant vertical dimension was used N=21 **CPAP** - nCPAP of the REMstar Pro system was used (Respironics, Herrsching, Germany). N= 22 **Placebo** - a thin (<1mm), hard acrylic-resin palatal splint with only a partial palatal coverage was used as a placebo N=21	Age >18 years, AHI between 5 and 45 events per hour, and a report of excessive daytime sleepiness (Epworth Sleepiness Score 6 10) or at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g. unrefreshing sleep and daytime fatigue Baseline AHI: MAD group - 22.1(10.8) nCPAP group - 20.9(9.8) Placebo group – 20.1 (8.7)	AHI- change score 6 months after the intervention AHI 12 months after the intervention AHI 18 months after the intervention Adverse events - side effects Adherence Follow up – 6, 12 and 18 months	Moderate severity OSAHS strata population (strata based on mean AHI)
Andren 2013[9] RCT Sweden	Oral devices – The active oral appliance with mandibular advancement (OAa) was custom-made and of a monoblock design, as previously described by Tegelberg et al. The OAa	Verified OSA defined as AHI ≥10, systemic hypertension defined as office systolic BP >140 mmHg or diastolic BP >90 mmHg at two separate occasions and were not currently being treated with	AHI ESS Systolic BP Follow up – 3 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	protruded the mandible to 70–75 % of the patient's maximum mandibular protrusive capacity (>4 mm). N=36 Placebo – The contro oral appliance OA (OAc) possessed the same feature as the active device except for the lack of any mandibular advancement (<0.5 mm). N=36	an OA or CPAP. Patients also had to possess a sufficient number of teeth for the retention of an OA. Baseline AHI: OA group – 23 (16) Placebo group – 24 (17)		
Barnes 2004[16] Crossover trial Australia	Oral Devices – (medical dental sleep appliance, R.J. Bird and V.K. Bird) mandibular advancement splint. custom-made N=99 CPAP- nasal continuous positive airway pressure (Sullivan Elite, ResMed Australia). CPAP use was measured with an inbuilt "time at pressure meter. N=97 No active treatment N=98	Subjects were middle aged (47.0 (0.9)), predominantly male (80%), and overweight (interquartile range body mass index, 27.8-32.8 kg/m²), with mild to moderate OSA (AHI, 5-30 per hour) Baseline AHI (overall): mean (SEM) - 21.3(1.3)	AHI ESS FOSQ- (mean score) SF 36 Adherence Systolic BP Preference Follow up – 3 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
de Britto Teixeira 2013[41] cross over study Brazil	Oral devices – A twin block (TB) experimental mandibular advancement device was modified for use in this situation. It consisted of two parts, one for the upper arch and one for the lower. It was fabricated from self-curing acrylic resin with occlusal coverage on all teeth so as to reduce changes in tooth positioning that might arise from its use. Each piece had, on its occlusal surface, bilateral slopes with approximately 45° inclination which, when joined, caused the mandible to advance by 75% of each patient's maximum mandibular advancement capacity. N=19 Placebo – The device used as placebo was an acrylic upper plate covering the palate, with a labial arch made of 0.9-mm wire contouring all the teeth and extending past the distal side of the last tooth, where it was fastened to the acrylic plate, in what is known as wraparound device.	Diagnosis of mild-to-moderate OSAS, with the exclusion of primary snorers (AHI < 5). Diagnosis was based on overnight polysomnography, considered the gold standard for OSAS diagnosis. The diagnosis of lack of nasal obstruction was done using magnetic resonance imaging. Baseline AHI: 16.3(7.2)	AHI Follow up – 10.5 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	N=19			
De Vries 2019[43] De Vries 2019[42] RCT Netherlands	Oral devices – patients were treated with a custom-made titratable biblock MAD (SomnomedDent MAD SomnoMed Australia/Europe AG) to start the mandible was set at approximately 60-70% of the patient's maximum advancement. N = 43 CPAP – patients were treated with auto-adjusting CPAP (Philips Respironics REMstar Auto A-flex, provided by VitalAire BV The Netherlands) for 3 weeks, after which the appropriate fixed CPAP pressure for each individual patient was set by a skilled, specialised nurse (i.e. highest pressure derived from the Hoffstein formula of the auto-adjusting CPAP) during the study patients were allowed to change their max and to use chin straps or a humidifier if desired. N= 42	All consecutive patients aged 18 years or older with an AHI of 15 to 30 events/h based on PSG (primarily of the obstructive type) and fulfilling the inclusion and exclusion criteria were invited to take part in a parallel multicentre randomised controlled trial and scheduled for a baseline visit. Baseline AHI - MAD group = 19.9 (18.0-23.8) CPAP group = 19.6 (16.8-24.7)	AHI SF – 36 vitality ESS EQ5D Objective adherence – hours per night and % of nights >4 hours Outcomes reported at 3, 6 or 12 months	Moderate severity OSAHS strata population (strata based on mean AHI)
Duran-Cantolla 2015[54]	Oral devices –Mandibular advancement device (MAD): The commercial device	Patients were excluded according to the following ex-clusion criteria:	AHI ESS	Moderate severity OSAHS strata population

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Study	Intervention and comparison	Population	Outcomes	Comments
Crossover trial Spain	Klearway TM (University of British Columbia, Vancouver, Canada) was used. The fabrication of the device was made on model casts of both jaws and was adapted to the patient's mouth by a dentist with the objective to achieve a sufficient and tolerable mandibular advancement, being at least 65% of the maximum protrusion capacity of the mandible. This phase may need more than one visit to the dentist and had a period of 4 weeks at maximum. N= 42 Placebo – the placebo device was the same as the MAD device but defined as a splint in centric occlusion and did not induce a mandibular advancement. N=42	- High-risk professions and/or controlling dangerous machines. - Moderate or severe somnolence during daytime. Baseline AHI - 15.3 (10.2)	Adherence Systolic BP Adverse effects Follow up – 16 weeks	(strata based on mean AHI)
Ferguson1996[62] Ferguson 1997[61] Crossover trial Canada	Oral devices – The anterior mandibular positioner (AMP) used during this study is a new appliance with several novel features. It is constructed of a methyl methacrylate material (SR-Ivocap; Elastomer Ivoclar Co, New York, USA) and the	24 patients with symptomatic mild to moderate OSA (AHI 15-55/hour of sleep diagnostic polysomnography) were recruited. Patients had at least 10 teeth in each of the maxillary and mandibular	AHI ESS Mild side effects Preference Follow up – 4 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	upper and lower portions of the appliance provide full occlusive coverage of teeth. A titanium hinge with the five holes connects upper and lower portions, which allow a small amount of lateral movement of the jaw. There is a space between the teeth to permit oral airflow. The amount of mandibular advancement was initially set at 70% of maximal mandibular advancement. The AMP was adjusted to maximise comfort by relieving pressure points on the teeth and gums. The amount of mandibular advancement was the progressively increased over the next three months by mean (SD) of 1.8(1.2) mm until snoring ceased and symptoms improved or until the patient could not tolerate further advancement. N=24 CPAP – nCPAP - was undertaken with either a REMstar Choice machine (Respironics Inc, Murrysville, Pensylvania, USA) or a Tranquility plus machine (Healthdyne Technologies,	arches, and lived in the metropolitan Vancouver area Baseline AHI - 25.3(15)		

Study	Intervention and comparison	Population	Outcomes	Comments
	Marrietta Georgia, USA) Which were most advanced nCPAP units available at the time of the study. N=24			
Glos 2016[78] Crossover trial Germany	Oral devices – If patients had been randomised to initially receive MAD therapy, the MAD (MAD SomnoDent®, Somnomed Europe AG, Zurich, Switzerland) was individually produced and fitted to the patient 1–2 weeks prior to the beginning of the therapy (T1) by the manufacturer (Somnomed Europe AG, Zurich, Switzerland) and by a dentist. Titration with the MAD took place during the first of the two titration nights with an individually adjusted protrusion of up to 70%of the possible maximum. If the AHI remained ≥10/h after N=48 CPAP – patients in the CPAP group received the CPAP (REMstar Pro, Philips Respironics, Murrysville, PA, USA) for a period of 12 weeks. During the two titration nights,	AHI of ≥5/h and an age of ≥18 years. Patients with severe OSA (AHI >30/h) requiring treatment were included only if they did not demonstrate clear indication for CPAP such as a severe cardiovascular risk, e.g., myocardial infarction, stroke, atrial fibrillation, resistant hypertension, or heart failure. An essential element for inclusion of any patient was a clinical symptom complex, as well as suffering owing to lack of refreshing sleep. Baseline AHI - 28.5(16.5) Includes mild moderate and severe population of patients	AHI Systolic BP ODI Follow up – 12 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	manual titration was performed to eliminate apnoeas, hypopneas, oxygen desaturations, and respiratory arousals. N=48			
Gotsopoulos 2002[79] Gotsopoulos 2004[80] Crossover trial Australia	Oral devices – The mandibular advancement splint (MAS) was custom-made, consisting of upper and lower removable oral appliances. N=67 Placebo – The placebo device consisted of the upper appliance alone and did not advance the mandible. N=67	Inclusion criteria were OSA on polysomnography (apnoea-hypopnea index [AHI] ≥ 10 per hour), at least 2 of the following symptoms—daytime sleepiness, snoring, witnessed apnoeas, fragmented sleep; age > 20 years; and minimum mandibular protrusion of 3 mm. Baseline RDI - mean (se) – 27(2)	AHI Systolic BP Adherence Follow up – 4 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)
Hoekema, 2007[93] RCT Netherlands	Oral devices – The oral appliance used in this study (Thornton adjustable positioner, airway management inc, Dallas, Tx, USA) positioned the patients mandible in a forward and downward position. By turning a screw, patients could	Male patients over the age of 20 years who underwent polysomnography and were diagnose as having OSAHS with at least 5 apnoeas or hypopneas per hour (i.e. AHI > 5).	AHI ESS Adherence Follow up – 2-3 months	Moderate severity OSAHS strata population (strata based on mean AHI)

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Study	Intervention and comparison	Population	Outcomes	Comments
	adjust the mandibular advancement by 0.2mm increments. When commencing oral-appliance therapy the mandible was set at approximately 50% of the patient's maximum advancement. after having accustomed to this protrusive position during a 2-week period, patients were allowed to further adjust their appliance during a 6 week periods. The titration of the device continued until symptoms abated or until further advancement caused discomfort. N=21 CPAP – CPAP titration was performed during an afternoon nap. this technique, aimed at abolishing all signs of apnoea, hypopnoea and snoring, has been shown an appropriate procedure for the effective titration of CPAP. Following titration, an 8 week follow up period that allowed for habituation and, if necessary, adjustments of CPAP therapy was arranged.	Included patients with mild, moderate and severe OSA. Baseline AHI - 26.8 (9.7 – 58.5)		

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Study	Intervention and comparison	Population	Outcomes	Comments
	N=27			
Lam 2007[121] RCT China	Oral devices – Subjects in the oral appliance group were referred to an orthodontist (KS) for a tailor-made nonadjustable oral appliance. The oral appliance was made of dental acrylic modified from a functional activator (Harvold type). It held the mandible in a forward direction with some vertical opening to keep the jaw at the most advanced position without causing discomfort. N=34 CPAP – hose in the CPAP group were prescribed CPAP (ARIA LX, Respironics, Atlanta, Georgia, USA) at a pre-titrated pressure. N=34 Placebo – Advice on general sleep hygiene measures were given, and those who were overweight were asked to attend a weight control programme in the Dietetics Unit, Queen Mary Hospital, Hong Kong SAR, China.	Inclusion criteria were apnoea–hypopnoea index (AHI) >5–40 and Epworth Sleepiness Scale (ESS) 19 .9 for those with AHI 5–20. Baseline AHI mean(se): OA group – 20.9(1.7) CPAP group – 23.8(1.9) Conservative management group - 19.3 (1.9)	AHI ESS SF36 – mental SF 36 – physical Adherence Systolic BP SAQLI Follow up – 10 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

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Study	Intervention and comparison	Population	Outcomes	Comments
	N= 33			
Marklund 2015[132] RCT Sweden	Oral devices – The oral appliance was made individually from plaster casts produced by a dental technician. It consisted of an upper and lower part of elastomer (SRIvocapElastomer; IvoclarVivadent 28) and was interconnected with a screw that allowed continuous advancement of the lower jaw. N= 45 Placebo – The placebo upper-jaw device consisted of a bilaminate splint with a hole in the anterior part to reduce size and improve retention to the palate by suction. N= 46	Patients who snored and patients with mild to moderate sleep apnoea with an apnoea-hypopnea index (AHI) lower than 30 were included. The patients also had daytime sleepiness according to 1 or more of the following criteria: (1) an ESS score of 10or higher; (2) daytime sleepiness assessed as “often” or “always,” or (3) unwillingly falling asleep during the daytime assessed as “sometimes,” “often,” or “always” (on a scale ranging of “never,” “seldom,” “sometimes,” “often,” and “always”), or (4) an irresistible tendency to fall asleep during the daytime 1 or more times per week.	FOSQ ESS SF36 AHI Adherence Adverse effects Follow up – 4 months	Moderate severity OSAHS strata population (strata based on mean AHI)
Naismith 2005[146] Cross over trial Australia	Oral devices – Baseline assessments were followed by a period of acclimatisation with a custom-made mandibular advancement splint, during which incremental advancement of the mandible to the maximum comfortable limit of advancement was	presence of at least 2 symptoms of OSA, an AHI >10 per hour, age over 20 years, and ability to protrude the mandible by at least 3mm Baseline AHI: OA group – 27.9(17.5)	AHI ESS Follow up – 4 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	achieved. Symptomatic response was not assessed during this period so as to avoid unblinding patients. The mean acclimatisation period was 8.3 weeks. N=73 Placebo – The control treatment consisted of a single upper plate that had no protrusive effect on the mandible. N=73	Control group – 25.9(13.2)		
Phillips 2013[167] Crossover trial Australia	Oral devices – The MAD was the Somnodent (SomnoMed Ltd., Sydney, Australia), a custom-fitted and titratable two-piece device with proved clinical effectiveness in treating OSA. The MAD was self-titrated by gradually advancing the device until the maximum comfortable limit of mandibular advancement was achieved. N=126 CPAP – The CPAP device used in the trial was the ResMed Autoset S8 (ResMed,	Patients with newly diagnosed OSA (apnoea hypopnea index [AHI] .10 events per h); aged 20 years or older; greater than or equal to two symptoms of OSA (snoring, fragmented sleep, witnessed apnoea's, or daytime sleepiness); and a willingness to use both treatments. Baseline AHI - 25.6(12.3)	AHI FOSQ SF36 ODI ESS Preference Adherence Follow up – 1 month	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	Bella Vista, Australia). A fixed CPAP pressure was determined using a previously validated autotitrating method based on the 95th percentile pressure that controlled most of the OSA events. N=126			
Quinnell 2014[175] Crossover trial United Kingdom	Oral devices – SleepPro 1 (SP1) (Meditas Ltd., Winchester, UK): A thermoplastic „boil and bite" device fitted by the patient following the manufacturer's printed instructions. All patients wore the device for a period of 6 weeks with 1 week wash out periods between.; SleepPro 2 (SP2 (Meditas Ltd., Winchester, UK): A semi-bespoke device, formed from a dental impression mould made by the patient. An impression kit was posted to the patient. All patients wore the device for 6 weeks with a 1-week washout period. Bespoke Device (bMAD) (Maxillofacial Laboratory, Department of Oral and	Patients aged ≥18 years with mild to moderate OSAHS confirmed by respiratory polysomnography (rPSG) (AHI 5–<30/h) and symptomatic daytime sleepiness (Epworth Sleepiness Scale (ESS) score ≥9) were recruited from Papworth Hospital sleep centre. Newly diagnosed patients not requiring or declining CPAP and existing CPAP intolerant patients were eligible. Baseline AHI - 13.8(6.2)	AHI ESS EQ5D SF-36 vitality Minor adverse events; Dryness/Bad taste/Numbness, Discomfort/ Mouth problems, Excessive salivation, Cold related, infection. Follow up – 6 weeks	Mild severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	Maxillofacial Surgery, Cambridge, UK): Custom-made MAD, professionally fitted by specialists in the NHS Maxillofacial laboratory at Addenbrooke's Hospital, UK. N=90 Placebo – no treatment N= 90			
Randerath 2002[181] Crossover trial Germany	Oral devices – ISAD an oral appliance with 2 thin thermoplastic parts, worn on the upper and lower jaws are connected by 2 adjustable telescopic guide rods in the vestibule. N=20 CPAP – patients were treated with commercially available CPAP devices (max IIMAP, Martinstried Germany). the treatment pressure was increased in incremental steps of 1xm H2O/h until respiratory disturbances were minimalised, and respiration related arousals were reduced to less than 5/h. N=20	AHI of 5/h min and 30/h max and clinical symptoms of OSAS. Baseline AHI - 17.5(7.7)	AHI Preference Adverse effects including; feeling of pressure in the mouth, discomfort in the mouth and TMJ Adherence Follow up – 6 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

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Study	Intervention and comparison	Population	Outcomes	Comments
Rietz 2018[185] RCT Sweden	Oral devices – A custom-made adjustable mandibular advancement device, the Herbst device, was used as active treatment. It consisted of 2 parts made of elastomer and connected by 2 lateral screws that enabled the continuous titration of the mandible forward. A mandibular advancement of 6 to 7 mm was intended for all patients. N=48 Placebo – The sham device consisted of an acrylic plate in the palate and did not influence the position of the mandible N=48	Snoring, daytime sleepiness defined as at least 1 positive answer on 4 different scales; and an apnoea-hypopnea index <30. Baseline AHI - 15(9.5)	AHI Adherence Systolic BP Follow up - 4 months	Moderate severity OSAHS strata population (strata based on mean AHI)
Schutz 2013[190] RCT Brazil	Oral devices – A mandibular repositioning appliance (Brazilian Dental Appliance, Sao Paulo, SP, Brazil) was individually constructed and installed. The Brazilian Dental Appliance is an adjustable OA made of acrylic resin that allows progressive mandibular protrusion. N=9	25 to 55 years of age Sedentary Body mass index less than or equal to 30 kg/m2 AHI.10/h Hemogram, cholesterol, HDL, triglycerides, fasting glucose, creatinine, TSH within the normal range Lung function test (spirometry), chest X-rays (for smokers and former	AHI SF 36 ESS Follow up - 2 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	CPAP – The patients received a fixed mode device (REMstarH Plus; Respironics Inc., Murrysville, PA) that allowed for pressure variations between 4 and 20 cm H2O. N= 9	smokers), resting and stress electrocardiogram and otorhinolaryngologic examination without significant changes Baseline AHI: OA group – 30.8(19) CPAP – 25.1(10.5)		
Tan 2002[203] Crossover trial United Kingdom	Oral devices – A soft, one-piece MAS was selected initially, similar to that described by Stradling et al. (1998). This vacuum-formed appliance was simple and cheap to construct and designed to hold the mandible forward at the maximum comfortable protrusion, with no deviation to either side and minimal jaw opening. The initial protrusive position approximated 75 per cent of maximal possible protrusion. Progressive advancement of the mandible was possible by taking a new jaw record and modifying the appliance. However due to complaints from patients a two-part semi-rigid silsensor (Erkodent gmbh, Tuttlingen, Germany) was used for the remainder of the patients. If randomised to MAS,	Entry criteria included males and females over the age of 18 years, an adequate dentition and periodontal status for support and retention of the oral appliance, no temporomandibular joint dysfunction, and no medical contraindications. Patients also had to be able to attend the sleep clinic and sleep laboratory as requested for the requirements of the study. Baseline AHI - 22.2(9.6)	AHI ESS Preference Follow up – 2 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	impressions were taken for appliance construction and lateral skull radiographs were obtained. Once the MAS had been fitted, patients were instructed to contact the clinician if unforeseen problems or break- ages occurred and were given appointments at two- and six-week intervals. Any adjustments to the appliance were made at the two-week clinic visit. N=24 CPAP – nCPAP was provided using the REM Star Choice machine (Respironics Inc., Medic- Aid, West Sussex, UK) at UCLH and the Sullivan Elite machine (Resmed UK Ltd, Abingdon, UK) at RBH. A comfortable nasal mask was selected, and nasal corticosteroid sprays were prescribed to relieve nasal congestion if necessary. This symptom did not require treatment during the MAS arm of the study in any individual. Correct nCPAP pressures were titrated individually. Patients were familiarised with the system and a sleep study			

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Study	Intervention and comparison	Population	Outcomes	Comments
	arranged to ascertain the optimal nCPAP pressure required to abolish the OSA. The patient then commenced the two-month trial period with instructions to contact the laboratory if problems developed. Routine appointments at the sleep laboratory were given for two and six weeks into the treatment period. N=24			
Wilhelmsson 1999[224] RCT Sweden	Oral devices – before the intervention a clinical examination of the stomatognathic system was carried out. The same dentist treated all patients and one dental technician was responsible for the manufacture of the dental appliances. The appliances were carefully designed and fabricated on dental casts of acrylic polymer at a dental laboratory. The appliances were used at night times only and advanced the mandible by 50% of the patient's maximum protrusive capacity. each patient was given an appointment for	Adult patients >20 and <65 with confirmed OSA (AHI >10). Baseline AHI: OA group – 18.2 (15.7 -20.8) UPPP group – 20.4 (17.4 – 23.3)	AHI ODI Follow up – 12 months	Moderate severity OSAHS strata population (strata based on mean AHI)

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Study	Intervention and comparison	Population	Outcomes	Comments
	adjustment and adaptation of the N=49 Surgery – The Uvulopalatopharyngoplasty (UPPP) was performed by the same ear, nose and throat surgeon using a standardised procedure described by Frjita. The procedure involved tonsillectomy regardless of the size of the tonsils, and resection of excess fat and mucosa of the soft palate, including the uvula. The palpable musculature was saved and several sutures approximated the anterior and posterior tonsillar pillars. The UPPP surgery was performed under general anaesthesia. N=46			
Yamamoto 2019[225] Crossover trial Japan	Oral devices – A dentist at Kyushu university hospital took the impression and bite registration of the patients and sent it to a central laboratory where all the MAD were made. MADs were Somnodent (Somnodent Inc., Sydney, Australia) and were custom-	Patients over 20 years old who had been diagnosed with OSA with an overall AHI of 20-40/h and supine dependency based on overnight polysomnography. other inclusion criteria were; two or more symptoms of OSA among night time	Systolic BP ODI ESS Adherence Follow up – 8 weeks	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	made and titrated with consideration of patient's comfort and the results of SP02 monitoring. The maximal advancement was set at 75% of maximum and vertical opening was decided as minimum of each patient. titration period took about 4 weeks and jaw positions were titrated in reference to patient's comfort. Effects of the MAD were evaluated at the end of the MAD treatment period (7-9 weeks after treatment) by a home sleep apnoea monitor. N=45 CPAP – Patients randomised to CPAP used a sleepmate S9 (Resmed, San Diego, CA, USA) or REMstar Pro System One 60 series (Phillips Respironics, Murryysvilles, PA, USA) in automatic pressure mode initially set between 4 and 12 cmH2co by referring the analysis of the pressure in our institute with a humidifier when needed. N=45	dyspnoea, fragmented sleep, non-restorative sleep, and excessive daytime sleepiness. Baseline AHI - 28.6(5.5)		

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1.4.3 Summary of clinical studies included in the evidence review (Oral devices compared to each other)- OSAHS

Table 3: Summary of clinical studies: oral devices compared to each other

Study	Intervention and comparison	Population	Outcomes	Comments
Johal 2017[108] Crossover trial United Kingdom	Intervention – Ready-made MRD The ready-made MRD (MRDr) selected was a preformed thermoplastic appliance, the "Snoreshield" (S4S, Sheffield, UK). Patients were instructed to fit the appliance as per the manufacturer's instructions, by soaking the device in warm water and fitting to the upper arch. The mandible was then protruded into the device. The appliance could be reheated at home for further manipulation as required, with a maximum permissible protrusion of 6 mm. N =25 Comparison – Custom-made MRD The custom-made MRD (MRDc;) selected was the "Medical Dental Sleep Appliance" (R.J. and V.K. Bird, Middle Park, Victoria, Australia).The appliance design exhibits minimal opening, is self-adjustable, and allows incremental advancement of	Inclusion criteria – The selection criteria for the trial were: adults (> 18 years), with a confirmed diagnosis of mild-moderate OSA (apnoea-hypopnea index [AHI] of 5–30 events/h); sufficient healthy teeth to retain an MRD; the absence of periodontal disease or temporomandibular joint dysfunction and no previous history of MRD use. Baseline AHI median (IQR) = 13.4 (11.6 -24.2)	Adherence AHI ESS FOSQ Follow up – 3 months	Mild severity OSAHS strata population (strata based on mean AHI)

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Study	Intervention and comparison	Population	Outcomes	Comments
	the mandible, up to a maximum of 9 mm. The appliance was constructed in a single laboratory, based on working models of the teeth and an inter-occlusal registration in the intercuspal position. It was fitted by an experienced orthodontist and the incremental method of advancing the mandible demonstrated. Subjects were advised to turn the screw on a weekly basis until sleep improved and symptoms resolved. N =25			
Pepin 2019[164] RCT France	Heat moulded titratable (semi-bespoke) device Thermoplastic heat-moulded titratable MAD (ONIRIS; ONIRIS SAS, Rueil Malmaison, France). Oniris is a two piece titratable thermoplastic MAD made of two stiff gutters on plaster-casts of dental arches (or in situ) coupled by two adjustable connecting rods allowing mandibular advancement to be set in steps of 1 mm and permitting	The study population consisted of adults (>18 years) with severe OSA refusing or not tolerating CPAP, without dental, periodontal or temporomandibular joint contraindications and naïve to MAD use. In line with the French Respiratory Society consensus, severe OSA was defined as an AHI≥15/hour with either severe daytime sleepiness or at least two of the following symptoms: severe nightly snoring,	AHI – change score ESS – change score SF-12 physical – change score SF-12 Mental – change score Systolic BP – change score Adherence hours per night Serious adverse events Follow up – 2 months	Moderate severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	freedom of jaw opening movements. Worn for 2 months N = 98 Custom-made Custom-made acrylic titratable MAD (TALI;ONIRIS SAS, Rueil Malmaison, France). TALI is a two-piece titratable custom-made MAD allowing one to set mandibular advancement in steps of 1 mm and allowing freedom of jaw opening movements. Worn for 2 months N= 100	gasping or choking sensations, unrefreshing sleep, fatigue and/or nocturia. Patients were recruited by private practice sleep clinics and university hospital sleep centres. Baseline AHI: TALI group = 27.1 (9.8) ONRIS group = 26.1 (11.1)		
Quinnell 2014[175] Crossover trial United Kingdom	Oral devices – SleepPro 1 (SP1) (Meditas Ltd., Winchester, UK): A thermoplastic “boil and bite“ device fitted by the patient following the manufacturers printed instructions. All patients wore the device for a period of 4 weeks with 1 week wash out periods between. SleepPro 2 (SP2 (Meditas Ltd., Winchester, UK): A semi-	Patients aged ≥18 years with mild to moderate OSAHS confirmed by respiratory polysomnography (rPSG) (AHI 5–<30/h) and symptomatic daytime sleepiness (Epworth Sleepiness Scale (ESS) score ≥9) were recruited from Papworth Hospital sleep centre. Newly diagnosed patients not requiring or declining	ESS AHI Follow up – 4 weeks	Mild severity OSAHS strata population (strata based on mean AHI)

Study	Intervention and comparison	Population	Outcomes	Comments
	bespoke device, formed from a dental impression mould made by the patient. An impression kit was posted to the patient. All patients wore the device for 4 weeks with a 1-week washout period. Bespoke Device (bMAD) (Maxillofacial Laboratory, Department of Oral and Maxillofacial Surgery, Cambridge, UK): Custom-made MAD, professionally fitted by specialists in the NHS Maxillofacial laboratory at Addenbrooke's Hospital, UK. N=90 Placebo – no treatment N= 90	CPAP and existing CPAP intolerant patients were eligible. Baseline AHI - 13.8(6.2)		

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review- Mandibular advancement splints compared to other interventions/no interventions/placebo

Table 4: Clinical evidence summary: Mandibular advancement splints compared to Placebo – Mild OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with mandibular advancement splint versus placebo (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better - boil and bite[6]	162[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, imprecision, indirectness		The mean AHI - in the boil and bite control groups was 14.6	The mean AHI - boil and bite in the intervention groups was 3.8 lower (6.88 to 0.72 lower)
Apnoea Hypopnoea Index (events/hr) Lower is better - semi-bespoke[7]	162[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean AHI - in the semi-bespoke control groups was 14.6	The mean AHI- semi-bespoke in the intervention groups was 4.9 lower (7.9 to 1.9 lower)
Apnoea Hypopnoea Index (events/hr) Lower is better custom-made[8]	162[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean AHI - in the custom-made control groups was 14.6	The mean AHI- custom-made in the intervention groups was 5.1 lower (8.03 to 2.17 lower)
EQ5D VAS score - boil and bite[6] Scale from: 0 to 100. higher is better	159[5] (1 study) 6 weeks	⨁⨁⊖⊖ LOW[1,2,5] due to risk of bias, indirectness		The mean EQ5D VAS score - in the boil and bite control groups was 74.32	The mean EQ5D VAS score - boil and bite in the intervention groups was 0.55 lower (5.9 lower to 4.8 higher)
EQ5D VAS score - semi-bespoke[7] Scale from: 0 to 100. higher is better	156[5] (1 study) 6 weeks	⨁⨁⊖⊖ LOW[1,2,5] due to risk of bias, indirectness		The mean EQ5D VAS score - in the semi-bespoke control groups was 74.32	The mean EQ5D VAS score - semi-bespoke in the intervention groups was 2.68 higher (2.31 lower to 7.67 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with mandibular advancement splint versus placebo (95% CI)
EQ5D VAS score - custom-made[8] Scale from: 0 to 100. higher is better	155[5] (1 study) 6 weeks	⨁⨁⊖⊖ LOW[1,2,5] due to risk of bias, indirectness		The mean EQ5D VAS score - in the custom-made control groups was 74.32	The mean EQ5D VAS score - custom-made in the intervention groups was 2.03 lower (7.09 lower to 3.03 higher)
SF36 vitality - boil and bite[6] Scale from: 0 to 100. higher is better	159[5] (1 study) 6 weeks	⨁⨁⊖⊖ LOW[1,2,5] due to risk of bias, indirectness		The mean SF36 vitality - in the boil and bite control groups was 42.95	The mean SF36 vitality - boil and bite in the intervention groups was 2.85 higher (4.28 lower to 9.98 higher)
SF36 vitality - semi-bespoke[7] Scale from: 0 to 100. higher is better	165[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean SF36 vitality - in the semi-bespoke control groups was 42.95	The mean SF36 vitality - semi-bespoke in the intervention groups was 8.72 higher (1.68 to 15.76 higher)
SF36 vitality - custom-made[8] Scale from: 0 to 100. higher is better	155[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean SF36 vitality - in the custom-made control groups was 42.95	The mean SF36 vitality - custom-made in the intervention groups was 11.08 higher (3.95 to 18.21 higher)
ESS (Epworth) - boil and bite[6] Scale from: 0 to 24. Lower is better	166[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean ESS - in the boil and bite control groups was 10.1	The mean ESS - boil and bite in the intervention groups was 1.6 lower (2.86 to 0.34 lower)
ESS (Epworth) - semi-bespoke[7] Scale from: 0 to 24. Lower is better	166[5] (1 study) 6 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean ESS - in the semi-bespoke control groups was 10.1	The mean ESS - semi-bespoke in the intervention groups was 2.1 lower (3.38 to 0.82 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with mandibular advancement splint versus placebo (95% CI)
ESS (Epworth) - custom-made[8] Scale from: 0 to 24. Lower is better	166[5] (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision		The mean ESS - in the custom-made control groups was 10.1	The mean ESS - custom-made in the intervention groups was 2.4 lower (3.63 to 1.17 lower)
Adverse events minor - boil and bite[6,9]	81[5] (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2,5] due to risk of bias, indirectness	RR 1.56 (1.27 to 1.91)	Moderate	
				577 per 1000	323 more per 1000 (from 156 more to 525 more)
Adverse events minor - semi-bespoke[7,9]	87[5] (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3,5] due to risk of bias, indirectness, imprecision	RR 1.51 (1.23 to 1.86)	Moderate	
				577 per 1000	294 more per 1000 (from 133 more to 496 more)
Adverse events minor - custom-made[8,9]	77[5] (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2,5] due to risk of bias, indirectness	RR 1.71 (1.41 to 2.07)	Moderate	
				577 per 1000	410 more per 1000 (from 237 more to 617 more)
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 or 2 increments because: The majority of the evidence included an indirect population of mild to moderate severity patients based on the AHI of included population (downgrade by one increment) or a very indirect population (downgrade by two increments)

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs EQ5D VAS – 10, ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.

5 Results for each MAD comparison are presented in separate analysis to avoid double counting the control arm due to the cross over design of the study.

6 A thermoplastic 'boil and bite' device fitted by the patient. Can be self-customised by remoulding.

7 A semi-bespoke device formed from a dental impression mould self-fitted by the patient. Can involve re-fitting with the assistance of a dentist when necessary

8 A custom-made mandibular advancement device professionally fitted by specialists.

9 minor adverse events included; dryness/bad taste/numbness, discomfort/ mouth problems, excessive salivation, cold related, infection.

Table 5: Clinical evidence summary: Mandibular advancement splint compared to Placebo – Moderate OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with- mandibular advancement splint versus placebo (95% CI)
Apnoea Hypopnoea Index (events/hr) Lower is better – final value	786 (8 studies) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean AHI in the placebo group was 21.03	The mean AHI in the oral device group was 9.57 lower (11.09 to 8.05 lower)
Apnoea Hypopnoea Index (events/hr) Lower is better – change score	38 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean AHI change score in the placebo group was 5.2	The mean AHI change score in the oral device group was 11.10 higher (4.57 to 17.63 lower)
ESS (Epworth) Scale from: 0 to 24. Lower is better.	586 (5 studies) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean ESS in the placebo groups was 9.62	The mean ESS in the oral device group was -1.08 lower (-1.83 to -0.32 lower)
ODI Lower is better	160 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean ODI in the placebo groups was 25.2	The mean ODI in the oral device groups was 1.4 lower (4.59 lower to 1.79 higher)
FOSQ (mean score) Scale from: 5 to 20. higher is better	251 (2 studies) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,4] due to risk of bias, , indirectness,		The mean FOSQ (mean score) in the placebo groups was 9.85	The mean FOSQ (mean score) in the oral device groups was 0.45 higher (0.69 lower to 1.60 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with- mandibular advancement splint versus placebo (95% CI)
		Inconsistency			
SF36 mental Scale from: 0 to 100. higher is better	158 (2 studies) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean sf36 mental in the placebo groups was 73.35	The mean sf36 mental in the oral device groups was 1.38 higher (3.53 lower to 6.29 higher)
SF36 Physical Scale from: 0 to 100. higher is better	158 (2 studies) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean sf36 physical in the placebo groups was 82.8	The mean sf36 physical in the oral device groups was 5.17 higher (0.57 to 9.77 higher)
Adherence hours per night	199 (2 studies) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean adherence hours per night in the placebo groups was 6.55	The mean adherence hours per night in the oral device groups was 0.07 lower (0.34 lower to 0.19 higher)
Systolic blood pressure	559 (6 studies) 6 months	⨁⨁⨀⨀ LOW[1,2,5] due to risk of bias, indirectness		The mean systolic blood pressure in the placebo groups was 126.8	The mean systolic blood pressure in the oral device groups was 2.27 lower (4.09 lower to 0.46 higher)
SAQLI Scale from: 1-7. higher is better	67 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean SAQLI in the placebo groups was 5	The mean SAQLI in the oral device groups was 0.5 higher (0.22 to 0.78 higher)
Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting[7]	39 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3]		The mean neurocognitive outcomes (scl-90-r) insufficiency of thinking and acting in the placebo groups was 16.3	The mean neurocognitive outcomes (scl-90-r) insufficiency of thinking and acting in the oral

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with- mandibular advancement splint versus placebo (95% CI)
		due to risk of bias, indirectness, imprecision			device groups was 0.5 lower (4.92 lower to 3.92 higher)
Adverse events-side effects (i.e. pain, hypersalivation, dryness, damage to dental restorations)	77 (1 study) 6 months	⨁⨁⨀⨀ MODERATE[2] due to indirectness	RR 1.06 (0.91 to 1.24)	868 per 1000	52 more per 1000 (from 78 more to 208 more)
TMD (Temporomandibular disorder) pain	39 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness	Not estimable[6]	-	-
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)-1 hour; MID for Systolic and Diastolic BP – 5 mm hg Established MIDs for SF-36 physical/mental- 2/3; FOSQ- 2; ESS -2.5; SAQLI – 2. GRADE default MID (0.5XSD) used for all other continuous outcomes.

4 Downgraded by 1 or 2 increments for heterogeneity, unexplained by subgroup analysis. Random effects analysis used

5 Systolic BP values differed at baseline for Andren 2013 (mean oral device basal value = 143.6 (8.8), placebo = 145.4 (9.4))

6 No events reported in both arms

7 For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information

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Table 6: Clinical evidence summary: Mandibular advancement splint compared to CPAP – Moderate OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP/APAP	Risk difference with mandibular advancement splint versus placebo (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr)-final value Lower is better	670 (8 studies) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean AHI in the CPAP group was 3.48	The mean AHI in the oral device group was 8.07 higher (6.69 to 9.45 higher)
Apnoea Hypopnoea Index (AHI) (events/hr)- change scoreLower is better	38 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean AHI change score in the CPAP group was 19.5	The mean AHI change score in the oral device group was 3.20 lower (9.24 to 9.55 lower)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better (12 months after intervention)	33 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean AHI (12 months after intervention) in the CPAP group was 19.6	The mean AHI (12 months after intervention) in the oral device group was 4 lower (11.11 lower to 3.11 higher)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better (18 months after intervention)	28 (1 study) 18 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean AHI (18 months after intervention) in the CPAP was 20.2	The mean AHI (18 months after intervention) in the oral device group was 5.2 lower (12.28 lower to 1.88 higher)
FOSQ (mean score) Scale from: 5-20 higher is better	376 (2 studies) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean FOSQ (mean score) in the CPAP group was 10.3	The mean FOSQ (mean score) in the oral device was 0.06 lower (0.25 lower to 0.25 higher)
SF36 Mental Scale from: 0 to 100. higher is better	302 (3	⨁⨀⨀⨀ VERY LOW[1,2,3]		The mean SF36 mental in the CPAP group was 71	The mean SF36 mental in the oral device group was 1.6 higher (2.14 lower to 5.33 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP/APAP	Risk difference with mandibular advancement splint versus placebo (95% CI)
	studies) 6 months	due to risk of bias, indirectness, imprecision			
SF36 Physical Scale from: 0 to 100. higher is better	302 (3 studies) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF36 physical in the CPAP group was 86.66	The mean sf36 physical in the oral device group was 0.08 lower (3.58 lower to 3.43 higher)
SF-36 Vitality Scale from: 0 to 100. higher is better	66 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,23] due to risk of bias and imprecision		The mean SF36 Vitality in the CPAP group was 60.7	The mean SF36 Vitality in the oral device group was 1.4 lower (12.81 lower to 10.01 higher)
EQ5D Scale from: 0 to 100. higher is better	66 (1 study) 12 months	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean EQ5D in the CPAP group was 74.4	The mean EQ5D in the oral device group was 3.3 higher (3.39 lower to 9.99 higher)
Systolic BP	388 (4 studies) 6 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, indirectness		The mean systolic BP in the CPAP group was 123.0	The mean systolic BP in the oral device group was 0.17 lower (2.45 lower to 2.11 higher)
ODI Lower is better	536 (4 studies) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3,4] due to risk of bias, indirectness, imprecision, inconsistency		The mean ODI in the CPAP group was 4.275	The mean ODI in the oral device group was 4.89 higher (2.68 to 7.09 higher)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP/APAP	Risk difference with mandibular advancement splint versus placebo (95% CI)
ESS (Epworth) Scale from: 0 to 24.Lower is better.	630 (8 studies) 6 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, indirectness		The mean ESS in the CPAP group was 6.71	The mean ESS in the oral device group was 0.04 lower (0.63 lower to 0.55 higher)
ESS (Epworth) 12 months Scale from: 0 to 24.Lower is better.	66 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias and imprecision		The mean ESS at 12 months in the CPAP group was 5.3	The mean ESS at 12 months in the oral device group was 1.8 lower (0.47 to 4.07 lower)
Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting[6]	38 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean neurocognitive outcomes (scl-90-r) insufficiency of thinking and acting in the CPAP group was 17.7	The mean neurocognitive outcomes (scl-90-r) insufficiency of thinking and acting in the oral device group was 1.9 lower (7.15 lower to 3.35 higher)
Preference number of patients (Barnes and Ferguson worked out from % of patients)	464 (4 studies) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3,4] due to risk of bias, inconsistency, indirectness, imprecision	RR 1.52 (0.77 to 3.00)	335 per 1000	174 more per 1000 (from 77 fewer to 670 more)
Adverse effects – mild Dichotomous[5]	80 (2 studies) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.39 (0.92 to 2.11)	450 per 1000	195 more per 1000 (from 40 fewer to 555 more)
Adherence hours per night (self-reported for oral devices)	468 (4	⨁⊖⊖⊖ VERY LOW[1,2,,4]		The mean adherence hours per night (self-reported for oral	The mean adherence hours per night (self-reported for oral

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP/APAP	Risk difference with mandibular advancement splint versus placebo (95% CI)
	studies) 6 months	due to risk of bias, inconsistency, indirectness		devices) in the control groups was 4.825	devices) in the intervention groups was 1.63 higher (1.35 to 1.89 higher)
Adherence hours per night (objective)	80 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean adherence hours per night (objective) in the control groups was 4.745	The mean adherence hours per night (objective) in the intervention groups was 0.50 higher (0.36 lower to 1.37 higher)
Adherence rate of use >4h per night % Scale from: 0 to 100.	80 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean adherence rate of use >4h per night % in the CPAP group was 62.7	The mean adherence rate of use >4h per night % in the oral device group was 8.1 higher (4.33 lower to 20.53 higher)
TMD (Temporomandibular disorder) pain	38 (1 study) 6 moths	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	Peto OR 0.11 (0.01 to 1.9)	105 per 1000	94 fewer per 1000 (from 104 fewer to 95 more
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)- 1 hour; MID for Systolic and Diastolic BP – 5 mm hg; Established MIDs for SF-36 physical/mental- 2/3; FOSQ-

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CPAP/APAP	Risk difference with mandibular advancement splint versus placebo (95% CI)

2 EQ5D VAS – 10; ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.
4 Downgraded by 1 or 2 increments for heterogeneity, unexplained by subgroup analysis (ESS and BMI). Random effects analysis used.
5 Adverse effects: Randerath 2002 study reported feeling of pressure in the mouth and on the face and early morning discomfort in the mouth and TMJ. Fergusson 1996 and 1997 study reported nasal congestion, sore teeth and jaw, excessive salivation, rhinorrhoea, eye irritation and a sense of suffocation.
6 For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information

Table 7: Clinical evidence summary: Mandibular advancement splints compared to surgery - Uvulopalatopharyngoplasty (UPPP) Moderate OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with mandibular advancement splint versus surgery (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better	84 (1 study) 6 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean AHI in the surgery groups was 11.7	The mean AHI in the oral device groups was 0.4 lower (1.55 lower to 0.75 higher)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better 12 months	80 (1 study) 12 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean AHI 12 months in the surgery groups was 10	The mean AHI 12 months in the oral device groups was 2.4 higher (0.89 to 3.91 higher)
ODI Lower is better	84 (1 study) 6 months	⨁⨁⨁⨀ MODERATE[1] due to risk of bias		The mean ODI in the surgery groups was 10.4	The mean ODI in the oral device groups was 0.2 lower (1.44 lower to 1.04 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Surgery	Risk difference with mandibular advancement splint versus surgery (95% CI)
ODI - 12 months Lower is better	80 (1 study) 12 months	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision		The mean ODI- 12 months in the surgery groups was 9.1	The mean ODI - 12 months in the oral device groups was 1.8 higher (0.21 to 3.39 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. GRADE default MID (0.5XSD) for all other continuous outcomes.

1.4.5 Quality assessment of clinical studies included in the evidence review- Mandibular advancement splints compared to each other

Table 8: Clinical evidence summary: Boil and bite/ready-made compared to custom-made – Mild OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Custom-made	Risk difference with Boil and bite versus custom-made (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better	81 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness,		The mean AHI in the control groups was 9.5	The mean AHI in the intervention groups was 1.3 higher (1.46 lower to 4.06 higher)
ESS Scale from: 0 to 24. Lower is better.	83 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean ESS in the control groups was 7.7	The mean ESS in the intervention groups was 0.8 higher (0.39 lower to 1.99 higher)
EQ5D - utility score	158 (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3]		The mean EQ5D- utility score in the control groups was 0.87	The mean EQ5D- utility score in the boil and bite groups was

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Custom-made	Risk difference with Boil and bite versus custom-made (95% CI)
Scale from 0-1. higher is better		due to risk of bias, indirectness, imprecision			0.01 lower (0.07 lower to 0.05 higher)
EQ5D – VAS Scale from 0-100. higher is better	158 (1 study) 6 weeks	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean EQ5D- VAS in the control groups was 77.29	The mean EQ5D- VAS in the boil and bite groups was 3.52 lower (8.58 lower to 1.54 higher)
SF-36 vitality scale from 0-100. higher is better	158 (1 study) 6 weeks	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF36 vitality in the control groups was 54.03	The mean SF36 vitality in the boil and bite groups was 8.23 lower (14.98 to 1.48 lower)
Minor adverse events	158 (1 study) 6 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, indirectness	RR 0.91 (0.85 to 0.99)	987 per 1000	89 fewer per 1000 (from 10 fewer to 148 fewer)
Preference	50 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness	RR 0.04 (00.1 to 0.28)	960 per 1000	922 fewer per 1000 (from 691 fewer to 864 fewer)
ODI Lower is better	50 (1 study) 3 months	⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean ODI in the control groups was 2.9	The mean ODI in the intervention groups was 2.7 higher (0.07 lower to 5.47 higher)
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for EQ5D – 0.03; EQ5D VAS – 10; ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.

Table 9:Clinical evidence summary: Boil and bite/ready-made compared to semi-bespoke – Mild OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Semi-bespoke	Risk difference with Boil and bite versus semi-bespoke (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better	81 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean AHI in the control groups was 9.7	The mean AHI in the intervention groups was 1.1 higher (1.73 lower to 3.93 higher)
ESS Scale from: 0 to 24. Lower is better.	83 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean ESS in the control groups was 8	The mean ESS in the intervention groups was 0.5 higher (0.73 lower to 1.73 higher)
EQ5D- utility score Scale from 0-1. higher is better	168 (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, indirectness, imprecision		The mean EQ5D- utility score in the control groups was 0.86	The mean EQ5D- - utility score in the intervention groups was 0 higher (0.07 lower to 0.07 higher)
EQ5D – VAS Scale from 0-100. higher is better	168 (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, indirectness, imprecision		The mean EQ5D-VASin the control groups was 77	The mean EQ5D- VAS in the intervention groups was 3.23 lower (8.11 lower to 1.65 higher)
SF-36 Vitality Scale from 0-100. higher is better	168 (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean sf-36 vitality in the control groups was 51.67	The mean sf-36 vitality in the intervention groups was 5.87 lower (12.53 lower to 0.79 higher)
Minor adverse events	159 (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness	RR 1.03 (0.92 to 1.16)	872 per 1000	26 more per 1000 (from 70 fewer to 140 more)
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Semi-bespoke	Risk difference with Boil and bite versus semi-bespoke (95% CI)
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for EQ5D – 0.03; EQ5D VAS – 10; ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.					

Table 10: Clinical evidence summary: semi-bespoke compared to custom-made – Mild OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with custom-made	Risk difference with Semi-bespoke versus custom-made (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better	81 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean AHI in the control groups was 9.5	The mean AHI in the intervention groups was 0.2 higher (2.47 lower to 2.87 higher)
ESS Scale from 0-24. Lower is better	83 (1 study) 1 month	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean ESS in the control groups was 7.7	The mean ESS in the intervention groups was 0.3 higher (0.9 lower to 1.5 higher)
EQ5D - utility score Higher is better Scale from 0-1. higher is better	164 (1 study) 6 weeks	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean EQ5D- utility score in the control groups was 0.87	The mean EQ5D- utility score in the semi-bespoke groups was 0.01 lower (0.07 lower to 0.05 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with custom-made	Risk difference with Semi-bespoke versus custom-made (95% CI)
EQ5D- VAS Scale from 0-100. higher is better	164 (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness,		The mean EQ5D- VAS in the control groups was 77.29	The mean EQ5D- VAS in the semi-bespoke groups was 0.29 lower (4.85 lower to 4.27 higher)
SF-36 Vitality Scale from 0-100. higher is better	164 (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness		The mean SF36 vitality in the control groups was 54.03	The mean SF36 vitality in the semi-bespoke groups was 2.36 lower (9.02 lower to 4.3 higher)
Minor adverse events	155 (1 study) 6 weeks	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, indirectness	RR 0.88 (0.81 to 0.97)	987 per 1000	118 fewer per 1000 (from 30 fewer to 188 more)
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs; EQ5D – 0.03; EQ5D VAS- 10; ESS -2.5GRADE default MID (0.5XSD) used for all other continuous outcomes.

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Table 11: Clinical evidence summary: heat moulded semi-bespoke compared to custom-made – Moderate OSAHS

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Custom-made	Risk difference with Heat moulded (semi-bespoke) versus custom-made (95% CI)
Apnoea Hypopnoea Index (AHI) (events/hr) Lower is better – change score	156 (1 study) 2 months	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, indirectness		The mean AHI in the control groups was -11.16	The mean AHI in the heat moulded group was 0.74 lower (3.92 lower to 2.44 higher)
ESS – change score Lower is better	182 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness		The mean ESS in the control groups was -3.34	The mean ESS in the heat moulded groups was 0.42 lower (1.58 lower to 0.74 higher)
SF-12 Mental change score higher is better	141 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF-12 mental score in the control groups was 5.27	The mean SF-12 mental score in the heat moulded groups was 3.8 higher (2.81 lower to 10.41 higher)
SF-12 physical change score higher is better	141 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF-12 physical score in the control groups was 4.22	The mean SF-12 physical score in the heat moulded groups was 3.49 higher (1.12 lower to 8.1 higher)
Systolic BP – change score	43 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean systolic BP in the control groups was -11.19	The mean systolic BP change score in the heat moulded groups was 6.83 higher (3.5 lower to 17.16 higher)
Adherence - hours per night	156 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean adherence - hours per night in the control groups was 6.8 hours	The mean adherence - hours per night in the heat moulded groups was 0.7 lower (1.12 to 0.28 lower)
Serious adverse events	156 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2,4]	RR 0 (-0.03 to 0.03)	Moderate	
					No events

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Custom-made	Risk difference with Heat moulded (semi-bespoke) versus custom-made (95% CI)
		due to risk of bias, indirectness, imprecision			0 more per 1000 (from 30 fewer to 30 more) No difference
Mortality	No outcome reported				

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MID for systolic BP – 5mmhg. Established MIDs for SF-36 physical/mental- 2/3; ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.

4 Risk Difference analysis used as there were 0 events. Impression was calculated as follows - No imprecision (sample size >350), Serious imprecision (sample size >70<350), Very serious imprecision(sample size <70)

Narrative results:

Data has been presented narratively for studies where the data could not be analysed in GRADE (data were presented as median (IQR) or as a mean without SD). Narrative data was considered alongside the GRADE evidence by the committee when making recommendations. The overall study quality was taken into account as GRADE analysis for each outcome could not be performed.

Mandibular advancement splint versus placebo – Moderate OSAHS

ESS (0-24, higher is worse) (very low quality)

Marklund 2015 reported a lower final ESS score in the mandibular advancement splint group (n=45) compared to the placebo group (n=46) (median (IQR) 6 (5-11) vs 9 (5-12)).

Mandibular advancement splints versus CPAP – Moderate OSAHS

AHI (very low quality)

De Vries 2019 reported a greater AHI reduction at 12 months with CPAP treatment (n=30) compared to treatment with mandibular advancement splint (n=24) (median (IQR) 0.8 (0.4-2.7) vs 5.9 (3.5-17.8)) in 54 participants.

Objective adherence (hours per night worn) (very low quality)

De Vries 2019 reported similar rates of adherence with both CPAP treatment (n=14) and mandibular advancement splint treatment (n=21) (median (IQR) 6.8 (5.2-7.6) vs 6.9 (3.5-7.9).

Objective adherence (>4h/night all nights %) (very low quality)

De Vries 2019 reported a greater % of patients using their CPAP device for over 4 hours per night than patients wearing their mandibular advancement splint for over 4 hours per night. (Median (IQR) 96.8 (68.4-100) n=21 vs 88.7 (52.2-100) n=14).

Ready-made versus custom-made – Mild OSAHS

AHI (very low quality)

Johal 2017 reported a greater AHI reduction at 3 months in the custom-made mandibular advancement splint group when compared to the ready-made mandibular advancement splint group (median (IQR) 4 (1-9.9) n=25 vs 9.6 (4.8-17.8) n=25).

FOSQ score (higher is better) (very low quality)

Johal 2017 reported a greater final FOSQ score in the custom-made group when compared to the ready-made group after 3 months of treatment (median (IQR) 104 (85.5-112.0) n=25 vs 96 (90.5-108.5) n=25).

ESS (Higher is worse) (very low quality)

Johal 2017reported lower ESS score in the custom-made group compared to the ready-made group after 3 months of treatment (median (IQR) 5 (3-8) n=25 vs 7 (4.5-11.5) n=25).

Adherence nights worn per week (very low quality)

Johal 2017 reported greater adherence in the number of nights per week worn with the custom-made mandibular advancement splint; compared to the ready-made mandibular advancement splint (median (IQR) 7 (5-7) n=25 vs 3 (0-6.5) n=25).

Adherence hours worn per night (very low quality)

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Johal 2017reported greater adherence with the custom-made mandibular advancement splint compared to the ready-made mandibular advancement splint in the number of hours the device was worn each night (median (IQR) 5 (3-7) n=25 vs 3 (0-6) n=25).

See Appendix F: for full GRADE tables.

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1.5 Economic evidence

1.5.1 Included studies

Four economic evaluations published in five papers were included in this review.[43, 139, 175, 194, 223] These are summarised in the health economic evidence profiles below (1.5.3) and the health economic evidence tables in Appendix H.

One of the studies was the published write up of the NICE technology assessment report for TA139.[139, 223]

1.5.2 Excluded studies

One economic study relating to this review question was identified but excluded due to limited applicability.[102] The study is listed in Appendix I with reason for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.5.3 Summary of studies included in the economic evidence review

Table 12: Health economic evidence profile: Conservative Management (1) versus Dental Devices (2)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Sharples 2014[194](UK)	Directly applicable [(a)]	Minor limitations [(b)]	• Probabilistic model based on meta-analysis of RCTs • Population: Adults diagnosed with mild or moderate OSA • Comparators: Conservative management, oral devices (semi-bespoke), CPAP • Time horizon: Lifetime	2−1[(c)]: £1,906	2−1: 0.285	2 vs 1: £6,687 per QALY gained	Results were not sensitive for this comparison
Weatherly 2009[139, 223] (UK)	Directly applicable [(d)]	Potentially serious limitation [(e)]	• Probabilistic model based on meta-analysis of RCTs • Population: Adults diagnosed with OSA • Comparators: Conservative management, oral devices, CPAP • Time horizon: Lifetime	2−1 [(f)]: £657	2−1: 0.33	2 vs 1: £2,000 per QALY gained	Probability Intervention 2 cost effective (£20K/30K threshold): 20%/17%

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) UK NHS perspective

(b) Authors have modelled cardiovascular risk using the Framingham risk calculator rather than the QRISK3 and also assume the entire model cohort drives.

(c) 2011 UK pounds

(d) UK NHS perspective

(e) A limitation of the study is that it determines severity of OSA according to the Epworth Sleepiness Score as opposed to the number of AHI events/hour therefore the estimate for the clinical effectiveness of CPAP may not be appropriate. Also the authors have modelled cardiovascular risk using the Framingham risk calculator rather than the QRISK3.

(f) 2005 UK pounds

Table 13: Health economic evidence profile: Dental devices (1) versus CPAP (2)

Study	Applicability	Limitations	Other comments	Costs	Health Outcomes	Cost effectiveness	Uncertainty
De Vries 2019[38] Netherlands	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Within-trial analysis (randomised crossover) • Population: Adults diagnosed OSA with an AHI of 15 to 30 events/h based on PSG (primarily of the obstructive type) • Comparator: MAD • Time horizon: 12 months	2-1: -£2,155[(c)]	2-1: -0.028	1 vs 2: [(d)] £77,725 per QALY gained	
Sharples 2014[194](UK)	Directly applicable [(e)]	Minor limitations [(f)]	• Probabilistic model based on meta-analysis of RCTs • Population: Adults diagnosed with mild or moderate OSA • Comparators: Conservative management, oral devices (semi-bespoke), CPAP Time horizon: Lifetime	2−1: £285[(g)]	2−1: 0.019	2 vs 1: £15,367 per QALY gained	Probability Intervention 2 cost effective (£20K/30K threshold): 52%/55% Results were sensitive to cost but not to treatment effects
Weatherly 2009[139, 223] (UK)	Directly applicable [(h)]	Potentially serious limitation [(i)]	• Probabilistic model based on meta-analysis of RCTs • Population: Adults diagnosed with OSA • Comparators: Conservative management, oral devices, CPAP • Time horizon: Lifetime	2−1: £504[(j)]	2−1: 0.13	2 vs 1: £3,899 per QALY gained	Above a willingness to pay of £20,000, intervention 3 had a probability of being cost-effective in excess of 95% compared with no-treatment.

(a) Netherlands perspective
(b) Short follow-up period, costs not obtained from UK sources, based on one trial.
(c) 2015 UK pounds, direct costs only
(d) NGC re-calculated ICER with direct medical costs only included
(e) UK NHS perspective
(f) Authors have modelled cardiovascular risk using the Framingham risk calculator rather than the QRISK3 and also assume the entire model cohort drives.
(g) 2011 UK pounds
(h) UK NHS perspective

(i) A limitation of the study is that it determines severity of OSA according to the Epworth Sleepiness Score as opposed to the number of AHI events/hour therefore the estimate for the clinical effectiveness of CPAP may not be appropriate. Also the authors have modelled cardiovascular risk using the Framingham risk calculator rather than the QRISK3.
(j) 2005 UK pounds

Table 14: Health economic evidence profile: No treatment (1) versus thermoplastic dental device (2) versus semi-bespoke dental device (3) versus bespoke dental devices (4)

Study	Applicability	Limitations	Other comments	Costs	Health Outcomes	Cost effectiveness	Uncertainty
Quinnell 2014[175] (UK)	Directly applicable [(a)]	Potentially serious limitations [(b)]	• Within trial analysis (randomised crossover trial – associated clinical paper • Population: Adults diagnosed with mild or moderate OSA • Comparators: No treatment; thermoplastic dental device; semi-bespoke dental device; bespoke dental device • Time horizon: 4 weeks	Intervention 1: £78.50 Intervention 2: £74.64 Intervention 3: £63.43 Intervention 4: £104.89	QALYs Intervention 1: 0.0649 Intervention 2: 0.0658 Intervention 3: 0.0658 Intervention 4: 0.0667	4 vs 3: £46,067 Intervention 1: Dominated by intervention 3 Intervention 2: Dominated by intervention 3	Above a willingness to pay of £20,000, intervention 3 had a probability of being cost-effective in excess of 95% compared with no-treatment.

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years
(a) UK NHS perspective
(b) The main limitation was that the trial duration was too brief (4 weeks) and therefore it is unclear whether the treatment benefits or resource uptake would be an appropriate proxy for what would occur over a lifetime horizon.
(c) 2011 UK pounds

1.5.4 Health economic modelling

This analysis was conducted as a sub-analysis of the main guideline model, which covered the diagnostic and treatment pathway for symptomatic people suspected of having OSAHS (See 'Economic analysis report' for full details).

1.5.4.1 Population and strategies evaluated

The modelled population were people with symptomatic mild OSAHS. By focusing on mild OSAHS we were able to compare oral devices with CPAP - CPAP for moderate and severe OSAHS was outside the scope of this guideline. The following treatment strategies were compared:

- Conservative management (Lifestyle advice)
- 'Boil and bite' mandibular advancement splint (MAS) and lifestyle advice
- Semi-bespoke MAS and lifestyle advice
- Custom-made MAS and lifestyle advice
- CPAP and lifestyle advice

1.5.4.2 Methods and data sources (Summary)

Treatment effects

- Each treatment was assumed to have an immediate impact on quality of life (measured in terms of EQ-5D). These were estimated from randomised trials comparing each intervention with conservative management.
- For CPAP, the difference in ESS change was pooled across all the trials of CPAP in mild OSAHS, giving a reduction of 2.87 compared with conservative management. This was mapped to an EQ-5D improvement of 0.028 using a published mapping equation. This was extrapolated for the whole treatment period.
- For the base case, the improvement in EQ-5D was 0.012, 0.011 and 0.023 for Boil and bite, semi-bespoke and custom-made MAS respectively. These were from the TOMADO trial in mild and moderate OSAHS. These were recorded at 4 weeks in the trial but were extrapolated for the duration of treatment. In an alternative scenario the EQ-5D improvement was calculated by mapping from the trial ESS: 0.015, 0.021 and 0.023 for Boil and bite, semi-bespoke and custom-made MAS respectively.
- Compared with conservative management, all of the treatments were assumed to have the same impact on the incidence of road traffic accidents. A proportion of the accidents are fatal, and so accidents are associated with reduced length of life. Non-fatal accidents are associated with reduced quality of life.
- For treated patients, the risk of an RTA was assumed to be the same as the general population. The treatment effect was OR=0.169, which was derived from TA139
- Although cardiovascular events are included in the model, for this mild OSAHS population we assumed that treatment had no impact.
- The rate at which people drop out from using CPAP was differentiated by time and by OSAHS severity. This was taken from a published cohort study. In the absence of additional evidence, the same dropout was assumed for mandibular advancement splints.
- The baseline probability of both cardiovascular events and RTAs were for men aged 50 at the commencement of treatment. The former was estimated using QRISK3 and the latter were from Department of Transport statistics.

CPAP costs

- The cost of fixed-pressure CPAP devices and consumables were extracted from the NHS Supply Chain catalogue.[151] The unweighted mean of different devices was used in the model base case - £206 (excluding VAT). The device costs were annuitized using a discount rate of 3.5% and assuming the equipment is replaced after 7 years.
- In addition to the device the following costs were included:
    - Telemonitoring costs for the first year ResMed (£45).
    - Consumables (£101 per year, excluding VAT)
    - Education and set up was costed as a respiratory consultant-led outpatient consultation (NHS Reference cost £146)
    - 3 month and then annual follow-up was a non-consultant-led outpatient consultation. (NHS Reference cost £120)
    - It was assumed that 18% of patients using fixed-CPAP would require re-titration (£16)

Oral device costs

- The unweighted average cost of 'boil and bite', semi-bespoke and custom-made mandibular advancement splints were £33, £118 and £296 respectively (excluding VAT). The source was publicly available prices for commonly used devices and expert opinion from the committee. The durability of these devices in the base case was assumed to be 4 months, 14 months, and 2 years respectively. Longer durability was assumed in sensitivity analyses.
- For boil and bite and semi-bespoke a respiratory outpatient appointment was assumed for education and set up and for 3 month and annual follow-up (NHS Reference cost £146). For custom-made devices this was done by a dentist (NHS Reference cost £113)

Other costs and effects

- The cost of treating RTAs was taken from Department of Transport data.
- The cost of treatment, standardised mortality ratios and utility (quality of life) lost associated with cardiovascular events were taken from various sources.

Computations

The key outcomes were mean NHS cost per patient and mean QALYs per patient. These were calculated using a state-transition (Markov) model structure. Costs and QALYs occurring in the future were discounted at 3.5% per year to be consistent with the NICE reference case. The results were calculated both:

- Deterministically, based on the point estimates of each input parameter.
- Probabilistically, based on a distribution for each input parameter (estimated using its standard error) and sampling the results 10,000 times before calculating a mean (Monte Carlo simulation.

1.5.4.3 Results

The base case results can be found in Table 15, Table 16 and Figure 1. The lowest cost strategy was conservative management followed by boil and bite MAS and the most costly was bespoke MAS. The quality of life treatment effect was greatest for CPAP and therefore CPAP had the most QALYs. At a threshold of £20,000 per QALY, CPAP was the most cost-effective treatment for mild OSAHS followed by custom-made MAS.

Table 15: Base case results – costs (deterministic)

Cost	Conservative management	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Intervention	146	3,130	3,188	3,617	3,355
Road traffic accidents	723	292	292	292	292
Cardiovascular events	6,024	6,037	6,037	6,037	6,037
Total	6,892	9,459	9,517	9,946	9,684

Table 16: Base case results - cost-effectiveness (probabilistic)

	Conservative management	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Costs	6,895	9,462	9,520	9,949	9,687
QALYs	13.35	13.53	13.52	13.66	13.72
Cost per QALY gained (vs conservative management)		14,127	15,537	9,985	7,665
Incremental net monetary benefit (INMB)*	0	1,067	754	3,064	4,493
Median Rank of INMB (95% confidence interval)*	4 (2, 5)	4 (1-5)	4 (1-5)	2 (1-5)	1 (1-4)
Probability highest rank*	0%	11%	11%	27%	51%

* INMB measured compared to conservative management and using a value of £20,000 per QALY gained

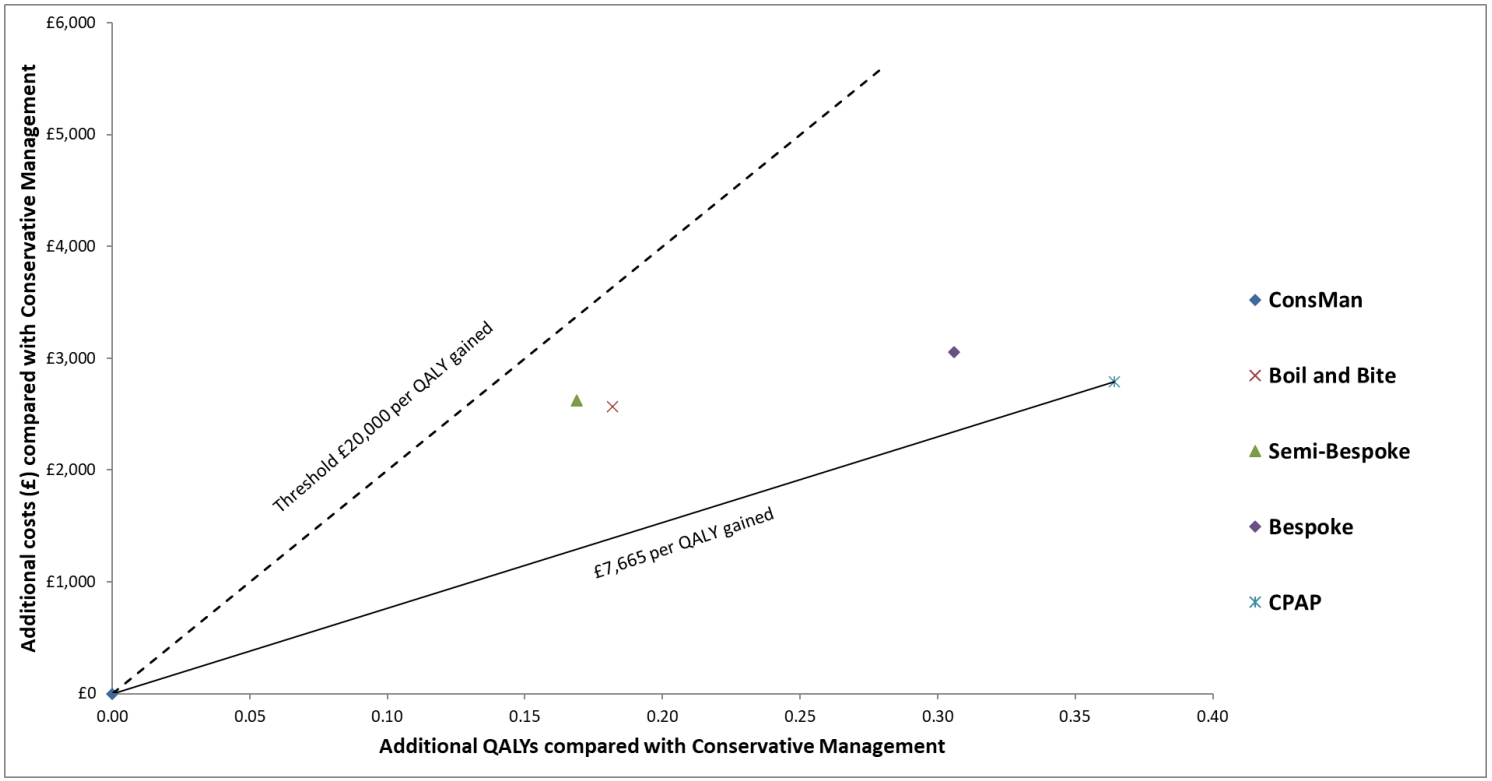

Figure 1: Cost effectiveness results - base case (probabilistic)

Compared to conservative management the cost per QALY gained varied between £6,500 and £15,300 for CPAP and between £5,100and £12,800 for custom-made MAS -Table 17. The ranking of treatments was quite stable across the analyses (Table 18). The only scenarios where CPAP was not the most cost-effective intervention was when all the assumptions least favourable to CPAP were used in combination. Custom-made MAS was cost-effective compared with semi-bespoke MAS although when the quality of life gain was estimated by mapping from the improvements in ESS seen in the trials the mean monetary net benefit was almost identical - Figure 2. Semi-bespoke MAS was more cost-effective than CPAP when this assumption was made in combination with assuming greater durability and improvement adherence.

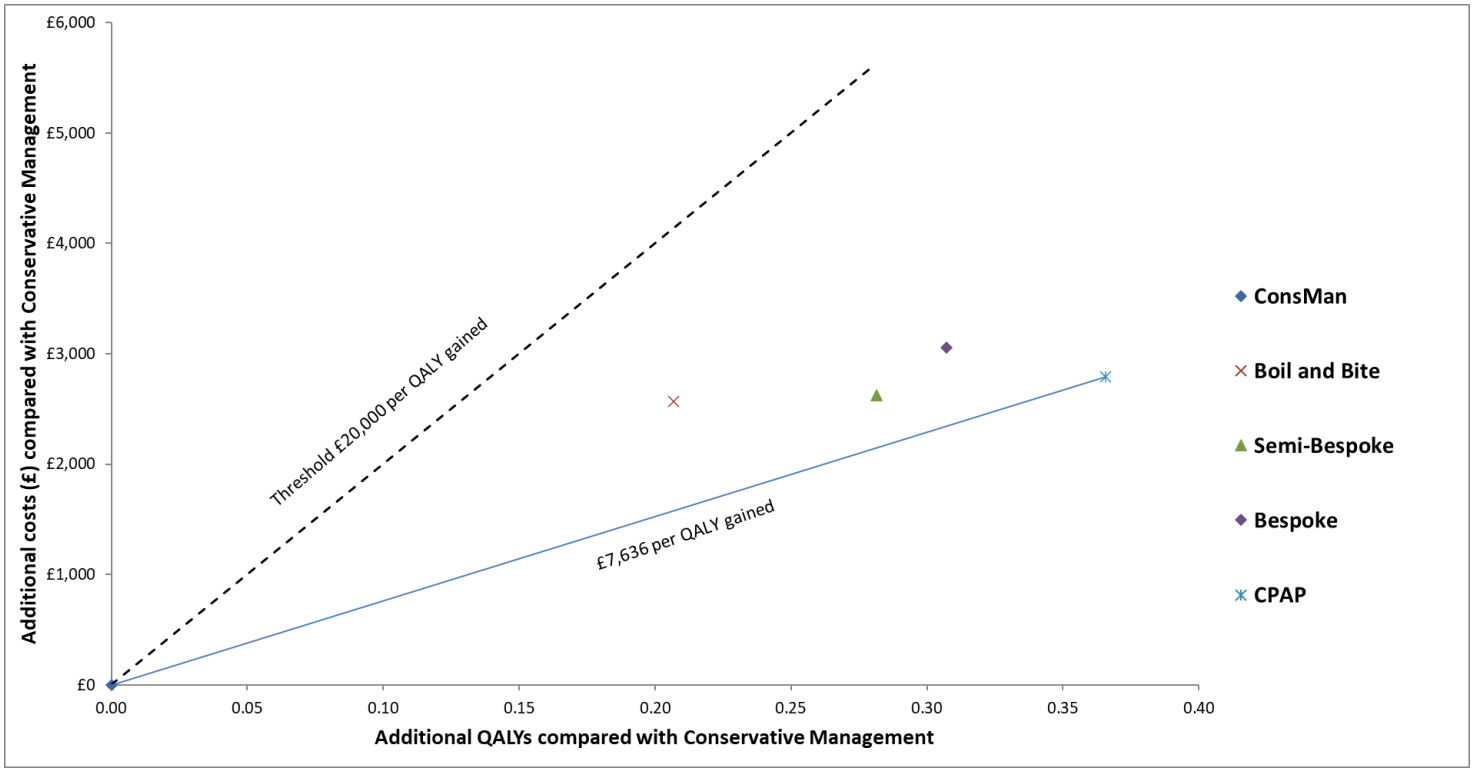

Figure 2: Cost effectiveness results when EQ-5D was mapped from ESS

Table 17: Sensitivity analysis - cost per QALY gained compared with conservative management (deterministic)

Analysis	Cost per QALY gained (versus Conservative Management)			
	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Base case results	14,452	15,601	9,932	7,636
CPAP more cost effective				
CV effects apply to CPAP	14,452	15,601	9,932	7,393
CPAP device lower cost	14,452	15,601	9,932	7,072
CPAP device cost and staff costs lower	14,452	15,601	9,932	6,738
All of the above (CPAP more cost effective)	14,452	15,601	9,932	6,513
Oral devices more cost effective				
CPAP device durability is 5 years	14,452	15,601	9,932	8,030
High CPAP cost: auto-CPAP with telemonitoring	14,452	15,601	9,932	9,138
High consumable cost for CPAP	14,452	15,601	9,932	10,769
CV treatment effect for oral devices	13,691	14,751	9,590	7,636
Improved adherence for bespoke and semi-bespoke oral devices	14,452	15,657	9,925	7,636
Low bespoke oral device cost	14,452	15,601	6,756	7,636
Longer durability for bespoke oral devices	14,452	15,601	6,989	7,636
Longer durability of boil and bite and semi-bespoke oral devices	9,957	13,967	9,932	7,636
Quality of life gains for oral devices mapped from ESS rather than direct EQ-5D data	12,413	9,323	9,941	7,636
All of the above (best case for bespoke oral devices)	13,691	14,826	5,109	12,881
All of the above (best case for semi-bespoke oral devices)	11,825	8,045	9,602	12,881
Cohort				
Low starting age of 30 years	11,605	12,464	8,376	6,540
High starting age of 80 years	18,163	19,747	12,775	9,214
Higher risk profile	15,017	16,213	10,358	7,944

Analysis	Cost per QALY gained (versus Conservative Management)			
	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Lower risk profile	16,870	18,274	10,968	8,440
Other				
Reduce treatment dropout rate by 20%	14,550	15,711	9,919	7,650
Increase treatment dropout rate by 20%	14,351	15,488	9,948	7,623
RTAs have larger impact (includes police costs and multiple casualties)	12,853	13,895	9,043	6,906
Treatment has no impact on RTAs	20,319	22,123	12,553	9,592
Least favourable assumptions for intervention	20,319	22,123	12,553	15,324

Table 18: Sensitivity analyses – net monetary benefit rank of treatment strategies (deterministic)

Analysis	Rank of net monetary benefit at £20,000 per QALY gained				
	Conservative management	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Base case results	5	3	4	2	1
CPAP more cost effective					
CV effects apply to CPAP	5	3	4	2	1
CPAP device lower cost	5	3	4	2	1
CPAP device and staff costs lower	5	3	4	2	1
All of the above (CPAP more cost effective)	5	3	4	2	1
Oral devices more cost effective					
CPAP device durability is 5 years	5	3	4	2	1
High CPAP cost: auto-CPAP with telemonitoring	5	3	4	2	1
High consumable cost for CPAP	5	3	4	2	1
CV treatment effect for oral devices	5	3	4	2	1
Improved adherence for bespoke and semi-bespoke oral devices	5	3	4	2	1
Low bespoke oral device cost	5	3	4	2	1

Analysis	Rank of net monetary benefit at £20,000 per QALY gained				
	Conservative management	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
Longer durability for bespoke oral devices	5	3	4	2	1
Longer durability of boil and bite and semi-bespoke oral devices	5	3	4	2	1
Quality of life gains for oral devices mapped from ESS rather than direct EQ-5D data	5	4	3	2	1
All of the above (best case for bespoke oral devices)	5	3	4	1	2
All of the above (best case for semi-bespoke oral devices)	5	4	1	2	3
Cohort					
Low starting age of 30 years	5	3	4	2	1
High starting age of 80 years	5	3	4	2	1
Higher risk profile	5	3	4	2	1
Lower risk profile	5	3	4	2	1
Other					
Reduce treatment dropout rate by 20%	5	3	4	2	1
Increase treatment dropout rate by 20%	5	3	4	2	1
RTAs have larger impact (includes police costs and multiple casualties)	5	3	4	2	1
Treatment has no impact on RTAs	3	4	5	2	1
Least favourable assumptions for intervention	3	4	5	1	2

1.5.5 Health economic evidence statements

Compared with conservative management

- Two cost-utility analyses found that mandibular advancement splints were cost effective compared with conservative management for people with mild or moderate OSAHS (£2,000-£6,700 per QALY gained). These studies were assessed as directly applicable with potentially serious limitations.
- One original cost-utility analysis found that
  - Custom-made mandibular advancement splints were cost effective compared with conservative management for people with mild OSAHS (£10,000 per QALY gained).
  - Semi-bespoke mandibular advancement splints were cost effective compared with conservative management for people with mild OSAHS (£15,500 per QALY gained).
  - Boil and bite mandibular advancement splints were cost effective compared with conservative management for people with mild OSAHS (£14,100 per QALY gained).

  This study was assessed as directly applicable with minor limitations.

Compared with CPAP

- Two cost-utility analyses found that CPAP was cost effective compared with mandibular advancement splints for people with OSAHS (£3,900-£15,400 per QALY gained). These studies were assessed as directly applicable with potentially serious limitations.
- One cost-utility analysis found that mandibular advancement splints were not cost effective compared with CPAP for people with moderate OSAHS (£77,700 per QALY gained). This study was assessed as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that
  - CPAP was cost effective compared with boil and bite mandibular advancement splints for people with mild OSAHS (£1,200 per QALY gained).
  - CPAP was cost effective compared with semi-bespoke mandibular advancement splints for people with mild OSAHS (£900 per QALY gained).
  - Custom-made mandibular advancement splints were dominated by CPAP for people with mild OSAHS.

  This study was assessed as directly applicable with minor limitations.

Comparisons of different oral devices

- One cost-utility analysis found that
  - Custom-made mandibular advancement splints were not cost effective compared with boil and bite and semi-bespoke devices for people with OSAHS (£36,400 and £45,600 per QALY gained).
  - Boil and bite mandibular advancement splints were not cost effective compared with semi-bespoke devices for people with OSAHS (£136,800 per QALY gained).

  This study was assessed as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that
  - custom-made mandibular advancement splints were cost effective compared with
    - boil and bite mandibular advancement splints for people with mild OSAHS (£3,900 per QALY gained)
    - semi-bespoke mandibular advancement splints for people with mild OSAHS (£3,100 per QALY gained).
  - When mapping from ESS to EQ-5D, custom-made mandibular advancement splints was cost effective at £20,000 per QALY compared with

- semi-bespoke mandibular advancement splints for people with mild OSAHS (£16,700 per QALY gained).

This study was assessed as directly applicable with minor limitations.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee considered the outcomes of health-related quality of life and mortality as critical outcomes for decision making. Other important outcomes included sleepiness scores (e.g. Epworth), Apnoea-Hypopnoea index (AHI), oxygen desaturation index (ODI), CO2 control, adverse effects of treatment, disruption of partner's sleep, driving outcomes, neurocognitive outcomes, adherence in hours of use and expression of preference. The committee were also interested in the impact on co-existing conditions such as HbA1c for diabetes, cardiovascular events for cardiovascular disease and systolic blood pressure for hypertension.

No evidence was identified for the outcomes of disruption of partner's sleep, driving outcomes, impact on cardiovascular events or impact on HbA1c for diabetes.

1.6.1.2 The quality of the evidence

OSAHS

Mandibular advancement splint (MAS) compared to no intervention /CPAP/positional modifiers/surgery

There was evidence from 21 studies (twenty seven papers) comparing oral devices (mandibular advancement splints) with surgery/other interventions/no interventions: 13 studies (fifteen papers) compared oral devices (mandibular advancement splints) with CPAP in a moderate severity population, one crossover study compared oral devices (mandibular advancement splints) with a placebo in a mild severity population, 10 studies compared oral devices (mandibular advancement splints) with a placebo in a moderate severity population and one small study compared oral devices (mandibular advancement splints) with surgery in a moderate severity population. Studies varied in size but generally consisted of a small population ranging from 18 to 126 participants.

There was no evidence comparing oral devices with positional modifiers.

The majority of studies included a mixed OSAHS severity population based on AHI scores. When a mixed severity population was included (i.e. mild and moderate severity OSAHS), the severity of the majority of the population was determined by the mean value and the study was downgraded for indirectness.

The populations recruited to the studies were predominately male with a diagnosis of OSAHS. At baseline the majority of the study populations had high BMIs over 30 kg/m^2 and ESS scores over 9, indicating they had excessive sleepiness and were obese. These characteristics were taken into consideration as subgroups, and subgroup analyses were performed when the presence of heterogeneity was identified across studies.

The majority of studies employed customised and titratable mandibular advancement splints. There was no evidence regarding tongue retaining devices or tongue stabilising devices. The committee did not make any research recommendation for tongue devices as they did not consider this to be a research priority topic.

The committee considered the clinical importance for AHI on a case by case basis, taking into consideration the baseline AHI and the improvement in severity of sleep apnoea.

The quality of the evidence varied from moderate, to very low quality; the majority of the evidence was downgraded due to risk of bias, indirectness and imprecision. Risk of bias was most commonly due to selection and blinding bias. As comparator groups often received either a different intervention or usual care (only 8 studies employed a placebo device), there was no participant or investigator blinding in many of the studies. Combined with the subjective nature of the outcomes, this was deemed to create a high risk of bias. Indirectness was present in many of the studies due to the inclusion of mixed severity OSAHS populations, combining people with mild, moderate or severe OSAHS. Imprecision was also present for a number of the outcomes with confidence intervals crossing the MID thresholds. The low quality of evidence, small study sizes and uncertainty around the effect estimate was taken into consideration by the committee when assessing the evidence base in this review.

COPD-OSAHS overlap syndrome

There was no evidence available for people with COPD-OSAHS overlap syndrome.

Different types of oral devices compared to each other

OSAHS

The committee wanted to look at different types of oral devices based on their fabrication/design, as there is variation in clinical practice in the type of oral devices that are prescribed.

There was evidence from three papers comparing different types of oral devices with each other. All included studies used a mandibular advancement splint (MAS). One paper included three devices, all compared to each other: a ready-made 'boil and bite' (mandibular advancement splints), a semi-customised (mandibular advancement splints) formed from a dental impression mould self-fitted by the patient, and a custom-made mandibular advancement splint professionally fitted by specialists. The second paper compared a ready-made heat moulded mandibular advancement splint with a fully custom-made titratable mandibular advancement splint in mild OSAHS. The final paper compared a semi-customised heat moulded titratable mandibular advancement splint with a fully custom-made titratable mandibular advancement splint in a moderate OSAHS population.

There was no evidence available for tongue retaining/tongue stabilising devices. The committee did not make any research recommendation for tongue devices as they did not consider this to be a research priority topic.

Based on mean AHI values, two studies were in a mild OSAHS population and one study was in a moderate OSAHS population. There was no evidence for the severe OSAHS population.

The quality of the evidence varied from low to very low quality. The majority of the evidence was downgraded due to due to risk of bias, indirectness of the population and imprecision. Risk of bias was most commonly due to blinding bias and incomplete outcome data. As the types of oral devices differed in appearance and two studies were of a cross over design there was no participant or investigator blinding in most of the studies. Combined with the subjective nature of the outcomes, this was deemed to create a high risk of bias. Indirectness was present in many of the studies due to the inclusion of mixed severity OSAHS populations, combining people with mild, moderate or severe OSAHS. Imprecision was also present for many outcomes with confidence intervals crossing the MID thresholds. The low quality of evidence and uncertainty around the effect estimate was taken into consideration by the committee when assessing the small evidence base for this comparison.

COPD-OSAHS overlap syndrome

There was no evidence available for COPD-OSAHS overlap syndrome.

1.6.1.3 Benefits and harms

OSAHS

Mild OSAHS

Mandibular advancement splint vs placebo

In the mild severity population with symptoms, the evidence came from one crossover study with 90 participants, which compared three different types of mandibular advancement splints to no treatment. Therefore, benefits and harms were considered independently for each type of mandibular advancement splint when compared to no treatment. For the critical outcome of quality of life, the evidence reported a benefit in the SF-36 vitality score for both the semi-customised and custom-made mandibular advancement splints when compared to no treatment. However, the committee acknowledged some uncertainty around the effect estimate with the confidence interval crossing the MID threshold. There was no clinically important difference for the boil and bite mandibular advancement splints when compared to no treatment for the same outcome. Minor adverse events (including excessive salivation, discomfort, dryness/bad taste and numbness) were commoner with all three types of mandibular advancement splint when compared to the no treatment arm. However, this result is to be expected as minor adverse events such as discomfort and excessive salivation would only be plausible with the use of an oral device, and no placebo device was used in this study. The committee concluded that small improvements in QOL for the custom-made and semi-customised mandibular advancement splints outweighed the harm of the minor adverse events.

The evidence suggested that there was no clinically important difference between mandibular advancement splints and no treatment in a mild OSAHS for the following outcomes: AHI, ESS and EQ5D VAS.

The committee discussed whether the study was of too short duration for maximum protrusion and therefore maximum benefit to be observed, in particular with the custom-made mandibular advancement splints. They felt if longer follow up had been performed, likely clinical benefits would have been even greater between the customised mandibular advancement splint and ready-made ‘boil and bite’ or semi-customised mandibular advancement splints.

Oral devices vs CPAP

There was no evidence available for mandibular advancement splints versus CPAP in a mild OSAHS.

Moderate OSAHS

Mandibular advancement splints vs placebo

In the moderate severity OSAHS population, the evidence from 8 studies suggested a clinical benefit for mandibular advancement splints when compared to a placebo for AHI. The evidence also showed a benefit for QOL in the SF36 physical domain in favour of mandibular advancement splints, although there was some uncertainty around the effect estimate with the confidence interval crossing the MID threshold.

The evidence suggested an increased frequency of adverse events i.e. pain, hyper salivation, dryness and damage to dental restorations with the oral devices. However, the committee noted that despite reaching the threshold for a clinically significant harm the findings were taken from one small crossover study so should be interpreted with caution.

Adverse events of TMD pain showed some benefit in favour of oral devices. However, the committee noted that the findings were taken from one small study so should be interpreted with caution.

Narrative results from one study reported a lower final ESS score in the mandibular advancement splints treatment group which was a clinically significant benefit. Because this is a narrative study no confidence intervals were reported, and the committee treated the result with caution.

The evidence revealed that there was no clinically important difference between mandibular advancement splints and placebo in a moderate severity population for the following outcomes: ESS (other than the narrative study discussed above), ODI, FOSQ, SF-36 mental, adherence, systolic blood pressure, SAQLI and neurocognitive outcomes. For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information.

Mandibular advancement splints vs CPAP

The evidence suggested a benefit of mandibular advancement splints for one of the critical quality of life outcomes, EQ5D, when compared to CPAP at 12 months. However, this benefit was only reported in one study and was just below the threshold for clinical significance. The evidence from 4 studies also showed a clinical benefit for patient reported outcomes including ease of use scores and patient preference, which is a widely reported benefit of mandibular advancement splints when compared to CPAP. However, the committee acknowledged the large uncertainty around the effect estimate with the confidence interval crossing both MIDs.

The evidence suggested a benefit in patient adherence with mandibular advancement splints. However, the committee concluded that this evidence should be discounted as the measure of adherence for mandibular advancement splints was largely self-reported, while CPAP adherence was taken as an objective reading from the machine in the majority of studies. The committee therefore agreed that this was a flawed comparison.

The evidence reported a benefit of CPAP for AHI final values in 8 studies and ODI final values in 4 studies at <6 months post treatment. The committee noted these benefits to be clinically important but acknowledged the uncertainly around the effect estimate for ODI. Another small study reported in narrative format showed an improvement in AHI with CPAP at 12 months, but this was not deemed to be clinically important and was of very low quality. The same study also reported two adherence outcomes in narrative form, but both of these showed no clinical difference in % of nights the treatment device was worn for over 4 hours, nor in hours worn per night.

Adverse events of nasal congestion, difficulty chewing, sense of suffocation and discomfort were reported in one small study and showed a benefit in favour of CPAP. The committee noted that the side effects are usually transient.

The evidence suggested that there was no clinically important difference between mandibular advancement splints and CPAP for the following outcomes: AHI change score, AHI at 12 months and 18 months, EQ5D VAS, FOSQ, SF36 mental and physical, systolic BP, oxygen desaturation %, ESS and neurocognitive outcomes. The committee noted that there was benefit of CPAP for some outcomes, but this was not consistent, and the evidence was low to very low quality, with uncertainty around the effect sizes. For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information.

Mandibular advancement splints vs surgery

The evidence was available from one small study in people with moderate OSAHS comparing a mandibular advancement splint and uvulopalatopharyngoplasty (UPPP) surgery.

The evidence suggested no clinical difference in AHI and ODI final values at 6 and 12 months post treatment.

Severe OSAHS

There was no evidence for people with severe OSAHS who are intolerant to CPAP.

COPD-OSAHS overlap syndrome

There was no evidence for oral devices/mandibular advancement splint in COPD-OSAHS overlap syndrome. The committee discussed whether evidence from people with OSAHS could be used for people with COPD-OSAHS overlap syndrome. They agreed that the differences between these two groups are too great to allow them to make a consensus recommendation based on the evidence in OSAHS. The committee were also aware of the potential risks of the long-term use of mandibular advancement splints to include a change in the patient's bite and they agreed that the treatment should be restricted to where there is proven or suggested benefit. They also agreed that patients with COPD-OSAHS overlap syndrome are also at risk of or have ventilatory failure and mandibular advancements splints are not appropriate in those circumstances.

The committee were not sure if there was any clinical justification for use of oral devices in this population, so they did not make a research recommendation.

Oral devices compared to each other

Mild OSAHS

Ready-made/boil and bite vs custom-made

The evidence from one crossover study suggested a benefit of custom-made mandibular advancement splints for the quality of life outcome, SF-36 vitality. However, the committee noted the uncertainty around the effect estimate with the confidence interval crossing the MID threshold. Additionally, patient preference reported in one small study showed a clinical benefit of the custom-made device.

The evidence for the outcome AHI showed no clinical difference in one study, but in another small study reported narratively there was an improvement in AHI in the custom-made device group at 3 months. The committee deemed this to be clinically important, but they acknowledged that the study was unsuitable for full GRADE analysis and was therefore of very low quality. This study also reported narrative results for adherence and showed a clinical benefit with the custom-made mandibular advancement splints for nights per week on which the device was worn, and hours worn per night. However, it showed no clinical difference for FOSQ and ESS and again the committee acknowledged that this evidence was of very low quality.

The committee noted that the lack of convincing benefit with the custom-made mandibular advancement splints could be explained by the relatively short study duration hence the lack of time for maximum protrusion to occur and maximum benefit to be observed. They reasoned that, if longer follow up had been performed, clinical benefits would probably have been greater between the customised MAS and ready-made 'boil and bite' or semi-customised mandibular advancement splints. Despite a lack of convincing evidence in favour of mandibular advancement splints (MAS) in the mild severity population committee agreed that MAS still be considered as a treatment option for people with symptomatic

OSAHS, based on: the improvement in patients' SF-36 vitality score, small improvements in AHI and ESS values, along with the lack of any major reported adverse events.

The evidence suggested no clinical difference between ready-made and custom-made mandibular advancement splints for the outcomes: ESS, ODI, mean oxygen saturation and minimum oxygen saturation.

Ready-made vs semi-customised mandibular advancement splints

The evidence from one cross over study suggested that there was a small benefit in the QOL outcome SF-36 vitality with the ready made mandibular advancement splints compared to the semi-customised device, although there was uncertainty around the effect estimate.

There was no clinical difference between ready-made mandibular advancement splints and semi-customised mandibular advancement splints for AHI and ESS, minor adverse events, EQ5D VAS and EQ5D at 6 weeks post treatment.

Semi-customised made vs custom-made

The evidence for this comparison came from 1 study and suggested that there was a small benefit for the QOL outcome SF-36 vitality with the custom-made mandibular advancement splints, when compared to the semi-customised device, however, this did not reach clinical significance. The committee noted this difference could be explained by the relatively short duration of the trial. The evidence showed that the custom-made mandibular advancement splints caused more minor adverse events, but many of these were transient effects.

There was no clinical difference between the semi-customised and custom-made mandibular advancement splints for: AHI, ESS, EQ5D VAS and EQ5D at 6 weeks post treatment.

Moderate OSAHS

Semi-customised vs custom-made

The evidence from one study suggested a clinical benefit with the custom-made mandibular advancement splints compared to semi-customised splints for systolic blood pressure at 2 months post treatment. However, for the outcomes of SF-12 mental and physical change scores, the evidence reported a benefit of the heat-moulded mandibular advancement splints when compared to the custom-made device. All these outcomes displayed uncertainly around the effect estimate with confidence intervals crossing MID thresholds.

The evidence suggested that there was no clinical difference between semi-customised and custom-made mandibular advancement splints for: AHI, ESS, serious adverse events, adherence (self-reported) at 2 months post treatment.

There was no evidence comparing different types of mandibular splints in people with severe OSAHS.

Mandibular advancement splints for OSAHS- committee's consideration of the evidence to make recommendations

Mild OSAHS

The committee acknowledged the limited quality, number of studies and the lack of long-term data for mandibular advancement splints in people with mild OSAHS. One study showed little benefit of mandibular advancement splints compared with no treatment, but the committee agreed that the duration of the study was not sufficient for the true benefit to be assessed. The committee also noted the evidence from studies in people with moderate OSAHS which showed clinical benefit compared to placebo, and also showed better ease of use and patient preference scores compared with CPAP. An economic analysis showed that CPAP was slightly more cost effective than customised mandibular advancement splints, but the

committee agreed the difference was small and they did not want to exclude these devices as an option, bearing in mind that some people find CPAP unacceptable.

The committee discussed whether mandibular advancement splints may be preferable in those people with mild OSAHS and BMI of less than 35 kg/m^2 with predominant insomnia, difficulty initiating sleep, sleep disturbance and sleep fragmentation, but the committee agreed there is no evidence for this. Most mandibular advancement splints work by advancing the mandible anteriorly to help prevent upper airway collapse and in turn enlarging the upper airway space. There are currently no reliable investigations or well-defined clinical features to help clinicians decide objectively which patients are best suited to mandibular advancement splint treatment. The committee however noted that patients with certain skeletal abnormalities, such as a small or retro positioned lower jaw may particularly benefit from mandibular advancement splint treatment. Conversely, patients with a BMI over 35 kg/m^2 tend to have poorer outcomes with mandibular advancement splint treatment. The committee stated that clinicians also need to be aware that patients with periodontal disease, dental decay or TMJ dysfunction need these conditions treated prior to using mandibular advancement splints.

The committee also noted that mandibular advancement splints in mild symptomatic OSAHS population should be worn for at least three months in order to determine clinical effectiveness, as titration to advance the mandible into an efficacious position takes time. The committee agreed that mandibular advancement splint follow up should ensure optimised OSAHS symptom control and ideally a repeat sleep study to show improvement of OSAHS.

The committee agreed that there should be consideration given to linking up sleep, dental and primary care teams for these patients. Creating a standardised pathway for anyone performing this work would be helpful, including access to sleep study results for the person fitting the mandibular advancement splints, performing repeat sleep study once mandibular advancement splints has been optimally titrated and regular dental follow up.

Mandibular advancement splints are not suitable for children and young people because they may adversely affect development of dentition, therefore the committee agreed that mandibular advancement splints should only be used in people over 18 years of age. The committee agreed that 18 is a suitable age for mandibular advancement splints to be considered however they noted that clinicians may wish to exercise caution patients with a Class III occlusion but the dental changes that could take place are just as relevant in more ‘mature’ adult patients with this occlusion.

The evidence was unclear about the best type of mandibular advancement splint, but from their experience, the committee agreed that customised devices fitted by a suitably trained dentist, are superior to semi-customised and ready-made (also called 'boil and bite') splints. Despite higher initial costs to make and fit, customised devices are more durable and longer lasting than the other devices.. They are also preferred by patients. Semi-customised devices also last longer than ready-made devices and are cheaper than customised devices. Both customised and semi-customised devices were shown to be more cost effective than ready-made devices. The committee noted that semi-customised devices may be inappropriate for people with untreated dental decay or active periodontal disease, those with few teeth or no teeth, and for people with generalised tonic-clonic seizures, due to potential risk of dislodging during a seizure. They noted that there are no contraindications to a standard, well-fitted dental device of any type which requires a mould to be taken and a suitably qualified dentist to fit for any seizure type, including GTCS. The only potential contraindication in people GTCS is loose fitting dentures or a badly fitting boil and bite device not fitted by dentist.

Based on the limited evidence and their experience, the committee agreed that customised and semi-customised mandibular advancement splints should be considered as a treatment option for people with mild symptomatic OSAHS who have symptoms that affect their usual

daytime activities if they are unable to tolerate or decline to try CPAP, if they are aged 18 and over and have optimal dental and periodontal health... Experienced specialist care is needed to use semi-customised devices in people with few or no teeth.

The committee observed that careful patient selection is vital and further research is needed to determine which patients with mild OSAHS would benefit most from mandibular advancement splint therapy. They developed a research recommendation to inform future guidance (Appendix J.2).

Some people with mild OSAHS currently use mandibular advancement splints. Many of these will be using less effective ready-made devices bought by patients. It is expected that there will be increased uptake of customised and semi-customised mandibular advancement splints and therefore a resource increase from this recommendation. NHS provision of dental services producing mandibular advancement splints is currently limited. Mandibular advancement splints need replacing at regular intervals and people using them need follow-up to assess efficacy.

Moderate OSAHS

Although CPAP is the treatment of choice for people with moderate or severe OSAHS, many people are unable to tolerate it. The evidence showed that in people with moderate OSAHS there was some benefit of mandibular advancement splints compared to CPAP and placebo and the committee agreed that they could be considered as an alternative treatment to CPAP in moderate OSAHS population, if CPAP is not tolerated or if they decline to try CPAP, are aged over 18 years and have optimal dental and periodontal health.

The committee noted that these devices may be contraindicated in some people, and that people with a BMI over 35 kg/m^2 tend to have poorer outcomes.

Overall, the evidence for types of mandibular advancement splints suggested that there was a small benefit of the custom-made mandibular advancement splints when compared to the ready-made and semi-customised devices, particularly in the quality of life outcomes. The committee discussed that the studies were of too short duration to demonstrate any significant difference in clinical effectiveness with custom-made devices which require a period of adjustment/titration to maximise their effectiveness. They stated that in people with mild OSAHS, a minimum of 3 months use is essential to see improvement in clinical outcomes and in people with moderate OSAHS or those with failed CPAP, at least 6 months use of mandibular advancement splints is essential to see improvement in clinical outcomes.

From their experience, the committee agreed that customised devices fitted by a suitably trained dentist, are superior to semi-customised and ready-made (also called 'boil and bite') splints. Despite higher initial costs to make and fit, customised devices are more durable and longer lasting than the other devices. They are also preferred by patients. Semi-customised devices also last longer than ready-made devices and are cheaper than customised devices. Both customised and semi-customised devices were shown to be more cost effective than ready-made devices.

Mandibular advancement splints are not suitable for people under 18 years because they may adversely affect development of dentition, hence the committee agreed that mandibular advancement splints should only be used in people over 18 years of age. The committee agreed that 18 is a suitable age for mandibular advancement splints to be considered however they noted that clinicians may wish to exercise caution patients with a Class III occlusion but the dental changes that could take place are just as relevant in more ‘mature’ adult patients with this occlusion.

Semi-customised devices may be inappropriate for people with untreated dental decay or active periodontal disease, with few teeth or who are edentulous, and for people with

generalised tonic-clonic seizures, due to potential risk of dislodging during a seizure.. They noted that there are no contraindications to a standard, well-fitted dental device of any type which requires a mould to be taken and a suitably qualified dentist to fit for any seizure type, including GTCS. The only potential contraindication in people GTCS is loose fitting dentures or a badly fitting boil and bite device not fitted by dentist. Experienced specialist care is needed to use semi-customised devices in people with few or no teeth.

It is expected that there will be increased uptake of customised and semi-customised mandibular advancement splints and therefore a resource increase from this recommendation. NHS provision of dental services producing mandibular advancement splints is currently limited. Mandibular advancement splints need replacing at regular intervals and people using them need follow-up to assess efficacy and dentition.

All studies included evidence for mandibular advancement splints (MAS), and no evidence was found for tongue retaining devices or tongue stabilising devices, hence the committee made recommendations for this type of oral device only. The committee did not make any research recommendation for tongue devices as they did not consider this to be a research priority topic.

Severe OSAHS

There was no evidence for people with severe OSAHS who are intolerant to CPAP. In the absence of evidence for mandibular advancement splints in people with severe OSAHS the committee agreed that the evidence for moderate OSAHS could be extrapolated for severe OSAHS. The committee also made a research recommendation on mandibular advancement splints for severe OSAHS.

COPD-OSAHS overlap syndrome

There was no evidence for the use of mandibular advancement splints in people with COPD-OSAHS overlap syndrome. The committee discussed whether evidence from people with OSAHS could be used for people with COPD-OSAHS overlap syndrome. They agreed that these groups are too great to allow them to make a consensus recommendation based on the evidence in OSAHS The committee were also aware of the potential risks of the long-term use of mandibular advancement splints to include a change in the patient's bite and they agreed that the treatment should be restricted to where there is proven or suggested benefit. They also agreed that patients with COPD-OSAHS overlap syndrome are also at risk of or have ventilatory failure and mandibular advancements splints are not appropriate in those circumstances.

1.6.2 Cost effectiveness and resource use

Oral devices need replacing at regular intervals and require some follow up to assess efficacy. It is expected that the cost will be partially offset by a reduction in NHS costs associated with reduced road traffic accidents.

Two published economic evaluations from a UK NHS perspective found that oral devices were cost effective compared with conservative management. These two studies and a third study from the Netherlands compared oral devices with CPAP and in all three studies CPAP was the more cost-effective intervention, although it had less QALYs in the Dutch study. Only one economic evaluation compared different oral devices (in a mild/moderate OSAHS population). However, this study was assessed to have serious limitations. In particular, the time horizon was too short to assess the comparative costs of replacing the devices at suitable intervals. Therefore, an original decision model was developed to assess the cost effectiveness of oral devices compared to both CPAP and conservative management for people with mild OSAHS.

The model calculated QALYs using EQ-5D scores for each intervention from trial evidence, either directly measured or mapped from ESS. CPAP was found to have the highest QALYs followed by customised mandibular advancement splint. CPAP cost £8,500 per QALY gained compared with conservative management. The cost per QALY for customised mandibular advancement splint compared with conservative management was quite similar (£10,700) but CPAP was dominant. A number of sensitivity analyses were conducted. CPAP remained the most cost-effective strategy each time, except when all of the assumptions that were least favourable to CPAP were used in combination. In all scenarios both CPAP and custom-made MAS were cost effective compared with conservative management.

Boil and bite devices were found to be cost-effective compared to conservative management, but they were less effective and cost effective than customised devices.

Semi-customised devices were cost effective compared with conservative management. Using directly measured EQ-5D data they were not as cost effective as customised splints but they were similar when mapping to EQ-5D from ESS, which the committee considered to be an equally reasonable approach. The published economic evaluation also found that semi-customised splints were less effective than customised splints but more cost effective. However, the committee considered that the study had under-estimated the durability of customised splints. Furthermore, the results of that study appeared to be strongly influenced by non-OSAHS health costs, which could have been due to random variation and small sample size rather than true treatment effects.

The committee agreed that in symptomatic patients with mild OSAHS, CPAP should be offered as first-line treatment, as it has the strongest evidence base and was shown to be cost-effective compared to conservative management. For people who cannot tolerate CPAP the committee recommended custom-made or semi-customised mandibular advancement splints. This was because both were cost effective compared with conservative management but there was uncertainty about which was the most cost effective.

There was a lack of good quality evidence identifying any clinical and physiological phenotypes that would predict treatment response to CPAP or a MAS to suggest which treatment was more effective in people with mild symptomatic OSAHS. OSA severity, the nature of symptoms (e.g. sleepiness, sleep fragmentation, insomnia, nocturnal choking), along with patient preference should all be taken into account. CPAP was more cost-effective than oral devices, but the committee agreed research in this area was needed. The committee recommended research into which clinical and physiological phenotypes predict treatment response to mandibular advancement splints, so that this treatment might be targeted on those people who will benefit the most.

All of the evidence for oral devices was from trials with mixed populations (mild and moderate OSAHS), therefore it is not possible to differentiate the cost effectiveness of oral devices in those two populations. Although the model, specifically looked at mild OSAHS, it seemed reasonable to conclude that customised or semi-bespoke mandibular advancement would also be cost effective in adults with moderate OSAHS who cannot tolerate CPAP.

There was no evidence for oral devices in COPD-OSAHS overlap syndrome hence the committee did not make any recommendation for this population.

1.6.3 Other factors the committee took into account

The committee did not look for evidence on the use of oral devices or mandibular advancement splints in people with OHS. They agreed that these interventions are not appropriate for use in OHS because they will not control carbon dioxide (CO_2) in this population.

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Appendices

Appendix A: Review protocols

Table 19: Review protocol: oral devices

ID	Field	Content
0.	PROSPERO registration number	Not registered in PROSPERO
1.	Review title	Oral devices
2.	Review question	What is the clinical and cost effectiveness of different types of oral devices for managing obstructive sleep apnoea/hypopnoea syndrome (OSAHS), and COPD-OSAHS overlap syndrome?
3.	Objective	To determine the clinical and cost effectiveness of oral devices for managing OSAHS and COPD-OSAHS overlap syndrome.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

5.	Condition or domain being studied	Obstructive sleep apnoea/hypopnoea syndrome is the most common form of sleep disordered breathing. The question will also cover COPD-OSAHS overlap syndrome (the coexistence of obstructive sleep apnoea/hypopnoea syndrome and chronic obstructive pulmonary disease).
6.	Population	Inclusion: People (16 and older) with OSAHS, and COPD-OSAHS overlap syndrome (OS) Population will be stratified by: • Population: OSAHS, COPD-OSAHS overlap syndrome • Severity: Mild, moderate, severe (based on AHI/ODI) • Phenotype – with sleepiness vs without sleepiness When a mixed severity population is included the severity of the majority of the population will be used by taking the mean AHI of the patients included and the study will be downgraded for indirectness. Exclusion: Children and young people (under 18) Severity: Mild OSAHS: AHI >5 but <15 Moderate OSAHS: AHI >/= 15 but <30 Severe OSAHS: AHI >/= 30 Include- oral devices vs CPAP/placebo for mild and moderate OSAHS.

		Include- oral vs CPAP/placebo for severe OSAHS when intolerant to CPAP.
7.	Intervention/Exposure/Test	• Any intraoral prostheses -mandibular advancement splints, mandibular advancement devices, mandibular repositioning appliances, or dental orthosis, tongue retaining devices, or tongue stabilizing devices. Different types of oral devices: • self-customised/self-moulded/ready made • semi-customised/ semi-bespoke • full customised/fully bespoke
8.	Comparator/Reference standard/Confounding factors	• Surgery • other non-surgical intervention (positive airway pressure variants, positional modifiers) • Combination therapy (combination of oral devices and any non-surgical/surgical interventions) • No intervention (placebo, inactive control therapy)/ usual care as defined in the studies (including lifestyle advice etc) Types of oral devices: Compare different types of oral devices with each other.
9.	Types of study to be included	• RCTs • Systematic review of RCTs • Minimum duration of follow-up 1 months • Parallel or crossover to be included

10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• Generic or disease specific quality of life measures (continuous) • Mortality (dichotomous)
13.	Secondary outcomes (important outcomes)	• Sleepiness scores (continuous, e.g. Epworth) • Apnoea-Hypopnoea index or respiratory disturbance index (continuous) • Oxygen desaturation index (continuous) • CO2 control (continuous) • Adverse effects of treatment (rates or dichotomous) • disruption of partner's sleep • Driving outcomes (continuous) • Neurocognitive outcomes (continuous) • Adherence in hours of use (continuous) • Patient preference (continuous) • Impact on co-existing conditions: o HbA1c for diabetes (continuous) o Cardiovascular events for cardiovascular disease (dichotomous) o Systolic blood pressure for hypertension (continuous)

		Outcomes will be separated into short term (latest follow-up to 6 months) and long term (latest follow-up beyond 6 months)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.
17.	Analysis of sub-groups	• Gender (females versus male), as a gender difference for treatment preference and tolerance has been observed in some studies; • Race (Caucasian versus Asian), as there is significant anatomical difference between Caucasians and Asians that may affect the treatment effectiveness or preference; • High risk occupational groups (for example heavy goods vehicle drivers) vs general population • Sleepiness – Epworth >9 vs Epworth 9 or less • Coexisting conditions – type 2 diabetes vs atrial fibrillation vs hypertension vs none • BMI – obese vs non-obese • Intervention – custom-titratable vs custom-non-titratable vs non-custom • Intervention – custom-titratable vs custom-non-titratable vs non-custom- • Titratable vs non-titratable
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	NA – not registered on PROSPERO
22.	Anticipated completion date	NA – not registered on PROSPERO
24.	Named contact	5a. Named contact National Guideline Centre

		5b Named contact e-mail SleepApnoHypo@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Sharangini Rajesh, Senior systematic reviewer Audrius Stonkus, Systematic reviewer Emtiyaz Chowdhury (until January 2020), Health economist David Wonderling, Head of health economics Agnes Cuyas, Information specialist (till December 2019) Jill Cobb, Information specialist
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10098
29.	Other registration details	NA – not registered
30.	Reference/URL for published protocol	NA – not registered
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	NA
33.	Details of existing review of same topic by same authors	N/A
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Table 20: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[147] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.

- If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as ‘Not applicable’.
- Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Sleep Apnoea search strategy 6 oral devices

This literature search strategy was used for the following review;

- What is the clinical and cost effectiveness of different types of oral devices for managing obstructive sleep apnoea/hypopnoea syndrome (OSAHS), obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[147]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 21: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 7 July 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 7 July 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 7 of 12 CENTRAL to 2020 Issue 7 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 29 November 2018	None

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/

15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	exp Orthodontic Appliances/
29.	Orthotic Devices/ or Splints/ or Mandibular Advancement/
30.	((oral or intraoral or intra-oral) adj3 (device* or prosthes* or appliance* or splint*)).ti,ab.
31.	(MAD or MADs or MAS or MRS).ti,ab.
32.	((dental or orthodontic* or orthosis or orthotic) adj3 (device* or prosthes* or appliance* or splint*)).ti,ab.
33.	(tongue adj3 (device* or prosthes* or appliance* or splint* or retain* or reposition* or stabiliz* or stabilis* or advancement or advancing or retention or protruding or protrude or protruded or protrusion or forward or mouthpiece*)).ti,ab.
34.	(mandib* adj3 (device* or prosthes* or appliance* or splint* or advancement or advancing or protruding or protrude or protruded or protrusion or reposition* or position*)).ti,ab.
35.	(Mouth guard* or mouthguard*).ti,ab.
36.	(SleepPro or Somnolis or Somnofit or Snore Defense or Snoreeze or Anti Snore or Anti-Snoring or SnoreWizard or Snore Wizard or VitalSleep).ti,ab.
37.	or/28-36
38.	27 and 37
39.	randomized controlled trial.pt.
40.	controlled clinical trial.pt.
41.	randomi#ed.ti,ab.
42.	placebo.ab.
43.	randomly.ti,ab.
44.	Clinical Trials as topic.sh.
45.	trial.ti.
46.	or/39-45
47.	Meta-Analysis/
48.	exp Meta-Analysis as Topic/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.

54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	38 and (46 or 57)

Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	exp orthodontic device/
27.	orthosis/ or splint/ or mandibular advancement/
28.	((oral or intraoral or intra-oral) adj3 (device* or prosthes* or appliance* or splint*)).ti,ab.
29.	(MAD or MADs or MAS or MRS).ti,ab.
30.	((dental or orthodontic* or orthosis or orthotic) adj3 (device* or prosthes* or appliance* or splint*)).ti,ab.
31.	(tongue adj3 (device* or prosthes* or appliance* or splint* or retain* or reposition* or stabiliz* or stabilis* or advancement or advancing or retention or protruding or protrude or protruded or protrusion or forward or mouthpiece*)).ti,ab.
32.	(mandib* adj3 (device* or prosthes* or appliance* or splint* or advancement or advancing or protruding or protrude or protruded or protrusion or reposition* or position*)).ti,ab.
33.	(Mouth guard* or mouthguard*).ti,ab.
34.	(SleepPro or Somnolis or Somnofit or Snore Defense or Snoreeze or Anti Snore or Anti-Snoring or SnoreWizard or Snore Wizard or VitalSleep).ti,ab.

35.	or/26-34
36.	25 and 35
37.	random*.ti,ab.
38.	factorial*.ti,ab.
39.	(crossover* or cross over*).ti,ab.
40.	((doubl* or singl*) adj blind*).ti,ab.
41.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
42.	crossover procedure/
43.	single blind procedure/
44.	randomized controlled trial/
45.	double blind procedure/
46.	or/37-45
47.	systematic review/
48.	meta-analysis/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	36 and (46 or 57)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#2.	(sleep* near/4 (apnea* or apnoea* or hypopnea* or hypopnoea*)):ti,ab
#3.	(sleep* near/4 disorder* near/4 breath*):ti,ab
#4.	(OSAHS or OSA or OSAS):ti,ab
#5.	(obes* near/3 hypoventil*):ti,ab
#6.	pickwick*:ti,ab
#7.	(OR #1-#6)
#8.	MeSH descriptor: [Orthodontic Appliances] explode all trees
#9.	MeSH descriptor: [Orthotic Devices] this term only
#10.	MeSH descriptor: [Splints] this term only
#11.	MeSH descriptor: [Mandibular Advancement] this term only
#12.	((oral or intraoral or intra-oral) near/3 (device* or prosthes* or appliance* or splint*)):ti,ab
#13.	(MAD or MADs or MAS or MRS):ti,ab
#14.	((dental or orthodontic* or orthosis or orthotic) near/3 (device* or prosthes* or appliance* or splint*)):ti,ab
#15.	(tongue near/3 (device* or prosthes* or appliance* or splint* or retain* or reposition* or stabiliz* or stabilis* or advancement or advancing or retention or protruding or protrude or protruded or protrusion or forward or mouthpiece*)):ti,ab

#16.	(mandib* near/3 (device* or prosthes* or appliance* or splint* or advancement or advancing or protruding or protrude or protruded or protrusion or reposition* or position*)):ti,ab
#17.	(Mouth guard* or mouthguard*):ti,ab
#18.	(SleepPro or Somnolis or Somnofit or Snore Defense or Snoreeze or Anti Snore or Anti-Snoring or SnoreWizard or Snore Wizard or VitalSleep):ti,ab
#19.	(OR #8-#18)
#20.	#7 and #19

Epistemonikos search terms

1.	((title:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*) OR abstract:((sleep apnea syndromes) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (apn?ea* OR hypopn?ea*)) OR (sleep* AND (disorder* OR breath*)) OR (OSAHS OR OSA OR OSAS) OR (obes* AND hypoventil*) OR pickwick*)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to sleep apnoea population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

B.2.1 Health economic studies strategy

Table 22: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 6 July 2020	Exclusions Health economics studies
Embase	2014 – 6 July 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

	exp Sleep Apnea Syndromes/
1.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
2.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
3.	(OSAHS or OSA or OSAS).ti,ab.
4.	(obes* adj3 hypoventil*).ti,ab.
5.	pickwick*.ti,ab.
6.	or/1-6
7.	limit 7 to English language
8.	letter/
9.	editorial/

10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/9-16
17.	randomized controlled trial/ or random*.ti,ab.
18.	17 not 18
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/19-25
26.	8 not 26
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/28-43
44.	27 and 44

Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6

8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Sleep Apnea Syndromes EXPLODE ALL TREES
#2.	(sleep* adj4 (apn?ea* or hypopn?ea*))
#3.	(sleep* adj4 disorder* adj4 breath*)
#4.	(OSAHS or OSA or OSAS)
#5.	(obes* adj3 hypoventil*)
#6.	(pickwick*)
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

B.2.2 Quality of life studies strategy

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 26 November 2019	Exclusions Quality of life studies
Embase	1974 – 26 November 2019	Exclusions Quality of life studies

Medline (Ovid) search terms

1.	exp Sleep Apnea Syndromes/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter/
10.	editorial/
11.	news/
12.	exp historical article/
13.	Anecdotes as Topic/
14.	comment/
15.	case report/
16.	(letter or comment*).ti.
17.	or/9-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animals/ not humans/
21.	exp Animals, Laboratory/
22.	exp Animal Experimentation/
23.	exp Models, Animal/
24.	exp Rodentia/
25.	(rat or rats or mouse or mice).ti.
26.	or/19-25
27.	8 not 26
28.	quality-adjusted life years/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.

33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	27 and 47

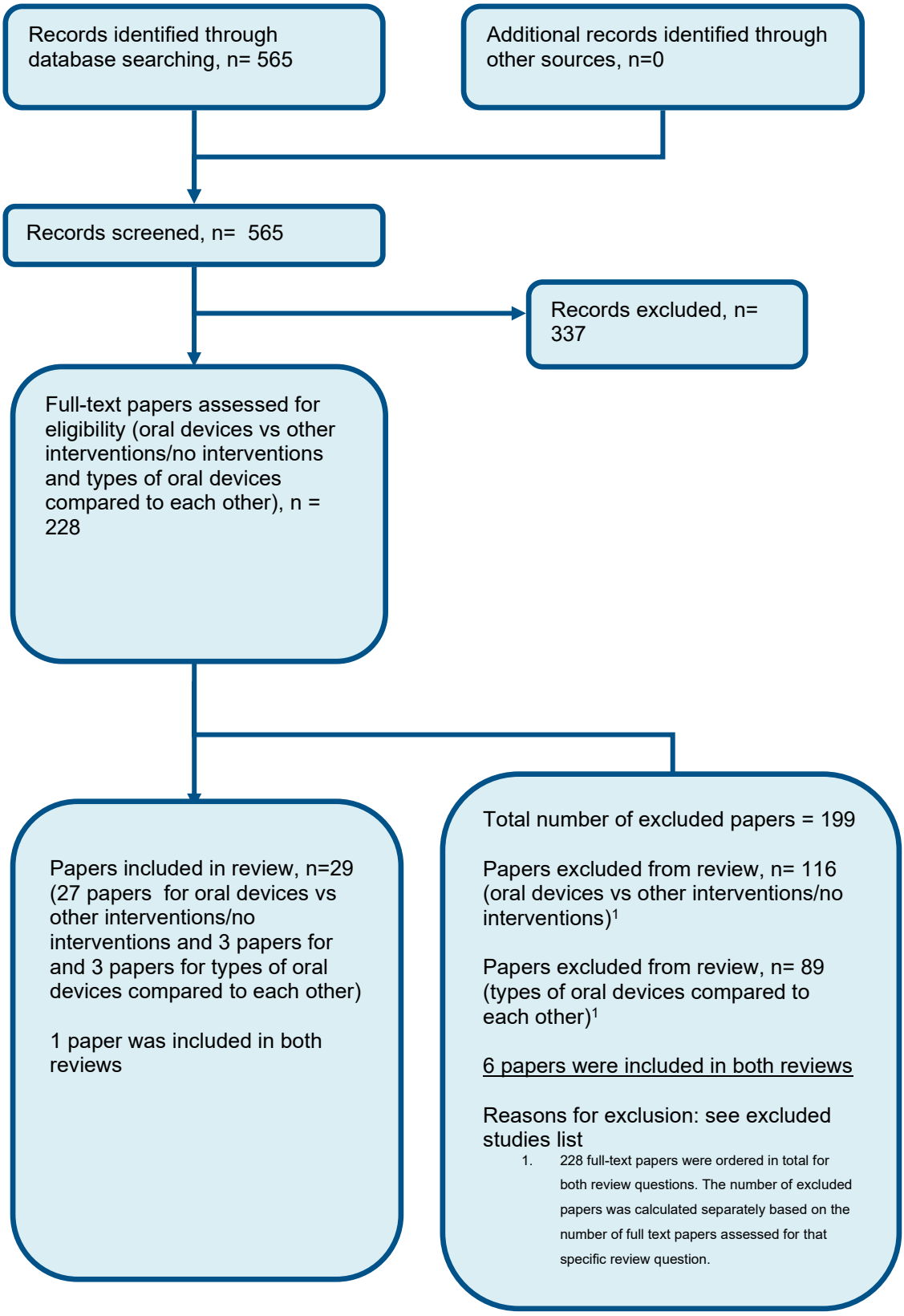
Embase (Ovid) search terms

1.	exp Sleep Disordered Breathing/
2.	(sleep* adj4 (apn?ea* or hypopn?ea*)).ti,ab.
3.	(sleep* adj4 disorder* adj4 breath*).ti,ab.
4.	(OSAHS or OSA or OSAS).ti,ab.
5.	(obes* adj3 hypoventil*).ti,ab.
6.	pickwick*.ti,ab.
7.	or/1-6
8.	limit 7 to English language
9.	letter.pt. or letter/
10.	note.pt.
11.	editorial.pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/9-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice).ti.
24.	or/16-23
25.	8 not 24

26.	quality adjusted life year/
27.	"quality of life index"/
28.	short form 12/ or short form 20/ or short form 36/ or short form 8/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.
41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/26-46
48.	25 and 47

Appendix C: Clinical evidence selection

Figure 3: Flow chart of clinical study selection for the review of oral devices



Appendix D: Clinical evidence tables

Mandibular advancement splints compared to other interventions/no interventions

Study (subsidiary papers)	**Aarab 2011[2] (Aarab 2011[3], Aarab 2017[4], Nikolopoulou 2017[154],Nikolopoulou 2020[152])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Netherlands; Setting: Eligible OSA patients, living in the greater Amsterdam area, were referred to the Slotervaart Medical Center by their family physician. All patients underwent a thorough medical examination, including a full PSG recording, at the Departments of Neurology, Pulmonary Medicine, and ENT, as well as a thorough dental examination at the Department of Oral Kinesiology of the Academic Center for Dentistry Amsterdam (ACTA)
Line of therapy	1st line
Duration of study	Intervention + follow up: 6, 12 and 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years, an apnoea-hypopnea index (AHI) between 5 and 45 events per hour, and a report of excessive daytime sleepiness (Epworth Sleepiness Score 6 10) or at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g. unrefreshing sleep and daytime fatigue excessive daytime sleepiness (Epworth Sleepiness Score 6 10) or at least two of the symptoms suggested by the

Study (subsidiary papers)	Aarab 2011[2] (Aarab 2011[3], Aarab 2017[4], Nikolopoulou 2017[154],Nikolopoulou 2020[152])
	American Academy of Sleep Medicine Task Force, e.g. unrefreshing sleep and daytime fatigue
Exclusion criteria	Medical - Respiratory/sleep disorder other than OSA; BMI over 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)
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): 52.0 (9.6). Gender (M:F): 47/17. Ethnicity: Dutch
Further population details	1. BMI: BMI of 30 kg/m^2 or more (MAD 27.1(3.2); nCPAP 30.7 (3.7); 31.1(4.7); Dropouts 27.8(4.1)). 2. Co-existing conditions: Not stated / Unclear 3. Gender: Not applicable 4. High risk occupation group: Not applicable 5. Race: Not applicable 6. Sleepiness: ESS >9 (ESS >=10).
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Oral devices. an individually fabricated MAD with an adjustable protrusive mandibular position at a constant vertical dimension was use Duration 6 months (+/-2months). Concurrent medication/care: All patients underwent throughout medical examination, including full PSG recording, at the departments of neurology, Pulmonary medicine, and ENT, as well as through dental examination at the department of Oral Kinesiology at the Academic Center for dentistry Amsterdam (ACTA) Indirectness: No indirectness Further details: 1. Intervention type: Not applicable (n=22) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). CPAP - nCPAP of the REMstar Pro system was used (Respironics, Herrsching, Germany). Duration 6 months (+/-2months). Concurrent medication/care: All patients underwent throughout medical examination, including full PSG recording, at the departments of neurology, Pulmonary medicine, and ENT, as well as through dental examination at the department of Oral Kinesiology at the Academic Center for

Study (subsidiary papers)	Aarab 2011[2] (Aarab 2011[3], Aarab 2017[4], Nikolopoulou 2017[154],Nikolopoulou 2020[152])
	dentistry Amsterdam (ACTA). Indirectness: No indirectness Further details: 1. Intervention type: Not applicable (n=21) Intervention 3: No intervention - Placebo. Placebo - a thin (<1mm), hard acrylic-resin palatal splint with only a partial palatal coverage was used as a placebo. Duration 6 months (+/-2months). Concurrent medication/care: All patients underwent throughout medical examination, including full PSG recording, at the departments of neurology, Pulmonary medicine, and ENT, as well as through dental examination at the department of Oral Kinesiology at the Academic Center for dentistry Amsterdam (ACTA). Indirectness: No indirectness Further details: 1. Intervention type: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: AHI/RDI at >1 month
- Actual outcome for Mild-moderate: AHI (difference between baseline and therapy evaluation) at short term follow up; Group 1: mean 16.3 (SD 10.3); n=20, Group 2: mean 19.5 (SD 8.7); n=18
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3
- Actual outcome for Mild-moderate: AHI (difference between baseline and therapy evaluation) at 6 months after short term therapy evaluation; Group 1: mean 15.6 (SD 10.1); n=17, Group 2: mean 19.6 (SD 10.7); n=16
Risk of bias: All domain - ; Indirectness of outcome: No indirectness
- Actual outcome for Mild-moderate: AHI (difference between baseline and therapy evaluation) at 12 months after short term therapy evaluation; Group 1: mean 15 (SD 10.5); n=15, Group 2: mean 20.2 (SD 8.6); n=13
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 2: Adverse effects of treatment at >1 month
- Actual outcome for Mild-moderate: Side effects at short term follow up; Group 1: 48/20, Group 2: 15/18; Comments: Oral devices group: Sensitive teeth upon awakening - 13, discomfort in wearing - 10; hyper salivation - 9; dry mouth - 4; feeling of changed occlusion - 9, difficulty swallowing - 3;
CPAP group: Dry mouth-3, problems with expiration against the positive pressure of the mask - 5; nasal congestion - 2; conjunctivitis - 2; difficulty changing sleep position - 3

Study (subsidiary papers)	Aarab 2011[2] (Aarab 2011[3], Aarab 2017[4], Nikolopoulou 2017[154],Nikolopoulou 2020[152])
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 - Actual outcome for Mild-moderate: TMD (temporomandibular disorder) pain at 6 months after short term therapy evaluation; Group 1: 0/20, Group 2: 2/18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 3: Adherence in hours of use at >1 month - Actual outcome for Mild-moderate: Compliance at short term follow up; Group 1: mean 90.6 % of the nights used (SD 13.3); n=20, Group 2: mean 82.9 % of the nights used (SD 27.2); n=18 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus NO ACTIVE TREATMENT Protocol outcome 1: AHI/RDI at >1 month - Actual outcome for Mild-moderate: AHI (difference between baseline and therapy evaluation) at short term follow up; Group 1: mean 16.3 (SD 10.3); n=20, Group 2: mean 5.2 (SD 10.5); n=19 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 2: Adverse effects of treatment at >1 month - Actual outcome for Mild-moderate: Side effects at short term follow up; Group 1: 48/20, Group 2: 0/19; Comments: Oral devices group: Sensitive teeth upon awakening - 13, discomfort in wearing - 10; hyper salivation - 9; dry mouth - 4; feeling of changed occlusion - 9, difficulty swallowing - 3; Placebo group - none reported - Actual outcome for Mild-moderate: TMD (temporomandibular disorder) pain at 6 months after short term therapy evaluation; Group 1: 0/20, Group 2: 0/19 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3 Protocol outcome 3: Adherence in hours of use at >1 month - Actual outcome for Mild-moderate: Compliance at short term follow up; Group 1: mean 90.6 % of the nights used (SD 13.3); n=20, Group 2: mean 93.9 %	

Study (subsidiary papers)	Aarab 2011[2] (Aarab 2011[3], Aarab 2017[4], Nikolopoulou 2017[154],Nikolopoulou 2020[152])
of the nights used (SD 15.7); n=19 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; Sleepiness score at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Andren 2013[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in Sweden; Setting: Department of Clinical Physiology at Västmanland County Hospital, Västerås, Sweden
Line of therapy	Unclear
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate

Study	Andren 2013[9]
Subgroup analysis within study	Not applicable
Inclusion criteria	Verified OSA defined as an apnoea hypopnea index (AHI) ≥10, systemic hypertension defined as office systolic BP >140 mmHg or diastolic BP >90 mmHg at two separate occasions, and were not currently being treated with an OA or CPAP. Patients also had to possess a sufficient number of teeth for the retention of an OA.
Exclusion criteria	Office systolic BP >180 mmHg or diastolic BP >110 mmHg, body mass index (BMI) over 35 kg/m^2, atrial fibrillation, chronic obstructive lung disease, epilepsy, severe psychiatric disease, maximal protrusion of the mandible <6 mm, and an inability to speak or understand the Swedish language.
Recruitment/selection of patients	The patients were consecutively recruited from the Department of Clinical Physiology at Västmanland County Hospital, Västerås, Sweden, to where they had been referred for an ambulatory somnographic recording.
Age, gender and ethnicity	Age - Mean (SD): oral device = 57 (8), control = 59 (9). Gender (M:F): 57/15. Ethnicity: unclear
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: HTN 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: patients with severe OSA included with mild and moderate based on AHI
Interventions	(n=36) Intervention 1: Oral devices. The active OA with mandibular advancement (OAa) was custom-made and of a monoblock design, as previously described by Tegelberg et al. The OAa protruded the mandible to 70–75 % of the patient's maximum mandibular protrusive capacity (>4 mm). Duration 3 months. Concurrent medication/care: The patients were informed that there were two types of devices to be evaluated but not informed on which one of the devices they would receive. Ambulatory somnographic recordings were made with a validated portable digital recording unit with sensors for the registration of airflow, saturation, respiratory movements of the chest, body position, and snoring sounds (Embletta PDS device; Medcare Flaga, Iceland). The recordings were undertaken in the patient's home, transmitted to a computer, and analysed manually by one experienced technician blinded to the intervention type. At the 3-month follow-up, the patients slept with the OA in situ during registration. Indirectness: No indirectness (n=36) Intervention 2: No intervention - Placebo. The control OA (OAc) possessed the same feature as the

Study	Andren 2013[9]
	active device except for the lack of any mandibular advancement (<0.5 mm). Duration 3 months. Concurrent medication/care: The patients were informed that there were two types of devices to be evaluated but not informed on which one of the devices they would receive. Ambulatory somnographic recordings were made with a validated portable digital recording unit with sensors for the registration of airflow, saturation, respiratory movements of the chest, body position, and snoring sounds (Embletta PDS device; Medcare Flaga, Iceland). The recordings were undertaken in the patient's home, transmitted to a computer, and analysed manually by one experienced technician blinded to the intervention type. At the 3-month follow-up, the patients slept with the OA in situ during registration. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO

Protocol outcome 1: Sleepiness score at >1 month - The ESS scores improved significantly in the active compared with the control group (−4.3 vs. −2.1; P<0.006)
- Actual outcome for Moderate: ESS - change score at 3 months;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 2 (excluded due to normal ambulatory BP), also one patient from control group withdrew and did not attend follow-up. Two patients from active groups did not use their OA but attended follow up and were analysed as members of active group (ITT)

Protocol outcome 2: AHI/RDI at >1 month - The ESS scores improved significantly in the active compared with the control group (−4.3 vs. −2.1; P<0.006)
- Actual outcome for Moderate: AHI - change score at 3 months;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 2

Protocol outcome 3: Daytime Mean systolic blood pressure for hypertension at >1 month
- Actual outcome for Moderate: systolic blood pressure at 3 months; Group 1: mean 141.3 mmHg (SD 10.5); n=36, Group 2: mean 144.9 mmHg (SD 10.9); n=36
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: serious indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 2

Study	Andren 2013[9]
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Study	Barnes 2004[16]
Study type	RCT (Patient randomised; Crossover: 2 week washout period between treatments)
Number of studies (number of participants)	1 (n=114)
Countries and setting	Conducted in Australia; Setting: Two Australian centres (Austin Health, Melbourne, Victoria and Daw park Repatriation General hospital, Adelaide, South Australia)
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Subjects were middle aged (47.0 (0.9)), predominantly male (80%), and overweight (interquartile range body mass index, 27.8-32.8 kg/m²), with mild to moderate OSA (AHI, 5-30 per hour)
Exclusion criteria	not specified

Study	Barnes 2004[16]
Recruitment/selection of patients	not stated
Age, gender and ethnicity	Age - Mean (SD): 47.0(0.9). Gender (M:F): Define. Ethnicity: not stated
Further population details	1. BMI: BMI of 30 kg/m^2 or more (Interquartile body mass index, 27.8-32.8 kg/m²). 2. Co-existing conditions: Not stated / Unclear 3. Gender: Not stated / Unclear (80% male). 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9 (10.7(0.4)).
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Oral devices. mandibular advancement splint medical dental sleep appliance , Sullivan elite, res medMAS/ custom-made Duration 3 months. Concurrent medication/care: At the beginning of the trial and at the end of each 3-month treatment period, all subjects underwent overnight polysomnography, comprehensive neurobehavioral testing, 24-hour ambulatory blood pressure, and echocardiography. Indirectness: No indirectness Further details: 1. Intervention type: Physical (MAS). (n=97) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). CPAP. Duration 3 months. Concurrent medication/care: At the beginning of the trial and at the end of each 3-month treatment period, all subjects underwent overnight polysomnography, comprehensive neurobehavioral testing, 24-hour ambulatory blood pressure, and echocardiography. Indirectness: No indirectness Further details: 1. Intervention type: Electronic (CPAP). (n=98) Intervention 3: No intervention - Placebo. Placebo. Duration 3 months. Concurrent medication/care: At the beginning of the trial and at the end of each 3-month treatment period, all subjects underwent overnight polysomnography, comprehensive neurobehavioral testing, 24-hour ambulatory blood pressure, and echocardiograph. Indirectness: No indirectness Further details: 1. Intervention type: Not applicable (Placebo).
Funding	Funding not stated

Study	Barnes 2004[16]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP) Protocol outcome 1: Quality of life at >1 month - Actual outcome for Mild-moderate: FOSQ mean score at 3 months; Group 1: mean 3.3 (SD 0.1); n=80, Group 2: mean 3.3 (SD 0.1); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 - Actual outcome for Mild-moderate: SF36 at 3 months; Group 1: mean 73.7 (SD 1.2); n=80, Group 2: mean 74.1 (SD 1.2); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Mild-moderate: ESS at 3 months; Group 1: mean 9.2 (SD 0.4); n=80, Group 2: mean 9.2 (SD 0.4); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Mild-moderate: AHI at 3 months; Group 1: mean 14 (SD 1.1); n=80, Group 2: mean 4.8 (SD 0.5); n=80 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14; Group 2 Number missing: 8 Protocol outcome 4: ODI at >1 month - Actual outcome for Mild-moderate: oxygen desaturation index at 3 months; Group 1: mean 8.1 (SD 1.3); n=80, Group 2: mean 1.6 (SD 0.2); n=80 Risk of bias: All domain - ; Indirectness of outcome: Serious indirectness Protocol outcome 5: Adherence in hours of use at >1 month - Actual outcome for Mild-moderate: Adherence hours per week at 3 months; Group 1: mean 5.3 (SD 0.3); n=80, Group 2: mean 4.2 (SD 0.3); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable	

Study	Barnes 2004[16]
to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 Protocol outcome 6: Patient preference at >1 month - Actual outcome for Mild-moderate: treatment preference at 3 months; both subjects with OSA and their domestic partners felt that the placebo tablet was easiest to use, but that CPAP worked best (56% subjects and 53% partners) and was overall preferred treatment for 44% subjects and 40 % partners. MAS was overall preferred treatment for £)% of the subjects and 36 % of the domestic partners; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 Protocol outcome 7: Systolic blood pressure for hypertension at >1 month - Actual outcome for Mild-moderate: 24 hour mean systolic BP at 3 months; Group 1: mean 126.7 (SD 1); n=80, Group 2: mean 127.3 (SD 1.2); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work - 5, moved away - 1, unable to tolerate - 1, subject illness - 1 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO Protocol outcome 1: Quality of life at >1 month - Actual outcome for Mild-moderate: FOSQ at 3 months; Group 1: mean 3.3 (SD 0.1); n=80, Group 2: mean 3.3 (SD 0.1); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 - Actual outcome for Mild-moderate: SF36 at 3 months; Group 1: mean 73.7 (SD 1.2); n=80, Group 2: mean 71.4 (SD 1.4); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Mild-moderate: ESS at 3 months; Group 1: mean 9.2 (SD 0.4); n=80, Group 2: mean 10.2 (SD 0.4); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study	Barnes 2004[16]
Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Mild-moderate: AHI at 3 months; Group 1: mean 14.1 (SD 1.1); n=80, Group 2: mean 20.3 (SD 1.1); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 4: ODI at >1 month - Actual outcome for Mild-moderate: oxygen desaturation index at 3 months; Group 1: mean 8.1 (SD 1.3); n=80, Group 2: mean 12.5 (SD 1.6); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 5: Adherence in hours of use at >1 month - Actual outcome for Mild-moderate: Adherence hours per night at 3 months; Group 1: mean 5.5 hours per night (SD 0.3); n=80, Group 2: mean 3.6 hours per night (SD 0.3); n=80; Comments: CPAP use was measured objectively by an inbuilt meter, which measured time at pressure. MAS was assessed subjectively with a subject diary Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 - Actual outcome for Mild-moderate: Adherence hours per week at 3 months; Oral devices - 5.3 (0.3) hours per night placebo tablets - patients took placebo pills for 94.3 +/- 1.2% of the nights; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 6: Patient preference at >1 month - Actual outcome for Mild-moderate: treatment preference at 3 months; both subjects with OSA and their domestic partners felt that the placebo tablet was	

Study	Barnes 2004[16]
easiest to use, but that CPAP worked best (56% subjects and 53% partners) and was overall preferred treatment for 44% subjects and 40 % partners. MAS was overall preferred treatment for £)% of the subjects and 36 % of the domestic partners; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Protocol outcome 7: Systolic blood pressure for hypertension at >1 month - Actual outcome for Mild-moderate: 24 hour mean systolic at 3 months; Group 1: mean 126.7 (SD 1); n=80, Group 2: mean 128.2 (SD 1.2); n=80 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 14, Reason: teeth unsuitable - 5, time commitments - 2, unable to tolerate 2, moved away -1, unrelated illness -1, lost weight and felt better - 1, lost to follow up - 1; Group 2 Number missing: 8, Reason: work 4, time commitments 2n only wanted CPAP 1, subject illness 1 Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Study	De Britto Teixeira 2013[41]
Study type	RCT (Patient randomised; Crossover)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in Brazil; Setting: Department of Orthodontics at the School of Dentistry, State University of Rio de Janeiro.

Study	De Britto Teixeira 2013[41]
Line of therapy	Unclear
Duration of study	Intervention time: 10.5 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of mild-to-moderate OSAS, with the exclusion of primary snorers (AHI < 5). Diagnosis was based on overnight polysomnography, considered the gold standard for OSAS diagnosis. The diagnosis of lack of nasal obstruction was done using magnetic resonance imaging.
Exclusion criteria	The following patients were excluded from the study: (a) those who did not have at least eight teeth per arch as they were unable to adequately retain the dental devices, (b) those with severe periodontal problems since the force delivered by the device to the teeth might cause tooth loss, and (c) those with a history of temporomandibular disorders due to the fact that the mechanics deployed by the mandibular advancement device generates tension in the joint that might aggravate this disorder.
Recruitment/selection of patients	Patients were selected by two neurologists certified in sleep medicine. These physicians screened subjects in their private offices based on medical history and evidence of obstructive sleep apnoea syndrome by means of overnight polysomnography, in addition to a diagnosis indicating that airflow obstruction was not located in the upper portion of the upper airway (nose or nasopharynx). Based on this diagnosis, whenever they believed a patient could be treated with an oral appliance, he/she was referred for evaluation to the orthodontic clinic of the postgraduate program in Orthodontics at the School of Dentistry, State University of Rio de Janeiro.
Age, gender and ethnicity	Age - Mean (SD): 48.6 (9.6). Gender (M:F): 11/8. Ethnicity: unclear

Study	De Britto Teixeira 2013[41]
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Not stated / Unclear
Extra comments	None
Indirectness of population	Serious indirectness: Patients of mild (8), moderate (10) and severe (1) AHI included
Interventions	(n=19) Intervention 1: Oral devices. A twin block (TB) experimental mandibular advancement device was modified for use in this situation. It consisted of two parts, one for the upper arch and one for the lower. It was fabricated from self-curing acrylic resin with occlusal coverage on all teeth so as to reduce changes in tooth positioning that might arise from its use. Each piece had, on its occlusal surface, bilateral slopes with approximately 45° inclination which, when joined, caused the mandible to advance by 75% of each patient's maximum mandibular advancement capacity. Duration 10.5 months. Concurrent medication/care: The polysomnographies took place in two particular clinics in Rio de Janeiro, Brazil. Both used the same device (Alice model, Philips Respironics, Bothell, Washington, USA). All patients who participated in the project used both types of devices (experimental and control). Patients were instructed to wear the devices only during sleep, regardless of the time of day. The order of use was randomly chosen by draw. The placebo device was worn for a mean of 3.8 months (SD = 0.8); after which, the patients were subjected to follow-up polysomnography. TB was used for a mean of 6.5 months (SD = 2.0), and overnight polysomnography was performed after this period to assess the results. Before placing the second device, patients spent a week wearing nothing in order to avoid any interference with the results. Indirectness: Serious indirectness; Indirectness comment: pts included with mild, moderate and 1 severe based on AHI value (n=19) Intervention 2: No intervention - Placebo. The device used as placebo was an acrylic upper plate covering the palate, with a labial arch made of 0.9-mm wire contouring all the teeth and extending past the distal side of the last tooth, where it was fastened to the acrylic plate, in what is known as wraparound device. Duration 10.5 months. Concurrent medication/care: The polysomnographies took place in two particular clinics in Rio de Janeiro, Brazil. Both used the same device (Alice model, Philips Respironics, Bothell, Washington, USA). All patients who participated in the project used both types of devices (experimental and control). Patients were instructed to wear the devices only during sleep, regardless of the time of day. The

Study	De Britto Teixeira 2013[41]
	order of use was randomly chosen by draw. The placebo device was worn for a mean of 3.8 months (SD = 0.8); after which, the patients were subjected to follow-up polysomnography. TB was used for a mean of 6.5 months (SD = 2.0), and overnight polysomnography was performed after this period to assess the results. Before placing the second device, patients spent a week wearing nothing in order to avoid any interference with the results. Indirectness: Serious indirectness; Indirectness comment: pts with mild, moderate and 1 severe based on AHI score were included
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO Protocol outcome 1: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 3-6 months; Group 1: mean 11.7 (SD 9.4); n=19, Group 2: mean 19.6 (SD 14.8) n= 19 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: patients with mild, moderate and 1 severe based on AHI score were included; Blinding details: Follow up period was a mean of 3.8 months in the placebo group and 6.5 in the oral device group; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; Sleepiness score at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study (subsidiary papers)	De Vries 2019[43] (De Vries 2019[42])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=86)

Study (subsidiary papers)	De Vries 2019[43] (De Vries 2019[42])
Countries and setting	Conducted in Netherlands; Setting: multiple centres in The Netherlands
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	All consecutive patients aged 18 years or older with an AHI of 15 to 30 events/h based on PSG (primarily of the obstructive type) and fulfilling the inclusion and exclusion criteria were invited to take part in a parallel multi centre randomised controlled trial and scheduled for a baseline visit.
Age, gender and ethnicity	Age - Mean (SD): 50.7 (9.7). Gender (M:F): 70/15. Ethnicity: unclear
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Not applicable 3. Gender: Systematic review: mixed (mostly male). 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Oral devices. Patients were treated with a custom-made titratable biblock MAD (SomnomedDent MAD SomnoMed Australia/Europe AG.) to start the mandible was set at approximately 60-70% of the patient's maximum advancement.

Study (subsidiary papers)	De Vries 2019[43] (De Vries 2019[42])
	. Duration 12 months. Concurrent medication/care: patients attended follow up appointments at 3, 6 and 12 months. in case of unsuccessful treatment (i.e. <50% reduction in AHI), adjustments to the therapy were made and a second PSG was scheduled. at 12 months a final PSG was performed. for each patient the same type of PSG (in laboratory/home based) was performed during follow up as on baseline. Indirectness: No indirectness Further details: 1. Intervention type: Not applicable 2. Type of device: Titratable (n=42) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). dose/quantity, brand name, extra details. Duration 12 months. Concurrent medication/care: patients attended follow up appointments at 3, 6 and 12 months. in case of unsuccessful treatment (i.e. <50% reduction in AHI), adjustments to the therapy were made and a second PSG was scheduled. at 12 months a final PSG was performed. for each patient the same type of PSG (in laboratory/home based) was performed during follow up as on baseline. Indirectness: No indirectness
Funding	Other author(s) funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP) - Actual outcome for Moderate: SF-36 vitality at 12 months; Group 1: mean 59.3 (SD 24.2); n=29, Group 2: mean 60.7 (SD 22.5); n=37 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: compliance failure or stopped ; Group 2 Number missing: 5, Reason: compliance failure or stopped - Actual outcome for Moderate: SF-36 Physical at 12 months; Group 1: mean 81.9 (SD 21.7); n=29, Group 2: mean 81.8 (SD 19.7); n=37; SF-36 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: compliance failure or stopped ; Group 2 Number missing: 5, Reason: compliance failure or stopped - Actual outcome for Moderate: SF-36 mental at 12 months; Group 1: mean 72.6 (SD 21.7); n=29, Group 2: mean 76 (SD 18.7); n=37; SF-36 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: compliance failure or stopped ; Group 2 Number	

Study (subsidiary papers)	De Vries 2019[43] (De Vries 2019[42])
missing: 5, Reason: compliance failure or stopped - Actual outcome for Moderate: QOL - EQ5D at 12 months; Group 1: mean 74.4 (SD 14.4); n=29, Group 2: mean 71.1 (SD 12.9); n=37; EQ5D 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: compliance failure or stopped ; Group 2 Number missing: 5, Reason: compliance failure or stopped - Actual outcome for Moderate: objective adherence (hours per night) at 12 months; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: read out failure, chip failure, loss to follow up, switched; Group 2 Number missing: 12, Reason: missing data, stopped, switched - Actual outcome for Moderate: objective adherence (>4 hours per night %) at 12 months; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: read out failure, chip failure, loss to follow up, switched; Group 2 Number missing: 12, Reason: missing data, stopped, switched Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: AHI at 12 months; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 19, Reason: 10 treatment failure, 5 stopped, 4 lost to follow up; Group 2 Number missing: 12, Reason: 8 compliance failure, 4 stopped - Actual outcome for Moderate: ESS at 12 months; Group 1: mean 7.1 (SD 5.2); n=29, Group 2: mean 5.3 (SD 3.9); n= 37 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: compliance failure or stopped ; Group 2 Number missing: 5, Reason: compliance failure or stopped - Actual outcome for Moderate: ESS at 3 months; Group 1: mean 5.3 (SD 3.1); n=17, Group 2: mean 5.4 (SD 3.8); n= 23 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9, Reason: compliance failure or stopped ; Group 2 Number missing: 9, Reason: compliance failure or stopped	
Protocol outcomes not reported by the study	Mortality at >1 month; AHI/RDI at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month; Cardiovascular events at >1 month

Study	Duran-Cantolla 2015[54]
Study type	RCT (Patient randomised; Crossover: 2 weeks)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Conducted in Spain; Setting: Interdisciplinary Unit of Sleep Disorders of Alava University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria: Adult subjects referred due to a clinical suspicion of OSA. Patients from both sexes were eligible to participate in this study and were selected according to the following inclusion criteria; age high than 18 years, Presence of chronic snoring (A patient is considered as chronic snorer if his/her bed mate/roommate reported to snore more than 5 days per week and this is corroborated by a respiratory polygraphy performed in the patient's own home. The result of the respiratory polygraphy should indicate the presence of snoring during at least 30% of the nocturnal period), Confirmed diagnosis of mild to moderate OSA (5 ≤AHI < 30) by polysomnography (PSG) and to have a roommate or bed mate to submit information.
Exclusion criteria	Patients were excluded according to the following exclusion criteria: - High-risk professions and/or controlling dangerous machines. - Moderate or severe somnolence during day time. - Coronary cardiopathy, acute vascular disease (less than three months), chronic and severe obstructive pulmonary disease, and chronic treatment with theophylline. - Temporo-mandibular joint problems or periodontitis. - Mandibular protrusion capacity less than 6 mm and/or less than 10teeth in each jaw. -Severe cognitive disorders and/or patients whose an-swers to the questionnaires will be altered by chronic

Study	Duran-Cantolla 2015[54]
	and severe diseases. - Pregnancy (since the third month of pregnancy to 3 months after birth delivery).
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): 46.5(9.3). Gender (M:F): 33/9. Ethnicity: n/a
Further population details	1. BMI: BMI of less than 30 kg/m^2 (27.7(3.2)). 2. Co-existing conditions: Not applicable 3. Gender: Not applicable 4. High risk occupation group: Not applicable 5. Race: Not applicable 6. Sleepiness: ESS >9 (12.2(4.3)).
Indirectness of population	Serious indirectness – includes mild and moderate severity AHI
Interventions	(n=42) Intervention 1: Oral devices. Oral device was defined as a splint in the centric occlusion that did not induce a mandibular advancement served as a control. Mandibular advancement device (MAD): The commercial device Klearway TM (University of British Columbia, Vancouver, Canada) was used. The fabrication of the device was made on model casts of both jaws and was adapted to the patient's mouth by a dentist with the objective to achieve a sufficient and tolerable mandibular advancement, being at least 65% of the maximum protrusion capacity of the mandible. This phase may need more than one visit to the dentist and had a period of 4 weeks at maximum. Duration 4 weeks. Concurrent medication/care: Initially, each patient was subjected to a period of 2 weeks without any treatment, followed by 4 weeks of adaptation and standardization of the device (MAD or PD), and 12 weeks of treatment. Once this period was finished, patients were switched to use the other device following the same protocol. Indirectness: No indirectness Further details: 1. Intervention type: Physical (oral device). (n=42) Intervention 2: No intervention – Placebo The placebo device was the same KlearwayTM device but in centric occlusion and did not provoke mandibular advancement. The dentist assured the absence of mandibular advancement and alteration to the TMJ position. The reference point was jaw position at the TMJ level in rest as measured by cephalometry. The PD adaptation may need more than one visit to the dentist and had a period of 4 weeks at maximum. Duration 4 weeks. Concurrent medication/care: Initially, each patient was subjected to a period of 2 weeks without any treatment, followed by 4 weeks of adaptation and standardization of the device (MAD or PD), and 12 weeks of treatment. Once this period was finished, patients were switched to use the other device following the same protocol. Indirectness: No indirectness

Study	Duran-Cantolla 2015[54]
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Mild-moderate: Epworth (0-24) at 4 weeks; Group 1: mean 10.3 (SD 4.2); n=39, Group 2: mean 9.8 (SD 4.4); n=38 Basal phase (n=42): 12.2 (4.3)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Mild-moderate: AHI at 4 weeks; Group 1: mean 11.9 (SD 15.5); n=39, Group 2: mean 25.9 (SD 26); n=38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4

Protocol outcome 3: Adverse effects of treatment at >1 month
- Actual outcome for Mild-moderate: Adverse effects of treatment total number at 4 weeks; Group 1: 36/39, Group 2: 33/38; Comments: secondary effects included: hypersalivation, dental or gingival pain, pain in the tongue temporal bite change, pain in the temporomandibular joint, mouth dryness, unspecific splint intolerance, damage to dental restorations, splint fracture
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4
- Actual outcome for Mild-moderate: Adverse effects-patients with mild secondary effects at 4 weeks; Group 1: 24/39, Group 2: 20/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4
- Actual outcome for Mild-moderate: Adverse effects-patients with moderate secondary effects at 4 weeks; Group 1: 7/39, Group 2: 13/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4
- Actual outcome for Mild-moderate: Adverse effects-patients with severe secondary effects at 4 weeks; Group 1: 5/39, Group 2: 0/38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4

Protocol outcome 4: Adherence in hours of use at >1 month
- Actual outcome for Mild-moderate: adherence hours per night at 4 weeks; Group 1: mean 6.4 (SD 2.4); n=39, Group 2: mean 6.2 (SD 2); n=38
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness

Study	Duran-Cantolla 2015[54]
of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 - Actual outcome for Mild-moderate: adherence >5 hours per night (n;%) at 4 weeks; Group 1: 34/39, Group 2: 29/38; Comments: Oral device group - 87.1 %; Placebo device 76.3% Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 4 Protocol outcome 5: Systolic blood pressure for hypertension at >1 month - Actual outcome for Mild-moderate: systolic blood pressure at 4 weeks; Group 1: mean 123.6 mmHg (SD 18.5); n=39, Group 2: mean 125.9 mmHg (SD 15.6); n=38 Basal phase (n=42) 123.8 mmHg (SD 9.9) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Study (subsidiary papers)	Ferguson 1997[61] (Ferguson 1996[62])
Study type	RCT (Patient randomised; Crossover: 2 weeks)
Number of studies (number of participants)	2 (n=24)
Countries and setting	Conducted in Canada; Setting: All patients were seen in the sleep disorders clinic at the Vancouver hospital and health sciences centre between February 1993 and April 1994
Line of therapy	1st line
Duration of study	Intervention + follow up: 4weeks

Study (subsidiary papers)	Ferguson 1997[61] (Ferguson 1996[62])
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	24 patients with symptomatic mild to moderate OSA (AHI 15-55/hour of sleep diagnostic polysomnography) were recruited. Patients had at least 10 teeth in each of the maxillary and mandibular arches, and lived in the metropolitan Vancouver area
Exclusion criteria	Less than 10 teeth in each of the maxillary and mandibular arches.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 44.0 (10.6). Gender (M:F): 19/4. Ethnicity: n/a
Further population details	1. BMI: BMI of 30 kg/m^2 or more (32(8.2)). 2. Co-existing conditions: Not applicable 3. Gender: Not applicable (mixed 19 men 5 female). 4. High risk occupation group: Not applicable 5. Race: Not applicable 6. Sleepiness: ESS >9 (10.7(3.4)).
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Oral devices. The anterior mandibular positioner (AMP) used during this study is a new appliance with several novel features. It is constructed of a methyl methacrylate material (SR-Ivocap; Elastomer Ivoclar Co, New York, USA) and the upper and lower portions of the appliance provide full occlusive coverage of teeth. A titanium hinge with the five holes connects upper and lower portions. This hinge allows a small amount of lateral movement of the jaw. There is a space between the teeth to permit oral airflow. The amount of mandibular advancement was initially set at 70% of maximal mandibular advancement. The AMP was adjusted to maximise comfort by relieving pressure points on the teeth and gums. The amount of mandibular advancement was the progressively increased over the next three months by mean (SD) of 1.8(1.2) mm until snoring ceased and symptoms improved or until the patient could not tolerate further advancement. Duration 4 months. Concurrent medication/care: Each patient underwent overnight

Study (subsidiary papers)	Ferguson 1997[61] (Ferguson 1996[62])
	polysomnography before recruitment to the study. Indirectness: No indirectness Further details: 1. Intervention type: Physical (Oral device - AMP). (n=24) Intervention 2: Non -surgical intervention - Positive airway pressure variants (CPAP, APAP). nCPAP - was undertaken with either a REMstar Choice machine (Respironics Inc., Murrysville, Pennsylvania, USA) or a Tranquility plus machine (Healthdyne Technologies, Marrietta Georgia, USA) Which were most advanced nCPAP units available at the time of the study. Duration 4 months. Concurrent medication/care: Each patient underwent overnight polysomnography before recruitment to the study. Indirectness: No indirectness Further details: 1. Intervention type: Electronic (CPAP).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Mild-moderate: Epworth sleepiness scale at 4 months; Group 1: mean 4.7 (SD 2.6); n=20, Group 2: mean 5.1 (SD 3.3); n=20
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Mild-moderate: AHI at 4 months; Group 1: mean 14.1 (SD 14.7); n=20, Group 2: mean 4 (SD 2.2); n=20
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4

Protocol outcome 3: ODI at >1 month
- Actual outcome for Mild-moderate: min sa02 at 4 months; Group 1: mean 75.8 % sao2 (SD 11.6); n=24, Group 2: mean 87.7 % sao2 (SD 2.4); n=24
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4

Protocol outcome 4: Adverse effects of treatment at >1 month
- Actual outcome for Mild-moderate: mild side effects at 4 months; AMP - mild side effects were common in the first month of treatment, these included sore teeth, sore jaw muscles, excessive salivation, and difficulty chewing in the morning. At the end of 4 month treatment period nine patients 45% had

Study (subsidiary papers)	Ferguson 1997[61] (Ferguson 1996[62])
persistent mild side effects and four (20%) hade moderate side effects. CPAP - at the end of four month period 4 patients treated with nCPAP had mild side effects, three (15%) had moderate side effects, and three (15%) had severe side effects; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4 Protocol outcome 5: Patient preference at >1 month - Actual outcome for Mild-moderate: Patient preference at 4 months; Patients were less satisfied with nCPAP (p<0.01) 16 patients (80%) were moderately or very satisfied with the AMP. 14 patients (70%) were very or moderately satisfied with CPAP; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4 - Actual outcome for Mild-moderate: patient preference - number of patients at 4 months; Group 1: 17/25, Group 2: 13/21 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 4; Group 2 Number missing: 4	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Glos 2016[78]
Study type	RCT (Patient randomised; Crossover: no wash out)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Germany; Setting: Centre for Sleep Medicine, Charité-Universitätsmedizin Berlin
Line of therapy	Unclear

Study	Glos 2016[78]
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	AHI of ≥5/h and an age of ≥18 years. Patients with severe OSA (AHI >30/h) requiring treatment were included only if they did not demonstrate clear indication for CPAP such as a severe cardiovascular risk, e.g., myocardial infarction, stroke, atrial fibrillation, resistant hypertension, or heart failure. An essential element for inclusion of any patient was a clinical symptom complex, as well as suffering owing to lack of refreshing sleep.
Exclusion criteria	Exclusion criteria were drug abuses, any medication intake that could influence sleep, any presence of sleep disorders other than OSA, any kind of specific medication for OSA in the patient's case history, prior use of any form of PAP therapy, any prior pharyngeal surgery (UPPP, LAUP, or RFT) for OSA therapy, any psychiatric or neurological diseases previously known or arising during the study that could impair compliance, atrial fibrillation, any medication that could affect heart rate, cranio mandibular disorders with restricted mobility of the lower jaw (especially restrictions to protrusion), acute to subacute dental treatment requirements (e.g., caries treatment), >8 stable natural teeth per jaw (with maximum average Perio test value per tooth <20), acute periodontal disease, class III dental relationship with anterior cross bite, participants in orthodontic retention for less than 6 months, and discontinuation of therapy or interruption of therapy for more than 1week. Participants who had taken part in a clinical pharmacological trial up to 4 weeks before entering the study were also excluded.
Recruitment/selection of patients	Eighty-four patients with suspicion of OSA syndrome were asked to participate in the study.
Age, gender and ethnicity	Age - Mean (SD): 49.5 (11.8). Gender (M:F): 33:7 Ethnicity: unclear

Study	Glos 2016[78]
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Not stated / Unclear 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: patients with mild, moderate and severe OSA included
Interventions	(n=48) Intervention 1: Oral devices. If patients had been randomised to initially receive MAD therapy, the MAD (MAD SomnoDent®, Somnomed Europe AG, Zurich, Switzerland) was individually produced and fitted to the patient 1–2 weeks prior to the beginning of the therapy (T1) by the manufacturer (Somnomed Europe AG, Zurich, Switzerland) and by a dentist. Titration with the MAD took place during the first of the two titration nights with an individually adjusted protrusion of up to 70%of the possible maximum. If the AHI remained ≥10/h after the first titration night, the protrusion was individually increased, as recorded by a gauge by another 10% of the patient's maximum protrusion capacity during the second titration night. After the 3 baseline nights the MAD was individually produced and fitted to the patient by a dentist 1–2 weeks prior to the beginning of this therapy. Duration 12 weeks. Concurrent medication/care: Patients were given a 6-channel ambulatory sleep apnoea monitoring device (Embletta pds, Embla Inc., Broomfield, CO, USA), which included recording airflow, snoring, thoracic and abdominal efforts, oxygen saturation, leg movements, and body position. In addition to a physical examination, a general medical case history, and a specific sleep disorder case history, patients were asked to complete the form on the Epworth Sleepiness Scale (ESS) as well as the Insomnia Severity Index (ISI). A dental examination and screening for cranio mandibular disorders (CMD) were performed by a dentist. At T1 in both treatment arms, patients were investigated by polysomnography (PSG) for three consecutive nights without gap. The first night served as baseline PSG, and the subsequent two nights were titration nights to the initial therapy upon randomisation. Criteria for the remaining in the study were an AHI of at least 5/h and exclusion of a relevant PLMD syndrome (PLMI <10/h) or other relevant movement disorders during baseline PSG. After the three baseline PSG nights at T1, the patients were sent home for 12 weeks of continuous use of therapy during sleep with either MAD or CPAP. Afterward, the patients were invited to the sleep lab for another 3 consecutive nights without gap by PSG. Indirectness: Serious indirectness; Indirectness comment: patients with mild, moderate and severe OSA all included (n=48) Intervention 2: Non -surgical intervention - Positive airway pressure variants (CPAP, APAP). patients in

Study	Glos 2016[78]
	the CPAP group received the CPAP (REMstar Pro, Philips Respironics, Murrysville, PA, USA) for a period of 12 weeks. During the two titration nights, manual titration was performed to eliminate apnoea's, hypopneas, oxygen desaturations, and respiratory arousals. Duration 12 weeks. Concurrent medication/care: Patients were given a 6-channel ambulatory sleep apnoea monitoring device (Embletta pds, Embla Inc., Broomfield, CO, USA), which included recording airflow, snoring, thoracic and abdominal efforts, oxygen saturation, leg movements, and body position. In addition to a physical examination, a general medical case history, and a specific sleep disorder case history, patients were asked to complete the form on the Epworth Sleepiness Scale (ESS) as well as the Insomnia Severity Index (ISI). A dental examination and screening for cranio mandibular disorders (CMD) were performed by a dentist. At T1 in both treatment arms, patients were investigated by polysomnography (PSG) for three consecutive nights without gap. The first night served as baseline PSG, and the subsequent two nights were titration nights to the initial therapy upon randomisation. Criteria for the remaining in the study were an AHI of at least 5/h and exclusion of a relevant PLMD syndrome (PLMI <10/h) or other relevant movement disorders during baseline PSG. After the three baseline PSG nights at T1, the patients were sent home for 12 weeks of continuous use of therapy during sleep with either MAD or CPAP. Afterward, the patients were invited to the sleep lab for another 3 consecutive nights without gap by PSG. Indirectness: Serious indirectness
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: AHI/RDI at >1 month
- Actual outcome for Moderate: AHI at 12 weeks; Group 1: mean 13.7 (SD 12); n=40, Group 2: 3.5 (SD 5.2) n =40
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 8, Reason: personal reasons, data loss; Group 2 Number missing: 8, Reason: 3 intolerance of CPAP, 2 insufficient compliance with CPAP, personal reasons

Protocol outcome 2: ODI at >1 month
- Actual outcome for Moderate: ODI at 12 weeks; Group 1: mean 11.8 (SD 11.4); n=40, Group 2: mean 4 (SD 6.5); n=40
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 8, Reason: personal reasons, data loss; Group 2 Number missing: 8, Reason: 3 intolerance of CPAP, 2 insufficient compliance with CPAP, personal reasons

Study	Glos 2016[78]
Protocol outcome 3: Systolic blood pressure for hypertension at >1 month - Actual outcome for Moderate: systolic BP at 12 weeks; Group 1: mean 119.6 mm hg (SD 12.6); n=40, Group 2: mean 119.6 mm hg (SD 10.5); n=40 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 8, Reason: personal reasons, data loss; Group 2 Number missing: 8, Reason: 3 intolerance of CPAP, 2 insufficient compliance with CPAP, personal reasons	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; Sleepiness score at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Study (subsidiary papers)	Gotsopoulos 2002[79] (Gotsopoulos 2004[80])
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	2 (n=67)
Countries and setting	Conducted in Australia; Setting: patients were recruited from a multidisciplinary sleep disorders clinic in a university teaching hospital
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Severe
Subgroup analysis within study	Not applicable

Study (subsidiary papers)	Gotsopoulos 2002[79] (Gotsopoulos 2004[80])
Inclusion criteria	Inclusion criteria were OSA on polysomnography (apnoea-hypopnea index [AHI] ≥ 10 per hour), at least 2 of the following symptoms—daytime sleepiness, snoring, witnessed apnoea's, fragmented sleep; age > 20 years; and minimum mandibular protrusion of 3 mm.
Exclusion criteria	Exclusion criteria were predominant central sleep apnoea, insufficient teeth for splint retention, or evidence of active periodontal disease or dental caries.
Recruitment/selection of patients	St George Hospital, Sydney, Australia.
Age, gender and ethnicity	Age - Mean (SD): 48 (11). Gender (M: F): Define. Ethnicity: unclear
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Not stated / Unclear
Indirectness of population	Serious indirectness: patients with moderate to severe OSA included based on AHI
Interventions	(n=67) Intervention 1: Oral devices. The mandibular advancement splint was custom-made, consisting of upper and lower removable oral appliances. The vertical height of the splint was kept to a minimum with the average thickness of each upper and lower appliance between 1.5 and 2.0 mm. Duration 4 weeks. Concurrent medication/care: At baseline patients completed the ESS and a symptoms questionnaire and overnight polysomnography. This was followed by a periods of acclimatization to the splint, during which the mandible was incrementally advanced until the maximum comfortable limit was reached. Patients then underwent a washout period and were randomly assigned to their treatment group. Indirectness: Serious indirectness; Indirectness comment: patients of moderate to severe OSA based on AHI were included. (n=67) Intervention 2: No intervention - Placebo. The control device consisted of the upper appliance alone and did not advance the mandible. Duration 4 weeks. Concurrent medication/care: At baseline patients completed the ESS and a symptoms questionnaire and overnight polysomnography. This was followed by a periods of acclimatization to the splint, during which the mandible was incrementally advanced until the maximum comfortable limit was reached. patients then underwent a washout period and were randomly assigned to their treatment group. Indirectness: Serious indirectness; Indirectness comment: Patients of moderate to severe OSA based on AHI were included

Study (subsidiary papers)	Gotsopoulos 2002[79] (Gotsopoulos 2004[80])
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO Protocol outcome 1: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness scale at 4 weeks; Group 1: mean 7 (SD 8.5); n=73, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 0; Group 2 Number missing: Protocol outcome 2: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 4 weeks; Group 1: mean 12 (SD 15.6); n=61, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality; Group 2 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality - Actual outcome for Moderate: RDI at 4 weeks; Group 1: mean 12 (SD 17.1); n=73, Group 2: mean 25 (SD 17.1); n=73 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 0; Group 2 Number missing: Protocol outcome 3: Adherence in hours of use at >1 month - Actual outcome for Moderate: % of nights used at 4 weeks; Group 1: mean 97 % (SD 7.8); n=61, Group 2: mean 97 % (SD 7.8); n=61 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality; Group 2 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality - Actual outcome for Moderate: hours per night used at 4 weeks; Group 1: mean 6.8 (SD 0.8); n=61, Group 2: mean 6.9 (SD 0.8); n=61 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality; Group 2 Number missing: 6, Reason: 1 died of cancer, 1 work commitments, 1 self-perceived improvement, 1 BP monitoring unavailable, 2 inadequate BP data quality	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month;

Study (subsidiary papers)	Gotsopoulos 2002[79] (Gotsopoulos 2004[80])
	Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Roukema 2007[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Netherlands; Setting: University medical centre Groningen, the Netherlands
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2-3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Male patients over the age of 20 years who underwent polysomnography and were diagnose as having OSAHS with at least 5 apnoeas or hypopneas per hour (i.e. AHI > 5).
Exclusion criteria	Previous treatment of OSAHS, morphological airway abnormalities requiring treatment, endocrine dysfunction, a reported or documented history of severe cardiac or pulmonary disease, moderate or severe periodic limb movement disorder, or a psychological disorder that precluded informed consent. Patients with a dental status that could complicate oral-appliance therapy were also excluded. Patients were also excluded if they did not have a heterosexual relationship, had DM, used beta blocker medication, or in case of a condition other than OSAHS that could affect testosterone secretion.

Study	Roukema 2007[93]
Recruitment/selection of patients	Patients were recruited through the department of home ventilation of the university medical centre Groningen, the Netherlands
Age, gender and ethnicity	Age - Mean (SD): 49 (9). Gender (M: F): 48/0. Ethnicity: unclear
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Not stated / Unclear 3. Gender: Male 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: patients with severe OSA based on AHI included.
Interventions	(n=21) Intervention 1: Oral devices. The oral appliance used in this study (Thornton adjustable positioner, airway management Inc., Dallas, Tx, USA) positioned the patient's mandible in a forward and downward position. By turning a screw, patients could adjust the mandibular advancement by 0.2mm increments. When commencing oral-appliance therapy the mandible was set at approximately 50% of the patient's maximum advancement. After having accustomed to this protrusive position during a 2-week period, patients were allowed to further adjust their appliance during a 6 week periods. The titration of the device continued until symptoms adapted or until further advancement caused discomfort. Duration 8 - 12+ weeks. Concurrent medication/care: At baseline sexual function was determined by administering all OSA patients to the Golombok rust inventory of sexual satisfaction. Testosterone levels were also measured and the ESS was administered. Severity of the disease was assesses based on the baseline polysomnographic study. After 8 weeks of using either intervention the treatment effect was assessed with a second polysomnographic study. For patients whose AHI was still > 5, treatment was adjusted if possible to improve effectiveness. In these patients the follow up period was extended another 4 weeks and the effect was assessed with a third polysomnographic study. This adjustment sequence continued until the AHI was <5 or until the adjustments became uncomfortable to the patient. At final follow up patients were administered the GRISS and ESS and underwent testosterone measurement. Indirectness: No indirectness (n=27) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). CPAP titration was performed during an afternoon nap. this technique, aimed at abolishing all signs of apnoea, hypopnea and snoring, has been shown an appropriate procedure for the effective titration of CPAP. Following titration, an 8 week follow up period that allowed for habituation and, if necessary adjustments of CPAP therapy was arranged.

Study	Roukema 2007[93]
	Duration 8 - 12+ weeks. Concurrent medication/care: At baseline sexual function was determined by administering all OSA patients to the Golombok rust inventory of sexual satisfaction. Testosterone levels were also measured and the ESS was administered. Severity of the disease was assesses based on the baseline polysomnographic study. After 8 weeks of using either intervention the treatment effect was assessed with a second polysomnographic study. For patients whose AHI was still > 5, treatment was adjusted if possible to improve effectiveness. in these patients the follow up period was extended another 4 weeks and the effect was assessed with a third polysomnographic study. This adjustment sequence continued until the AHI was <5 or until the adjustments became uncomfortable to the patient. At final follow up patients were administered the GRISS and ESS and underwent testosterone measurement. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Moderate: Epworth sleepiness scale at 8 - 12 weeks;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up ; Group 2 Number missing: 0

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Moderate: AHI at 8 - 12 weeks;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up ; Group 2 Number missing: 0

Protocol outcome 3: Adherence in hours of use at >1 month
- Actual outcome for Moderate: adherence hours per night at 8 - 12 weeks; Group 1: mean 7.1 hours (SD 1.1); n=20, Group 2: mean 6.3 hours (SD 1.3); n=27
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up ; Group 2 Number missing: 0
- Actual outcome for Moderate: adherence nights per week used at 8 - 12 weeks; Group 1: mean 7 nights (SD 0.2); n=20, Group 2: mean 6.8 nights (SD 0.6); n=27

Study	Roukema 2007[93]
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: lost to follow up ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Lam 2007[121]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=101)
Countries and setting	Conducted in Hong Kong (China); Setting: The University of Hong Kong, Queen Mary Hospital.
Line of therapy	Unclear
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were apnoea–hypopnoea index (AHI)>5–40 and Epworth Sleepiness Scale (ESS) 19 .9 for those with AHI 5–20.
Exclusion criteria	Exclusion criteria were the presence of sleepiness which may constitute risk to self or others, unstable medical diseases, coexistence of sleep disorders other than OSA, history of previous surgery to upper airway (except those for nasal problems) and pregnant women.
Recruitment/selection of patients	Subjects were consecutively recruited from the sleep laboratories of a university hospital and a regional hospital in Hong Kong.

Study	Lam 2007[121]
Age, gender and ethnicity	Age - Mean (range): mean and (SEM) CPAP=45 (1), Oral appliance = (45 (2), conservative = 47 (2). Gender (M:F): 79/22. Ethnicity: unclear
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: mild - mod patients on AHI scale included
Interventions	(n=34) Intervention 1: Oral devices. Subjects in the oral appliance group were referred to an orthodontist (KS) for a tailor-made nonadjustable oral appliance. The oral appliance was made of dental acrylic modified from a functional activator (Harvold type). It held the mandible in a forward direction with some vertical opening to keep the jaw at the most advanced position without causing discomfort. . Duration 10 weeks. Concurrent medication/care: Advice on general sleep hygiene measures were given. Subjects who were overweight were asked to attend a weight control programme in the Dietetics Unit, Queen Mary Hospital, Hong Kong SAR, China. Subjects underwent overnight PSG (Alice 3 or Alice 4 Diagnostics System, Respironics, Atlanta, USA) with documentation of sleep stages by EEG, respiratory movement by impedance plethysmography, air flow by nasal pressure sensor with thermistor back up, arterial oxygen saturation by pulse oximetry, snoring by tracheal microphone and sleep position by position sensor at baseline and at 10 weeks. . Indirectness: Serious indirectness; Indirectness comment: pts with mild - mod AHI scores included Further details: 1. Intervention type: 2. Type of device: (n=34) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). Those in the CPAP group were prescribed CPAP (ARIA LX, Respironics, Atlanta, Georgia, USA) at a pre-titrated pressure. . Duration 10 weeks. Concurrent medication/care: Advice on general sleep hygiene measures were given. Subjects who were overweight were asked to attend a weight control programme in the Dietetics Unit, Queen Mary Hospital, Hong Kong SAR, China Subjects underwent overnight PSG (Alice 3 or Alice 4 Diagnostics System, Respironics, Atlanta, USA) with documentation of sleep stages by EEG, respiratory movement by impedance plethysmography, air flow by nasal pressure sensor with thermistor back up, arterial oxygen saturation by pulse oximetry, snoring by tracheal microphone and sleep position by position sensor. . Indirectness: Serious indirectness; Indirectness comment: mild-mod AHI pts included Further details: 1. Intervention type: 2. Type of device: (n=33) Intervention 3: No intervention - Usual care (lifestyle advice etc.). Advice on general sleep hygiene measures were given, and those who were overweight were asked to attend a weight control programme in

Study	Lam 2007[121]
	the Dietetics Unit, Queen Mary Hospital, Hong Kong SAR, China. . Duration 10 weeks. Concurrent medication/care: Subjects underwent overnight PSG (Alice 3 or Alice 4 Diagnostics System, Respironics, Atlanta, USA) with documentation of sleep stages by EEG, respiratory movement by impedance plethysmography, air flow by nasal pressure sensor with thermistor back up, arterial oxygen saturation by pulse oximetry, snoring by tracheal microphone and sleep position by position sensor. At 10 weeks, all subjects were reassessed with the same battery of tests as at the baseline. Indirectness: Serious indirectness; Indirectness comment: mild-mod AHI pts included Further details: 1. Intervention type: 2. Type of device:
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Moderate: SAQLI at 10 weeks; Group 1: mean 5.5 (SD 0.6); n=34, Group 2: mean 5.5 (SD 1.2); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1
- Actual outcome for Moderate: SF-36 mental at 10 weeks; Group 1: mean 69.8 (SD 18.1); n=34, Group 2: mean 71.8 (SD 16.3); n=34; SF- 36 mental 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1
- Actual outcome for Moderate: SF-36 physical at 10 weeks; Group 1: mean 86.5 (SD 1.7); n=34, Group 2: mean 88.2 (SD 9.9); n=34; SF-36 physical 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1

Study	Lam 2007[121]
Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness scale at 10 weeks; Group 1: mean 9 (SD 5.8); n=34, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI final value at 10 weeks; Group 1: mean 10.6 (SD 9.1); n=34, Group 2: mean 2.8 (SD 6.4); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 4: ODI at >1 month - Actual outcome for Moderate: min o2 saturation % at 10 weeks; Group 1: mean 81 % (SD 9.3); n=34, Group 2: mean 87.2 % (SD 16.9); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 5: Adverse effects of treatment at >1 month - Actual outcome for Moderate: adverse events - various side effects at 10 weeks; Group 1: 54/34, Group 2: 42/34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 6: Adherence in hours of use at >1 month - Actual outcome for Moderate: adherence - hours per night at 10 weeks; Group 1: mean 6.4 hours (SD 1.2); n=34, Group 2: mean 4.2 hours (SD 0.6); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 - Actual outcome for Moderate: adherence - nights per week at 10 weeks; Group 1: mean 5.2 number of nights (SD 1.7); n=34, Group 2: mean 4.4 number of nights (SD 0.6); n=34	

Study	Lam 2007[121]
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 Protocol outcome 7: Systolic blood pressure for hypertension at >1 month - Actual outcome for Moderate: systolic BP at 10 weeks; Group 1: mean 125.9 mm hg (SD 19.2); n=34, Group 2: mean 123 mm hg (SD 14.6); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 1 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus USUAL CARE (LIFESTYLE ADVICE ETC) Protocol outcome 1: Quality of life at >1 month - Actual outcome for Moderate: SAQLI at 10 weeks; Group 1: mean 5.5 (SD 0.6); n=34, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 - Actual outcome for Moderate: SF-36 physical at 10 weeks; Group 1: mean 86.5 (SD 11.7); n=34, Group 2: mean 78.9 (SD 20.7); n=33; SF-36 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 - Actual outcome for Moderate: SF-36 mental at 10 weeks; Group 1: mean 69.8 (SD 18.1); n=34, Group 2: mean 68 (SD 14.3); n=33; SF-36 mental 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness score at 10 weeks; Group 1: mean 9 (SD 5.8); n=34, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were	

Study	Lam 2007[121]
referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 10 weeks; Group 1: mean 10.6 (SD 9.9); n=34, Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 4: ODI at >1 month - Actual outcome for Moderate: min oxygen saturation % at 10 weeks; Group 1: mean 81 % (SD 9.3); n=34, Group 2: mean 77.4 % (SD 11.5); n=33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5 Protocol outcome 5: Systolic blood pressure for hypertension at >1 month - Actual outcome for Moderate: systolic BP at 10 weeks; Group 1: mean 125.9 mm hg (SD 19.2); n=34, Group 2: mean 126.7 mm hg (SD 21.3); n=33 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: pts with mild - mod AHI included; Blinding details: overweight patients were referred to weight management Programme and different number of patients in each treatment group; Group 1 Number missing: 4; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Mortality at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month

Study	Marklund 2015[132]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Sweden; Setting: Department of Pulmonary Medicine at Umea University Hospital

Study	Marklund 2015[132]
Line of therapy	Unclear
Duration of study	Intervention + follow up: intervention + 4 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who snored and patients with mild to moderate sleep apnoea with AHI lower than 30 were included. The patients also had daytime sleepiness according to 1 or more of the following criteria: (1) an ESS score of 10or higher; (2) daytime sleepiness assessed as “often” or “always,” or (3) unwillingly falling asleep during the daytime assessed as “sometimes,” “often,” or “always” (on a scale ranging of “never,” “seldom,” “sometimes,” “often,” and “always”), or (4) an irresistible tendency to fall asleep during the daytime 1 or more times per week.
Exclusion criteria	Patients with tonsil hypertrophy criteria grade 3 or 4 on the Friedman scale 27 severe psychiatric diseases or dementia, untreated caries or periodontal disease, few teeth for anchoring a device, occupational drivers, participation in other studies, or patients with a bias with regard to the study (i.e. physicians or nurses at the clinic) were excluded.
Recruitment/selection of patients	Patients with snoring who were referred from the Department of Pulmonary Medicine at Umea University Hospital to the Department of Orthodontics at Umea University for treatment with oral appliances were asked to participate in the study.
Age, gender and ethnicity	Age - Mean (SD): experimental group = 49.8 (10.6), control = 54.1 (9.4). Gender (M:F): 62/29. Ethnicity: unclear
Further population details	BMI of 30 2 kg/m^2 or more.

Study	Marklund 2015[132]
Indirectness of population	Serious indirectness: patients with mild and moderate OSAHS included
Interventions	(n=45) Intervention 1: Oral devices. The oral appliance was made individually from plaster casts produced by a dental technician. It consisted of an upper and lower part of elastomer (SRIvocapElastomer; IvoclarVivadent 28) and was interconnected with a screw that allowed continuous advancement of the lower jaw. Duration 4 months. Concurrent medication/care: Polysomnographic sleep recordings (Embla, Natus Neurology) included continuous recordings of electroencephalogram (channels C3/M2 and C4/M1), electro-oculograms, sub-mental electromyography, nasal flow pressure sensor, piezoelectric belts (Resp-EZ, EPM Systems), pulse oximetry (NoninXPOD + 8000JSensorAdult FlexSystem, NoninMedical), piezo respiratory effort sensor (Pro-Tech, Philips), electrocardiograms (V5), and a body position sensor. Sensors were attached in the evening and the recordings were made at home. Indirectness: Serious indirectness; Indirectness comment: mix of mild to moderate patients (n=46) Intervention 2: No intervention - Placebo. The placebo upper-jaw device consisted of a bilaminate splint with a hole in the anterior part to reduce size and improve retention to the palate by suction. Duration 4 months. Concurrent medication/care: Polysomnographic sleep recordings (Embla, Natus Neurology) included continuous recordings of electroencephalogram (channels C3/M2 and C4/M1), electrooculograms, sub-mental electromyography, nasal flow pressure sensor, piezoelectric belts (Resp-EZ, EPM Systems), pulse oximetry (NoninXPOD + 8000JSensorAdult FlexSystem, NoninMedical), piezo respiratory effort sensor (Pro-Tech, Philips), electrocardiograms (V5), and a body position sensor. Sensors were attached in the evening and the recordings were made at home. Indirectness: Serious indirectness; Indirectness comment: mix of mild-moderate patients included
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO	

Study	Marklund 2015[132]
Protocol outcome 1: Quality of life at >1 month - Actual outcome for Moderate: FOSQ (mean score) at 4 months; Group 1: mean 17.6 (SD 2.3); n=45, Group 2: mean 16.4 (SD 3.4); n=46 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Moderate: SF36 - mental at 4 months; Group 1: mean 79.8 (SD 14.4); n=45, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Moderate: SF36 - physical at 4 months; Group 1: mean 90.7 (SD 12.6); n=45, Group 2: mean 86.7 (SD 14.6); n=46 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: ESS score at 4 months; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 4 months; Group 1: mean 6.7 (SD 4.9); n=45, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse effects of treatment at >1 month - Actual outcome for Moderate: adverse events - headaches present % at 4 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Adherence in hours of use at >1 month - Actual outcome for Moderate: adherence % of nights used at 4 months; Group 1: mean 86 % of nights (SD 16); n=45, Group 2: mean 83 % of nights (SD 21); n=46 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover	

Study	Marklund 2015[132]
- Low; Indirectness of outcome: Serious indirectness, Comments: mild - moderate patients included; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Naismith 2005[146]
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=73)
Countries and setting	Conducted in Australia; Setting: Sleep disorder clinic at St George hospital, Sydney, Australia
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of at least 2 symptoms of OSA, an AHI >10 per hour, age over 20 years, and ability to protrude the mandible by at least 3mm.

Study	Naismith 2005[146]
Exclusion criteria	Evidence of predominant central sleep apnoea on polysomnography, periodontal disease, insufficient teeth, exaggerated gag reflex, regular use of narcotics; sedatives or psychoactive medications, history of severe head injury or history of psychiatric disorder.
Recruitment/selection of patients	Subjects were prospectively recruited for the study through a multidisciplinary sleep disorders clinics in a university teaching hospital
Age, gender and ethnicity	Age - Mean (SD): 48.4 (11.0). Gender (M:F): 58/15. Ethnicity: unclear
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: patients with mild to moderate OSA based on AHI score included
Interventions	(n=73) Intervention 1: Oral devices. Baseline assessments were followed by a period of acclimatisation with a custom-made mandibular advancement splint, during which incremental advancement of the mandible to the maximum comfortable limit of advancement was achieved. Symptomatic response was not assessed during this period so as to avoid unblinding patients. The mean acclimatisation periods was 8.3 weeks. Duration 4 weeks. Concurrent medication/care: prior to treatment allocation all subjects completed a series of self-reported measures and underwent baseline nocturnal polysomnography and neuro psychological evaluation. Each treatment was administered for 4 weeks with 1 week wash out period. repeat polysomnography, BMI, neuropsychological evaluation and self-reported measures were conducted immediately after each treatment phase. Indirectness: Serious indirectness; Indirectness comment: patients with mild to moderate OSA based on AHI score were included. (n=73) Intervention 2: No intervention - Placebo. The control treatment consisted of a single upper plate that had no protrusive effect on the mandible. Duration 4 weeks. Concurrent medication/care: Prior to treatment allocation all subjects completed a series of self-reported measures and underwent baseline nocturnal polysomnography and neuropsychological evaluation. Each treatment was administered for 4 weeks with 1 week wash out period. Repeat polysomnography, BMI, neuropsychological evaluation and self-reported measures were conducted immediately after each treatment phase. Indirectness: Serious indirectness

Study	**Naismith 2005[146]**
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO Protocol outcome 1: Quality of life at >1 month - Actual outcome for Moderate: Beck depression inventory at 4 weeks; Group 1: mean 2.1 (SD 2.8); n=73, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: unclear; Group 2 Number missing: unclear Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness scale at 4 weeks; Group 1: mean 7.1 (SD 4.5); n=73, Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: unclear; Group 2 Number missing: unclear Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 4 weeks; Group 1: mean 12.2 (SD 23.3); n=73, Group 2: mean 24.5 (SD 14.5); n=73 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: unclear; Group 2 Number missing: unclear	
Protocol outcomes not reported by the study	Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	**Phillips 2013[167]**
Study type	RCT (Patient randomised; Crossover: 2 weeks)

Study	Phillips 2013[167]
Number of studies (number of participants)	1 (n=126)
Countries and setting	Conducted in Australia; Setting: Three sleep centres in Sydney, Australia
Line of therapy	Unclear
Duration of study	Intervention time: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AHI >10
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with newly diagnosed OSA (apnoea hypopnea index [AHI] .10 events per h); aged 20 years or older; greater than or equal to two symptoms of OSA (snoring, fragmented sleep, witnessed apnoea's, or daytime sleepiness); and a willingness to use both treatments.
Exclusion criteria	Previous OSA treatment or a need for immediate treatment based on clinical judgment; 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).
Recruitment/selection of patients	Patients were recruited from three sleep centres in Sydney according to the inclusion criteria. Before consenting, patients were told they would be compensated for participating in the study by receiving the treatment device recommended by their sleep physician at no cost.
Age, gender and ethnicity	Age - Mean (SD): 49.5 (11.2). Gender (M:F): 102/24. Ethnicity: unclear
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9

Study	Phillips 2013[167]
Indirectness of population	Serious indirectness: patients with moderate - severe OSA included
Interventions	(n=126) Intervention 1: Oral devices. The MAD was the Somnodent (SomnoMed Ltd., Sydney, Australia), a custom-fitted and titratable two-piece device with proved clinical effectiveness in treating OSA. The MAD was self-titrated by gradually advancing the device until the maximum comfortable limit of mandibular advancement was achieved. Duration 1 month. Concurrent medication/care: During each of the 4–6 weeks of acclimatization with each device, all patients were asked to use their device for as long as they could tolerate it on a nightly basis. After usage patterns had stabilized, treatment was considered to be optimized. All outcomes were assessed on three occasions, at baseline before treatment acclimatization and then at the end of each of the 1-month treatment arms. Indirectness: Serious indirectness; Indirectness comment: patients with moderate and severe OSA based on AHI included. (n=126) Intervention 2: Non -surgical intervention - Positive airway pressure variants (CPAP, APAP). The CPAP device used in the trial was the ResMed Autoset S8 (ResMed, Bella Vista, Australia). A fixed CPAP pressure was determined using a previously validated auto titrating method based on the 95th percentile pressure that controlled most of the OSA events. Duration 1 month. Concurrent medication/care: During each of the 4–6 weeks of acclimatization with each device, all patients were asked to use their device for as long as they could tolerate it on a nightly basis. After usage patterns had stabilized, treatment was considered to be optimized. All outcomes were assessed on three occasions, at baseline before treatment acclimatization and then at the end of each of the 1-month treatment arms. Indirectness: Serious indirectness; Indirectness comment: patients with moderate - severe OSA based on AHI included
Funding	Study funded by industry (funded by industry and Australian medical research council)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP) Protocol outcome 1: Quality of life at >1 month	

Study	Phillips 2013[167]
- Actual outcome for Moderate: FOSQ (mean score) at 1 month; Group 1: mean 17.3 (SD 2.078); n=108, Group 2: mean 17.3 (SD 2.078); n=108; Comments: results given as mean (SE) oral device = 17.3 (0.2) CPAP = 17.3 (0.2) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons - Actual outcome for Moderate: SF36 physical function at 1 month; Group 1: mean 84.7 (SD 19.74); n=108, Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons - Actual outcome for Moderate: SF36 mental health at 1 month; Group 1: mean 75.3 (SD 15.588); n=108, Group 2: mean 72.6 (SD 16.627); n=108; Comments: results presented as mean (SE) oral device = 75.3 (1.5) CPAP = 72.6 (1.6) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness score at 1 month; Group 1: mean 7.2 (SD 4.156); n=108, Group 2: mean 7.5 (SD 4.156); n=108; Comments: results in mean (SE) oral device = 7.2 (0.4) CPAP = 7.5 (0.4) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 1 month; Group 1: mean 11.1 (SD 12.1); n=108, Group 2: mean 4.5 (SD 6.6); n=108	

Study	Phillips 2013[167]
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 4: ODI at >1 month - Actual outcome for Moderate: ODI at 1 month; Group 1: mean 9 (SD 11.6); n=108,Group 2: mean 6 (SD 9.7): n= 108 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 5: Driving outcomes at >1 month - Actual outcome for Moderate: AusEd driving simulator - mean lane deviation at 1 month; Group 1: mean 58.7 cm (SD 24.94); n=108, Group 2: mean 59.6 cm (SD 23.09); n=108; Comments: results presented as mean (SE) oral device = 58.7 (2.4) CPAP = 59.6 (2.3) Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 6: Adherence in hours of use at >1 month - Actual outcome for Moderate: subjective compliance - hours per night at 1 month; Group 1: mean 6.5 hours per night (SD 1.3); n=108, Group 2: mean 5.2 hours per night (SD 2); n=108 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons Protocol outcome 7: Patient preference at >1 month - Actual outcome for Moderate: patient preferred treatment at 1 month; Group 1: 55/108, Group 2: 25/108 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 18, Reason: 2 non-compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons; Group 2 Number missing: 18, Reason: 2 non-	

Study	Phillips 2013[167]
compliant, 1 unable to tolerate CPAP, 1 serious adverse event, 1 adverse event, 1 unable to tolerate either device and various personal reasons	
Protocol outcomes not reported by the study	Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Neurocognitive outcomes at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Quinnell 2014[175]
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Papworth hospital sleep centre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥18 years with mild to moderate OSAHS confirmed by respiratory polysomnography (rPSG) (AHI 5–<30/h) and symptomatic daytime sleepiness (Epworth Sleepiness Scale (ESS) score ≥9) were recruited from

Study	Quinnell 2014[175]
	Papworth Hospital sleep centre. Newly diagnosed patients not requiring or declining CPAP and existing CPAP intolerant patients were eligible.
Exclusion criteria	Not reported
Age, gender and ethnicity	Age - Mean (SD): 50.9 (11.6). Gender (M:F): 72/18. Ethnicity: not stated
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Systematic review: mixed 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: mild and moderate OSAHS patients included
Interventions	(n=90) Intervention 1: Oral devices. SleepPro 1 (SP1) (Meditas Ltd., Winchester, UK): A thermoplastic „boil and bite" device fitted by the patient following the manufacturer's printed instructions. All patients wore the device for a period of 6 weeks with 1 week wash out periods between. Duration 6 weeks . Concurrent medication/care: unclear. Indirectness: No indirectness Further details: 1. Intervention type: (n=90) Intervention 2: No intervention - Usual care (lifestyle advice etc.) no treatment provided. Duration 4 weeks. Concurrent medication/care: no details. Indirectness: No indirectness Further details: 1. Intervention type: (n=90) Intervention 3: Oral devices. SleepPro 2 (SP2) (Meditas Ltd., Winchester, UK): A semi-bespoke device, formed from a dental impression mould made by the patient. An impression kit was posted to the patient. All patients wore the device for 6 weeks with a 1 week washout period. Duration 6 weeks. Concurrent medication/care: no details. Indirectness: No indirectness Further details: 1. Intervention type: (n=90) Intervention 4: Oral devices. Bespoke Device (bMAD) (Maxillofacial Laboratory, Department of Oral and Maxillofacial Surgery, Cambridge, UK): Custom-made MAD,

Study	Quinnell 2014[175]
	professionally fitted by specialists in the NHS Maxillofacial laboratory at Addenbrooke's Hospital, UK. . Duration 6 weeks. Concurrent medication/care: no details. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus USUAL CARE (LIFESTYLE ADVICE ETC)
Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Mild: ESS - SP1
at unclear; Group 1: mean 8.5 (SD 4); n=83, Group 2: mean 10.1 (SD 4.3); n=83
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 7, Reason: various reasons; Group 2 Number missing: 7, Reason: various reasons
- Actual outcome for Mild: ESS - SP2
at unclear; Group 1: mean 8 (SD 4.1); n=83, Group 2: mean 10.1 (SD 4.3); n=83
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 7, Reason: various reasons; Group 2 Number missing: 7, Reason: various reasons
- Actual outcome for Mild: ESS - bMAD
at unclear; Group 1: mean 7.7 (SD 3.8); n=83, Group 2: mean 10.1 (SD 4.3); n=3
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 7, Reason: various reasons; Group 2 Number missing: 7, Reason: various reasons

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Mild: AHI - SP1
at unclear; Group 1: mean 10.8 (SD 10.5); n=81,
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 9, Reason: various reasons; Group 2 Number missing: 9, Reason: various reasons
- Actual outcome for Mild: AHI - SP2
at unclear; Group 1: mean 9.7 (SD 88.9); n=81, Group 2: mean 14.6 (SD 10.5); n=81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 9, Reason: various reasons; Group 2 Number missing: 9, Reason: various reasons

Study	Quinnell 2014[175]
- Actual outcome for Mild: AHI - bMAD at unclear; Group 1: mean 9.5 (SD 8.4); n=81, Group 2: mean 14.6 (SD 10.5); n=81 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 9, Reason: various reasons; Group 2 Number missing: 9, Reason: various reasons	
Protocol outcomes not reported by the study	Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Randerath 2002[181]
Study type	RCT (Patient randomised; Crossover: no details provided)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Germany; Setting: department of sleep medicine university Witten/Herdecke
Line of therapy	Unclear
Duration of study	Intervention + follow up: intervention + 6 weeks follow up with each intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild-moderate
Subgroup analysis within study	Not applicable

Study	Randerath 2002[181]
Inclusion criteria	AHI of 5/h min and 30/h max and clinical symptoms of OSAS.
Exclusion criteria	AHI over 3/h, temporomandibular joint disorders, bruxism and patients with gaps in their dentition precluding fitting of the device.
Recruitment/selection of patients	Patients referred to a university sleep laboratory for the diagnosis and treatment of OSAS were investigated between January 1999 and December 1999 were investigated
Age, gender and ethnicity	Age - Mean (SD): 56.5 (10.2). Gender (M:F): 16/4. Ethnicity: unclear
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Not stated / Unclear 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Systematic review: mixed
Indirectness of population	Serious indirectness: patients of mild- moderate OSA were included
Interventions	(n=20) Intervention 1: Oral devices. ISAD an oral appliance with 2 thin thermoplastic parts, worn on the upper and lower jaws are connected by 2 adjustable telescopic guide rods in the vestibule. Duration 6 weeks. Concurrent medication/care: no details provided. Indirectness: Serious indirectness; Indirectness comment: patients of mild - moderate OSA included (n=20) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). patients were treated with commercially available CPAP devices (max IIMAP, Martinstried Germany). the treatment pressure was increased in incremental steps of 1xm H2O/h until respiratory disturbances were minimalised and respiration related arousals were reduced to less than 5/h. Duration 6 weeks. Concurrent medication/care: no details provided. Indirectness: Serious indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP) Protocol outcome 1: AHI/RDI at >1 month	

Study	Randerath 2002[181]
- Actual outcome for Moderate: AHI at 6 weeks; Group 1: mean 13.8 (SD 11.1); n=20, Group 2: mean 3.2 (SD 2.9); n=20 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Comments - ; Indirectness of outcome: Serious indirectness, Comments: patients of mild - moderate included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse effects of treatment at >1 month - Actual outcome for Moderate: discomfort at 6 weeks; Group 1: 8/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Comments - ; Indirectness of outcome: Serious indirectness, Comments: patients of mild - moderate included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adherence in hours of use at >1 month - Actual outcome for Moderate: adherence per night at 6 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High, Comments - ; Indirectness of outcome: Serious indirectness, Comments: patients of mild - moderate included; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Patient preference at >1 month - Actual outcome for Moderate: preference - ease of use 1-6 at 6 weeks; Group 1: mean 1.8 (SD 1.1); n=20, Group 2: mean 3.1 (SD 1.5); n=20 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - High; Indirectness of outcome: Serious indirectness, Comments: patients of mild - moderate included; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; Sleepiness score at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Rietz 2018[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in Sweden
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild: diagnosis of sleep apnoea or AHI <5
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Snoring, daytime sleepiness, defined as at least 1 positive answer on 4 different scales 11; and an apnoea-hypopnea index <30.
Exclusion criteria	Patients with severe psychiatric illnesses, including dementia; an inability to protrude the mandible for ≥5 mm; active periodontal disease or caries; few teeth for anchoring the device; tonsil hypertrophy (grade 3 or 4 on the Friedman Scale); participation in other studies; or a bias with regard to the study (i.e., physicians or nurses at the clinic) were excluded.
Recruitment/selection of patients	Patients who were referred from the Department of Medicine to the Department of Orthodontics for treatment with mandibular advancement devices were asked to participate in the study.
Age, gender and ethnicity	Age - Mean (SD): experimental = 49.6 (10.5) control = 54.5 (9.1). Gender (M:F): 58/27. Ethnicity: not stated

Study	Rietz 2018[185]
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Systematic review: mixed 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: included patients with a mild and moderate AHI scores
Interventions	(n=48) Intervention 1: Oral devices. A custom-made adjustable mandibular advancement device, the Herbst device, was used as active treatment. It consisted of 2 parts made of elastomer and connected by 2 lateral screws that enabled the continuous titration of the mandible forward. A mandibular advancement of 6 to 7 mm was intended for all patients. Duration 4 months. Concurrent medication/care: At baseline and follow-up, after 4 months, all the patients underwent polysomnographic sleep recordings and 24-hour ambulatory blood pressure monitoring (ABPM SpaceLabs Medical 90217 ambulatory blood pressure monitor). 12 Blood pressure was measured every 20 minutes. Indirectness: Serious indirectness; Indirectness comment: patients of mild - moderate AHI included Further details: 1. Intervention type: (n=48) Intervention 2: No intervention - Placebo. The sham device consisted of an acrylic plate in the palate and did not influence the position of the mandible. Duration 4 months. Concurrent medication/care: At baseline and follow-up, after 4 months, all the patients underwent polysomnographic sleep recordings and 24-hour ambulatory blood pressure monitoring (ABPM SpaceLabs Medical 90217 ambulatory blood pressure monitor). Blood pressure was measured every 20 minutes. Indirectness: Serious indirectness; Indirectness comment: patients with mild-moderate AHI scores included
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus PLACEBO

Protocol outcome 1: AHI/RDI at >1 month
- Actual outcome for Mild: AHI final value at 4 months; Group 1: mean 6.6 (SD 5); n=42, Group 2: mean 16.8 (SD 9.9); n=43
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Study	Rietz 2018[185]
Low; Indirectness of outcome: Serious indirectness, Comments: patients with mild-moderate AHI score included; Group 1 Number missing: 6, Reason: 3 did not tolerate devices and several excluded from analysis due to BP effects from other sources; Group 2 Number missing: 5, Reason: 2 did not tolerate devices and several excluded from analysis due to BP effects from other sources Protocol outcome 2: Adherence in hours of use at >1 month - Actual outcome for Mild: adherence % of nights used at 4 months; Group 1: mean 87 % (SD 17); n=42, Group 2: mean 82 % (SD 22); n=43 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: patients with mild- moderate AHI score included; Group 1 Number missing: 6, Reason: 3 did not tolerate devices and several excluded from analysis due to BP effects from other sources; Group 2 Number missing: 5, Reason: 2 did not tolerate devices and several excluded from analysis due to BP effects from other sources	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; Sleepiness score at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Schutz 2013[190]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Brazil; Setting: Sleep Disorders Ambulatory clinic, Sao Paulo Brazil
Line of therapy	Unclear
Duration of study	Intervention time: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Study	Schutz 2013[190]
Stratum	Moderate-severe
Subgroup analysis within study	Not applicable
Inclusion criteria	25 to 55 years of age Sedentary Body mass index less than or equal to 30 kg/m2 AHI.10/h Hemogram, cholesterol, HDL, triglycerides, fasting glucose, creatinine, TSH within the normal range Lung function test (spirometry), chest X-rays (for smokers and former smokers), resting and stress electrocardiogram and otorhinolaryngologic examination without significant changes
Exclusion criteria	Habits or occupations that lead to sleep deprivation or alterations in the sleep-wake cycle; history of regular sports activities;inability to perform physical exercise;other sleep disorders;anatomical obstructive upper airway: tonsils grade III and IV and septal deviation grade III (severe) that can affect the outcome of CPAP use; clinical disease decompensation (chronic obstructive pulmonary disease, asthma, interstitial lung diseases, neuromuscular diseases, heart failure, thyroid disease, rheumatologic and psychiatric diseases);use of sleeping pills; other treatments for OSAHS; loss of dental support that subsequently compromises the retention of OA; periodontal disease; dental crown/tooth root relationship less than or equal to 1; primary dental care (cavities, root canal treatment or retreatment or extensive dental prostheses); anterior open bite; protrusive displacement less than 5 mm; limited mouth opening; alcoholism
Recruitment/selection of patients	Patients with the clinical and polysomnographic criteria of OSAS were selected from the Sleep Disorders Ambulatory clinic (Disciplina de Medicina e Biologia do Sono - UNIFESP - EPM). The patients were pre-selected according to the inclusion and exclusion criteria.
Age, gender and ethnicity	Age - Mean (SD): oral device = 42.3 (6.2), CPAP group = 38.6 (8.1), exercise group = 42.3 (8.3). Gender (M:F): 25. Ethnicity: unclear

Study	Schutz 2013[190]
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Not stated / Unclear 3. Gender: Male 4. High risk occupation group: Systematic review: mixed 5. Race: Not stated / Unclear 6. Sleepiness: Not reported
Indirectness of population	Serious indirectness: patients with moderate and severe AHI scores included. only sedentary adults included
Interventions	(n=9) Intervention 1: Oral devices. A mandibular repositioning appliance (Brazilian Dental Appliance, Sao Paulo, SP, Brazil) was individually constructed and installed. The Brazilian Dental Appliance is an adjustable OA made of acrylic resin that allows progressive mandibular protrusion. Duration 2 months. Concurrent medication/care: Full-night polysomnography was performed by previously trained professionals using a polysomnographic recorder at baseline and 2 months. Indirectness: Serious indirectness (n=9) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). The patients received a fixed mode device (REMstarH Plus; Respironics Inc., Murrysville, PA) that allowed for pressure variations between 4 and 20 cm H2O. Duration 2 months. Concurrent medication/care: Full-night polysomnography was performed by previously trained professionals using a polysomnographic recorder at baseline and 2 months. Indirectness: Serious indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Moderate: SF-36 - Mental at 2 months; Group 1: mean 68 (SD 16.2); n=9, Group 2: mean 68.6 (SD 24.3); n=9; Short form 36 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: professional reasons, health problems; Group 2 Number missing: 6, Reason: failure to comply with CPAP use, inability to tolerate CPAP
- Actual outcome for Moderate: SF-36 - physical at 2 months; Group 1: mean 85 (SD 13); n=9, Group 2: mean 82.1 (SD 11.9); n=9; short form 36 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: professional reasons, health problems; Group 2

Study	Schutz 2013[190]
Number missing: 6, Reason: failure to comply with CPAP use, inability to tolerate CPAP Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness scale at 2 months; Group 1: mean 5 (SD 4.2); n=9, Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: professional reasons, health problems; Group 2 Number missing: 6, Reason: failure to comply with CPAP use, inability to tolerate CPAP Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 2 months; Group 1: mean 9.6 (SD 10.3); n=9, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 6, Reason: professional reasons, health problems; Group 2 Number missing: 6, Reason: failure to comply with CPAP use, inability to tolerate CPAP	
Protocol outcomes not reported by the study	Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Tan 2002[203]
Study type	RCT (Patient randomised; Crossover: 2 weeks)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in United Kingdom; Setting: Sleep clinics at University College London Hospital (UCLH) and the Royal Brompton Hospital (RBH).
Line of therapy	Unclear

Study	Tan 2002[203]
Duration of study	Intervention time: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Entry criteria included males and females over the age of 18 years, an adequate dentition and periodontal status for support and retention of the oral appliance, no temporomandibular joint dysfunction, and no medical contraindications. Patients also had to be able to attend the sleep clinic and sleep laboratory as requested for the requirements of the study.
Exclusion criteria	Exclusion criteria included: significant heart disease—myocardial infarction in the last 3 years, angina, and uncontrolled hypertension; co-existent chronic obstructive pulmonary disease; regular hypnotic use; epilepsy; an inadequate dentition; an arterial oxygen saturation of less than 60 per cent during the initial sleep study; and failure to understand the purpose of the study because of language difficulties.
Recruitment/selection of patients	Consecutive patients attending multidisciplinary sleep were invited to enter the study. The severity of OSA was determined by full polysomnography, and all patients who fulfilled the entry criteria of mild or moderate OSA (AHI less than 50) were invited to participate.
Age, gender and ethnicity	Age - Mean (SD): 50.9 (10.1). Gender (M:F): 20/4. Ethnicity: unclear
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Systematic review: mixed 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Not stated / Unclear
Indirectness of population	Serious indirectness: pts with AHI ranging from 10-49 events per hour were included in the study

Study	Tan 2002[203]
Interventions	(n=24) Intervention 1: Oral devices. A soft, one-piece MAS was selected initially, similar to that described by Stradling et al. (1998). This vacuum-formed appliance was simple and cheap to construct, and designed to hold the mandible forward at the maximum comfortable protrusion, with no deviation to either side and minimal jaw opening. The initial protrusive position approximated 75 per cent of maximal possible protrusion. Progressive advancement of the mandible was possible by taking a new jaw record and modifying the appliance. If randomised to MAS, impressions were taken for appliance construction and lateral skull radiographs were obtained. Once the MAS had been fitted, patients were instructed to contact the clinician if unforeseen problems or break- ages occurred, and were given appointments at two- and six-week intervals. Any adjustments to the appliance were made at the two-week clinic visit. Duration 2 months. Concurrent medication/care: Baseline overnight polysomnography was performed and baseline questionnaires completed. Patients were then randomised to two months treatment with either nCPAP or the MAS. Routine appointments at the sleep laboratory were given for two and six weeks into the treatment period. Indirectness: No indirectness (n=24) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). nCPAP was provided using the REM Star Choice machine (Respironics Inc., Medic- Aid, West Sussex, UK) at UCLH and the Sullivan Elite machine (Resmed UK Ltd, Abingdon, UK) at RBH. A comfortable nasal mask was selected and nasal corticosteroid sprays were prescribed to relieve nasal congestion if necessary. This symptom did not require treatment during the MAS arm of the study in any individual. Correct nCPAP pressures were titrated individually. Patients were familiarised with the system and a sleep study arranged to ascertain the optimal nCPAP pressure required to abolish the OSA. The patient then commenced the two-month trial period with instructions to contact the laboratory if problems developed. Routine appointments at the sleep laboratory were given for two and six weeks into the treatment period. Duration 2 months. Concurrent medication/care: Baseline overnight polysomnography was performed and baseline questionnaires completed. Patients were then randomised to two months treatment with either nCPAP or the MAS. Routine appointments at the sleep laboratory were given for two and six weeks into the treatment period. Indirectness: Serious indirectness; Indirectness comment: patients with mild-moderate AHI scores included
Funding	Funding not stated

Study	Tan 2002[203]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP) Protocol outcome 1: Sleepiness score at >1 month - Actual outcome for Moderate: Epworth sleepiness score at 2 months; Group 1: mean 9 (SD 5.1); n=24, Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 2: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 2 months; Group 1: mean 8 (SD 10.9); n=24, Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 3: ODI at >1 month - Actual outcome for Moderate: oxygen desaturation % at 2 months; Group 1: mean 4.8 (SD 2.7); n=24, Group 2: mean 3.3 (SD 1.6); n=24 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 4: Patient preference at >1 month - Actual outcome for Moderate: patient preference at 2 months; Group 1: 17/21, Group 2: 4/21 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Wilhelmsson 1999[224]
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Sweden; Setting: Central hospital Vasteras, Sweden
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients >20 and <65 with confirmed OSA (AHI >10).
Exclusion criteria	Individuals less than 20 and more than 65 years of age, AI more than 25, mental illness, drug misuse, significant nasal obstruction, insufficient teeth to anchor an appliance, pronounced dental malocclusion, severe cardiovascular disease and neurological or respiratory disease
Recruitment/selection of patients	patients with confirmed OSA were randomly assigned to either treatment with UPPP or dental device
Age, gender and ethnicity	Age - Mean (range): oral device = 49.3 (46.8-51.9), UPPP = 51.0 (49.1-52.9). Gender (M:F): 95/0. Ethnicity: unclear
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Systematic review: mixed 3. Gender: Male 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Not stated / Unclear
Indirectness of population	Serious indirectness: patients with mild to moderate OSA based on AHI included
Interventions	(n=49) Intervention 1: Oral devices. Before the intervention a clinical examination of the stomatognathic system was carried out. The same dentist treated all patients and one dental technician was responsible for the manufacture of the dental appliances. The appliances were carefully designed and fabricated on dental

	casts of acrylic polymer at a dental laboratory. The appliances were used at night times only and advanced the mandible by 50% of the patient's maximum protrusive capacity. each patient was given an appointment for adjustment and adaptation of the dental appliance 2 weeks after the initial visit. Further follow up visits were conducted with a clinical examination of the stomatognatic system performed at 3,6 and 12 months following intervention. Duration 12 months. Concurrent medication/care: Fibre optic pharyngoscopy with the Muller manoeuvre was performed before the intervention with the patients in a supine position. the procedure was repeated with the with the tip of the fibre laryngoscope in the mesopharynx to evaluate the collapse of the hypopharynx. the degree of collapse was recorded using a 5-point scale to evaluate the type of obstruction (i.e. I, II or III). sleep studies were performed at baseline and 6 and 12 months after intervention in the patients' homes with a portable unit by a blinded technician. (n=46) Intervention 2: Surgery. The Uvulopalatopharyngoplasty (UPPP) was performed by the same ear, nose and throat surgeon using a standardised procedure described by Frjita. the procedure involved tonsillectomy regardless of the size of the tonsils, and resection of excess fat and mucosa of the soft palate, including the uvula. the palpable musculature was saved and several sutures approximated the anterior and posterior tonsillar pillars. The UPPP surgery was performed under general anaesthesia. Duration 12 months. Concurrent medication/care: Fibre optic pharyngoscopy with the Muller manoeuvre was performed before the intervention with the patients in a supine position. The procedure was repeated with the tip of the fibre laryngoscope in the mesopharynx to evaluate the collapse of the hypopharynx. The degree of collapse was recorded using a 5-point scale to evaluate the type of obstruction (i.e. I, II or III). Sleep studies were performed at baseline and 6 and 12 months after intervention in the patients' homes with a portable unit by a blinded technician. Indirectness: Serious indirectness; Indirectness comment: patients with mild to moderate OSA were included based on their AHI score
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus SURGERY

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Moderate: experience of daytime sleepiness questionnaire at 6 and 12 months;
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 11, Reason: 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly after randomisation. 1 due to epilepsy, 1 because of recurrent apthous ulcer due to allergy to the polymer used and 2 could not thrive with the dental appliance. 2 stopped using after 6 months due to no improvement and 1 due to cancer diagnosis. ; Group 2 Number missing: 3, Reason: 2 reversed their decision and 1 diagnosed with gastric cancer

Protocol outcome 2: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 6 months; Group 1: mean 11.3 (SD 2.6); n=41, Group 2: mean 11.7 (SD 2.8); n=43 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 8, Reason: 4 withdrew after randomisation, 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly. 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly after randomisation. 1 due to epilepsy, 1 because of recurrent apthous ulcer due to allergy to the polymer used and 2 could not thrive with the dental appliance. ; Group 2 Number missing: 3, Reason: 2 reversed their decision and 1 diagnosed with gastric cancer - Actual outcome for Moderate: AHI - 12 months at 12 months; Group 1: mean 12.4 (SD 3.4); n=37, Group 2: mean 10 (SD 3.5); n=43 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 11, Reason: 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly after randomisation. 1 due to epilepsy, 1 because of recurrent apthous ulcer due to allergy to the polymer used and 2 could not thrive with the dental appliance. 2 stopped using after 6 months due to no improvement and 1 due to cancer diagnosis. ; Group 2 Number missing: 3, Reason: 2 reversed their decision and 1 diagnosed with gastric cancer Protocol outcome 3: ODI at >1 month - Actual outcome for Moderate: ODI at 6 months; Group 1: mean 10.2 (SD 2.6); n=41, Group 2: mean 10.4 (SD 3.2); n=43 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 8, Reason: 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly after randomisation. 1 due to epilepsy, 1 because of recurrent apthous ulcer due to allergy to the polymer used and 2 could not thrive with the dental appliance. 2 stopped using after 6 months due to no improvement and 1 due to cancer diagnosis. ; Group 2 Number missing: 3, Reason: 2 reversed their decision and 1 diagnosed with gastric cancer - Actual outcome for Moderate: ODI - 12 months at 12 months; Group 1: mean 10.9 (SD 3.7); n=37, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 11, Reason: 3 reversed their decision prior to treatment and 1 the device could not be anchored correctly after randomisation. 1 due to epilepsy, 1 because of recurrent apthous ulcer due to allergy to the polymer used and 2 could not thrive with the dental appliance. 2 stopped using after 6 months due to no improvement and 1 due to cancer diagnosis. ; Group 2 Number missing: 3, Reason: 2 reversed their decision and 1 diagnosed with gastric cancer	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Yamamoto 2019[225]
Study type	RCT (Patient randomised; Crossover: no washout period - 4 weeks test period authors state act as a washout between interventions)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Japan; Setting: Kyushu University Hospital or Saiseikai Futsukaichi Hospital, Japan
Line of therapy	Unclear
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients over 20 years old who had been diagnosed with OSA with an overall AHI of 20-40/h and supine dependency based on overnight polysomnography. other inclusion criteria were; two or more symptoms of OSA among night-time dyspnoea, fragmented sleep, non-restorative sleep, and excessive daytime sleepiness.
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients were tested for eligibility based on overnight polysomnography at Kyushu University Hospital or Saiseikai Futsukaichi Hospital. Suitable patients from either clinic were referred to the sleep apnoea centre of Kyushu university hospital from August 14 to September 2016.
Age, gender and ethnicity	Age - Mean (SD): 54.9 (12.2). Gender (M:F): Define. Ethnicity: unclear

Study	Yamamoto 2019[225]
Further population details	1. BMI: BMI of less than 30 2 kg/m^2. Co-existing conditions: Systematic review: mixed 3. Gender: Systematic review: mixed 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: patients with moderate and severe OSA included based on AHI value
Interventions	(n=45) Intervention 1: Oral devices. A dentist at Kyushu university hospital took the impression and bite registration of the patients and sent it to a central laboratory where all the MAD were made. MADs were Somnodent (Somnodent Inc., Sydney, Australia) and were custom-made and titrated with consideration of patient's comfort and the results of SP02 monitoring. The maximal advancement was set at 75% of maximum and vertical opening was decided as minimum of each patient. titration period took about 4 weeks and jaw positions were titrated in reference to patient's comfort. effects of the MAD were evaluated at the end of the MAD treatment period (7-9 weeks after treatment) by a home sleep apnoea monitor. Duration 8 weeks. Concurrent medication/care: Patients were assigned to either treatment group and after a test period of 4 weeks of each device the adherence was checked. at the end of the treatment period the severity of OSA was recorded using a home sleep apnoea monitor, along with respiratory events index and minimum spo2. (n=45) Intervention 2: Non-surgical intervention - Positive airway pressure variants (CPAP, APAP). Patients randomised to CPAP used a sleep mate S9 (Resmed, San Diego, CA, USA) or REMstar Pro System One 60 series (Phillips Respironics, Murrysvilles, PA, USA) in automatic pressure mode initially set between 4 and 12 cmH2co by referring the analysis of the pressure in our institute with a humidifier when needed. Duration 8 weeks. Concurrent medication/care: Patients were assigned to either treatment group and after a test period of 4 weeks of each device the adherence was checked. at the end of the treatment period the severity of OSA was recorded using a home sleep apnoea monitor, along with respiratory events index and minimum spo2. Indirectness: Serious indirectness
Funding	Equipment / drugs provided by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL DEVICES versus POSITIVE AIRWAY PRESSURE VARIANTS (CPAP, APAP)

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Moderate: Japanese Epworth sleepiness scale at 8 weeks; Group 1: mean 4.9 (SD 3.8); n=40, Group 2 mean 5 (SD 3.6); n=40

Study	Yamamoto 2019[225]
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue Protocol outcome 2: ODI at >1 month - Actual outcome for Moderate: Oxygen desaturation index at 8 weeks; Group 1: mean 8.7 (SD 6.8); n=40, Group 2: mean 5.5 (SD 4.3); n=40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue Protocol outcome 3: Adherence in hours of use at >1 month - Actual outcome for Moderate: adherence - minutes per night at 8 weeks; Group 1: mean 315.8 minutes (SD 127); n=40, Group 2: mean 274.5 minutes (SD 108.9); n=40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue - Actual outcome for Moderate: adherence - > 4 hours per night use % at 8 weeks; Group 1: mean 70.8 % (SD 27.4); n=40, Group 2: mean 62.7 % (SD 29.3); n=40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue Protocol outcome 4: Patient preference at >1 month - Actual outcome for Moderate: patient overall satisfaction % at 8 weeks; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue Protocol outcome 5: Systolic blood pressure for hypertension at >1 month - Actual outcome for Moderate: systolic BP at 8 weeks; Group 1: mean 121.7 mm hg (SD 12.4); n=40, Group 2: mean 122.1 mm hg (SD 13.4); n=40 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 5, Reason: technological issue with equipment 4; Group 2 Number missing: 5, Reason: 1 due to intolerance with CPAP and technological issue	

Study	Yamamoto 2019[225]
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; AHI/RDI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Mandibular advancement splints compared to each other

Study	Johal 2017[108]
Study type	RCT (Patient randomised; Crossover: 2 weeks)
Number of studies (number of participants)	1 (n=35)
Countries and setting	Conducted in United Kingdom; Setting: A single-center, hospital-based
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild: N/A
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	The selection criteria for the trial were: adults (> 18 years), with a confirmed diagnosis of mild-moderate OSA (AHI of 5–30 events/h); sufficient healthy teeth to retain an MRD; the absence of periodontal disease or temporomandibular joint dysfunction and no previous history of MRD use.
Exclusion criteria	not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 44.9 (11.5). Gender (M:F): 21/14. Ethnicity: not stated
Further population details	1. BMI: BMI of less than 30 kg/m^2 (BMI=28.7(5.3)). 2. Co-existing conditions: Not stated / Unclear 3. Gender: Not applicable (male/female = 21/14). 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9 (ESS =11 (6-16)).

Study	Johal 2017[108]
Indirectness of population	serious indirectness due to mixed OSHAS population included
Interventions	(n=35) Intervention 1: Self-customised/ready-made/self-moulded. The ready-made MRD selected was a preformed thermoplastic appliance, the “Snoreshield” (S4S, Sheffield, UK). Patients were instructed to fit the appliance as per the manufacturer’s instructions, by soaking the device in warm water and fitting to the upper arch. The mandible was then protruded into the device. The appliance could be reheated at home for further manipulation as required, with a maximum permissible protrusion of 6 mm. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Intervention type: Physical (the “Snoreshield” (S4S,Sheffield, UK)). 2. titratable: non-titratable (n=35) Intervention 2: full customised/fully bespoke . The custom-made MRD (selected was the “MedicalDental Sleep Appliance” (R.J. and V.K. Bird, Middle Park, Victoria, Australia) which had been previously evaluated. 10 The appliance design was regarded to meet the gold standard in light of the fact it exhibits minimal opening, is self-adjustable, and allows incremental advancement of the mandible, up to a maximum of 9 mm. The appliance was constructed in a single laboratory, based on working models of the teeth and an inter-occlusal registration in the intercuspal position. It was fitted by an experienced orthodontist and the incremental method of advancing the mandible demonstrated. Subjects were advised to turn the screw on a weekly basis until sleep improved and symptoms resolved. Duration 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Intervention type: Physical (The custom-made MRD). 2. titratable: titratable
Funding	No funding reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-CUSTOMISED/READY MADE/SELF-MOULDED versus FULL CUSTOMISED/FULLY BESPOKE

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Mild: SF 36 at 6 months; Median (IQR)
Ready-made - 2,615 (2,305.0 - 3,137.5)
Custom-made - 2,660 (2,420.0 - 3,180.0);
Risk of bias: All domain – very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 10
- Actual outcome for Mild: FOSQ at 6 months; Median (IQR)
Ready-made - 96 (80.5 - 108.5)
Custom-made - 104 (85.5 - 112.0);

Study	Johal 2017[108]
Risk of bias: All domain – very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 10 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Mild: ESS at 6 months; Mean; , Comments: Median (IQR) Ready-made - 7(4.5 - 11.5) Custom-made - 5(3-8); Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: ODI at >1 month - Actual outcome for Mild: ODI at 6 months; Group 1: mean 5.6 (SD 6.3); n=25, Group 2: mean 2.9 (SD 3.2); n=25 Risk of bias: All domain – very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 10 Protocol outcome 4: CO2 control at >1 month - Actual outcome for Mild: Mean Oxygen saturation (%) at 6 months; Mean; , Comments: Ready-made - 96.3 no SD Custom-made - 98.1 no SD; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Mild: Min Oxygen saturation (%) at 6 months; Mean; , Comments: Ready-made - 84.1 no SD Custom-made - 86.4 no SD; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Patient preference at >1 month - Actual outcome for Mild: preference at 6 months; Group 1: 1/25, Group 2: 24/25 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at >1 month; AHI/RDI at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Study	Pepin 2019[164]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=190)
Countries and setting	Conducted in France; Setting: multicentre trial
Line of therapy	Second line
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Moderate
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	The study population consisted of adults (>18 years) with severe OSA refusing or not tolerating CPAP, without dental, periodontal or temporomandibular joint contraindications and naïve to MAD use. In line with the French Respiratory Society consensus, severe OSA was defined as an AHI ≥15/hour with either severe daytime sleepiness or at least two of the following symptoms: severe nightly snoring, gasping or choking sensations, unrefreshing sleep, fatigue and/or nocturia. Patients were recruited by private practice sleep clinics and university hospital sleep centres. Baseline AHI Thermoplastic - 26(10.7) Custom-made –27.4(10.1)
Exclusion criteria	Severe psychiatric or neuromuscular disorders (at the investigators' judgement); more than 20 % of central sleep apnoea and hypopnea; OSA associated with coexistent sleep disorders (narcolepsy, hypersomnia, severe restless leg syndrome); MBI >30 kg²; ongoing or scheduled orthodontic treatment, unmanageable gag reflex; pregnant or breastfeeding women; patients with epilepsy; inability to give informed consent; patient included in another ongoing clinical study; and patient not covered by French health insurance system.

Study	Pepin 2019[164]
Age, gender and ethnicity	Age - Mean (SD): boil and bite 49.3(11.2); custom-made 52.9(12.2). Gender (M:F): 117/39. Ethnicity: not stated
Further population details	1. BMI: BMI of less than 30 kg/m^2 (boil and bite group 25.86(2.71) custom-group - 25.91(2.85)). 2. Co-existing conditions: Not stated / Unclear 3. Gender: Not applicable (mixed 117/39). 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: Not stated / Unclear
Indirectness of population	Serious indirectness: mean severity of the population
Interventions	(n=98) Intervention 1: Self-customised/readymade/self-moulded. Thermoplastic heat-moulded titratable MAD (ONIRIS; ONIRIS SAS, Rueil Malmaison, France). Oniris is a two piece titratable thermoplastic MAD made of two stiff gutters heat moulded on plaster-casts of dental arches (or in situ) coupled by two adjustable connecting rods allowing mandibular advancement to be set in steps of 1 mm and permitting freedom of jaw opening movements. Duration 2 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Intervention type: Physical 2. titratable: titratable (n=100) Intervention 2: full customised/fully bespoke . custom-made acrylic titratable MAD (TALI;ONIRIS SAS, Rueil Malmaison, France). Tali is a two-piece titratable acrylic custom-made MAD allowing one to set mandibular advancement in steps of 1 mm and allowing freedom of jaw opening movements. Duration 2 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Intervention type: Physical 2. titratable: titratable
Funding	Study funded by industry (This study was funded by ONIRIS (France). Data collection, quality control, management and analysis of the data were performed by the contract research organisation Euraxi (France). This work was also supported by the French National Research Agency (Agence Nationale de la Recherche) in the framework of the 'Investissements d'avenir' program (ANR-15-IDEX-02). the funding sources had no role in the study design, realisation, analyses, data interpretation, in writing the manuscript or in the decision to submit it for publication)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-CUSTOMISED/READY MADE/SELF-MOULDED versus FULL	

Study	Pepin 2019[164]
CUSTOMISED/FULLY BESPOKE Protocol outcome 1: Quality of life at >1 month - Actual outcome for Moderate: SF 12 Mental score at 2 months; Group 1: mean 9.07 (SD 21.25); n=60, Group 2: mean 5.27 (SD 17.68); n=81 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32 ; Group 2 Number missing: 17 - Actual outcome for Moderate: SF 12 Physical score at 2 months; Group 1: mean 7.71 (SD 13.02); n=60, Group 2: mean 4.22 (SD 14.81); n=81 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32 ; Group 2 Number missing: 17 - Actual outcome for Moderate: Systolic BP at 2 months; Group 1: mean -4.36 (SD 17.42); n=17, Group 2: mean -11.19 (SD 16.07); n=26 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 75 ; Group 2 Number missing: 72 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for Moderate: ESS at 2 months; Group 1: mean -3.76 (SD 4.16); n=87, Group 2: mean -3.34 (SD 3.77); n=95 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing:5 ; Group 2 Number missing: 3 Protocol outcome 3: AHI/RDI at >1 month - Actual outcome for Moderate: AHI at 2 months; Group 1: mean -11.9 (SD 9.43); n=69, Group 2: mean -11.16 (SD 10.8); n=87 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23 ; Group 2 Number missing: 11 Protocol outcome 4: Adverse effects of treatment at >1 month - Actual outcome for Moderate: serious adverse events at 2 months; Group 1: 0/69, Group 2: 0/87 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23 ; Group 2 Number missing: 11 Protocol outcome 5: Adherence self-reported at >1 month - Actual outcome for Moderate: self-reported adherence at 2 months; Group 1: mean – 6.1 (SD 1.5) n= 69, Group 2: 6.8 (SD 1.1) n= 87 Risk of bias: All domain – Very high, Selection - Low, Blinding - high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 13	
Protocol outcomes not reported by the study	Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; HbA1c for diabetes at >1 month Cardiovascular events at >1 month

Study	Quinnell 2014[175]
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Papworth hospital sleep centre
Line of therapy	1st line
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mild
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥18 years with mild to moderate OSAHS confirmed by respiratory polysomnography (rPSG) (AHI 5–<30/h) and symptomatic daytime sleepiness (Epworth Sleepiness Scale (ESS) score ≥9) were recruited from Papworth Hospital sleep centre. Newly diagnosed patients not requiring or declining CPAP and existing CPAP intolerant patients were eligible.
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): 50.9 (11.6). Gender (M:F): 72/18. Ethnicity: not stated
Further population details	1. BMI: BMI of 30 2 kg/m^2 or more. Co-existing conditions: Not stated / Unclear 3. Gender: Not stated / Unclear 4. High risk occupation group: Not stated / Unclear 5. Race: Not stated / Unclear 6. Sleepiness: ESS >9
Indirectness of population	Serious indirectness: mild and moderate OSAHS patients included
Interventions	(n=90) Intervention 1: Self-customised/ready-made/self-moulded. SleepPro 1 (SP1) (Meditas Ltd., Winchester, UK): A thermoplastic „boil and bite" device fitted by the patient following the manufacturer's printed instructions. all patients wore the device for a period of 4 weeks with 1 week wash out periods between.. Duration 4 weeks. Concurrent medication/care: Unclear. Indirectness: No indirectness Further details: 1. Intervention type: Physical 2. titratable: non-titratable (n=90) Intervention 2: semi-customised/ semi-bespoke. SleepPro 2 (SP2) (Meditas Ltd., Winchester, UK): A

Study	Quinnell 2014[175]
	semi-bespoke device, formed from a dental impression mould made by the patient. An impression kit was posted to the patient. all patients wore the device for 4 weeks with a 1 week washout period.. Duration 4 weeks. Concurrent medication/care: Unclear. Indirectness: No indirectness Further details: 1. Intervention type: Physical 2. titratable: (n=90) Intervention 3: full customised/fully bespoke . Bespoke Device (bMAD) (Maxillofacial Laboratory, Department of Oral and Maxillofacial Surgery, Cambridge, UK): Custom-made MAD, professionally fitted by specialists in the NHS Maxillofacial laboratory at Addenbrooke's Hospital, UK.. Duration 4 weeks. Concurrent medication/care: unclear. Indirectness: No indirectness Further details: 1. Intervention type: Physical 2. titratable: Not applicable
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-CUSTOMISED/READY MADE/SELF-MOULDED versus SEMI-CUSTOMISED/ SEMI-BESPOKE

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Mild: ESS at unclear; Group 1: mean 8.5 (SD 4); n=83, Group 2: mean 8 (SD 4.1); n=83
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 2: AHI/RDI at >1 month
- Actual outcome for Mild: AHI at unclear; Group 1: mean 10.8 (SD 9.5); n=81, Group 2: mean 9.7 (SD 8.9); n=81
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 9

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELF-CUSTOMISED/READY MADE/SELF-MOULDED versus FULL CUSTOMISED/FULLY BESPOKE

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Mild: ESS at unclear; Group 1: mean 8.5 (SD 4); n=83, Group 2: mean 7.7 (SD 3.8); n=83
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7

Protocol outcome 2: AHI/RDI at >1 month

Study	Quinnell 2014[175]
- Actual outcome for Mild: AHI at unclear; Group 1: mean 10.8 (SD 9.5); n=81, Group 2: mean 9.5 (SD 8.4); n=81 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 9 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEMI-CUSTOMISED/ SEMI-BESPOKE versus FULL CUSTOMISED/FULLY BESPOKE Protocol outcome 1: Sleepiness score at >1 month - Actual outcome for Mild: ESS at unclear; Group 1: mean 8 (SD 4.1); n=83, Group 2: mean 7.7 (SD 3.8); n=83 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 2: AHI/RDI at >1 month - Actual outcome for Mild: AHI at unclear; Group 1: mean 9.7 (SD 8.9); n=81, Group 2: mean 9.5 (SD 8.4); n=81 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 9	
Protocol outcomes not reported by the study	Quality of life at >1 month; Mortality at >1 month; ODI at >1 month; CO2 control at >1 month; Adverse effects of treatment at >1 month; Disruption of partners sleep at >1 month; Driving outcomes at >1 month; Neurocognitive outcomes at >1 month; Adherence in hours of use at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Systolic blood pressure for hypertension at >1 month

Appendix E: Forest plots

E.1 Oral devices (mandibular advancement splints) compared to Placebo (mild OSAHS)

Figure 1: AHI – Boil and bite (lower is better)

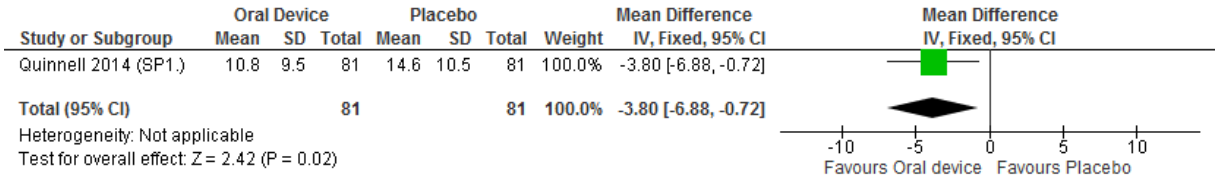


Figure 2: AHI – Semi-bespoke (lower is better)

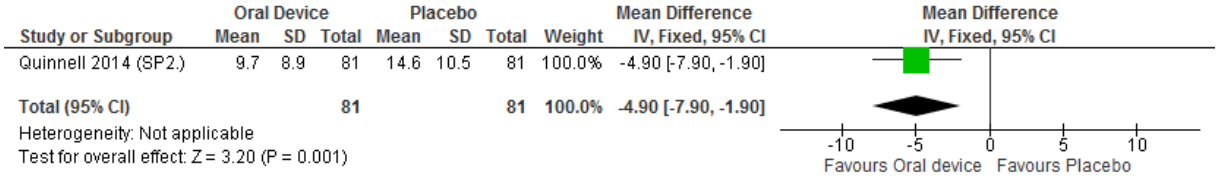


Figure 3: AHI – custom-made (lower is better)

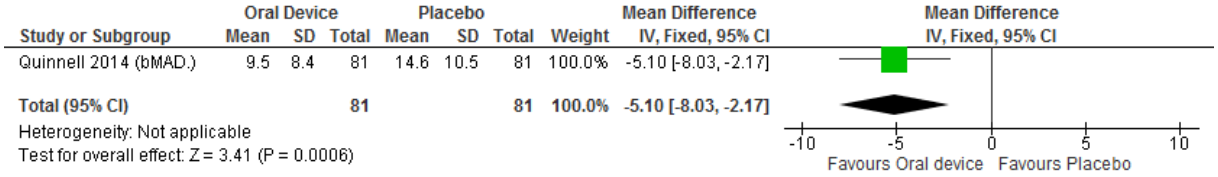


Figure 4: EQ5D VAS score – boil and bite (0-100, higher is better)

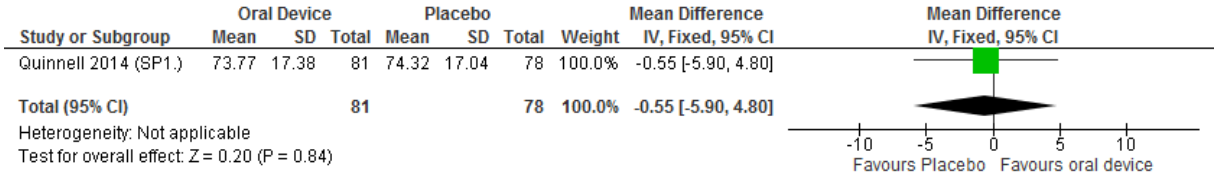


Figure 5: EQ5D VAS score – semi-bespoke (0-100, higher is better)

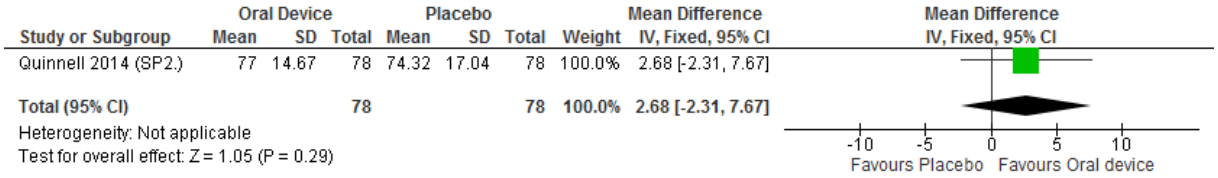


Figure 6: EQ5D VAS score – custom-made (0-100, higher is better)

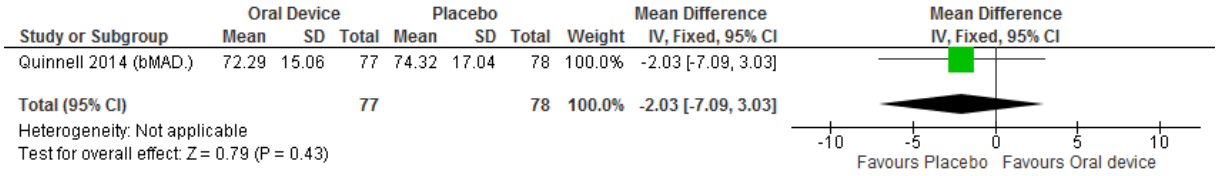


Figure 7: SF-36 Vitality – boil and bite (0-100, higher is better)

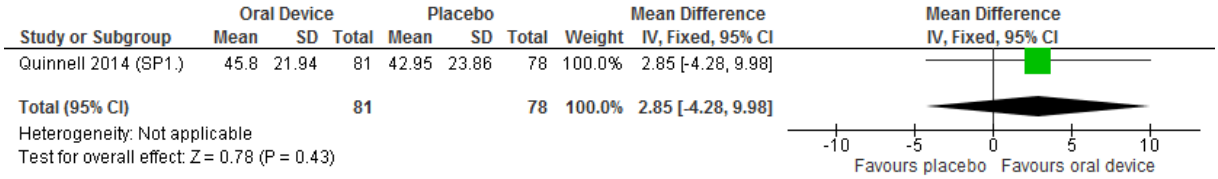


Figure 8: SF-36 Vitality – semi-bespoke (0-100, higher is better)

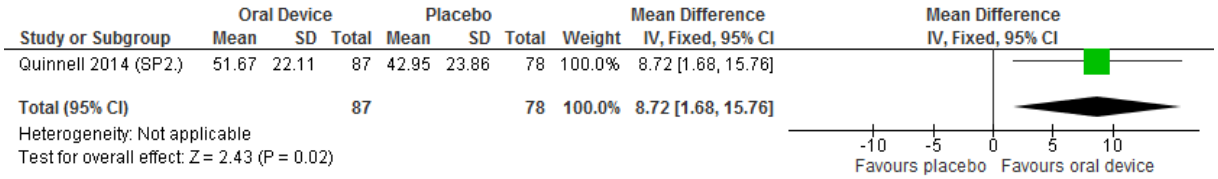


Figure 9: SF-36 Vitality – custom-made (0-100, higher is better)

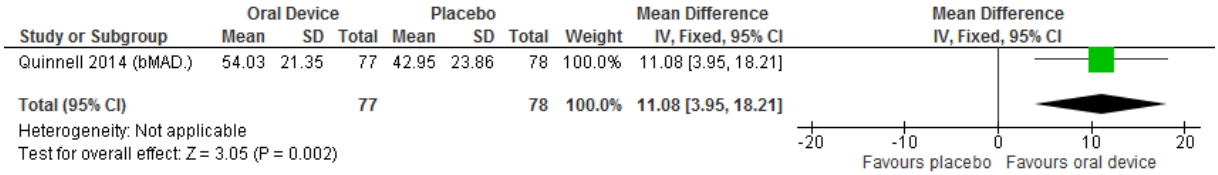


Figure 10: ESS (Epworth) - boil and bite (0-24, higher is worse)

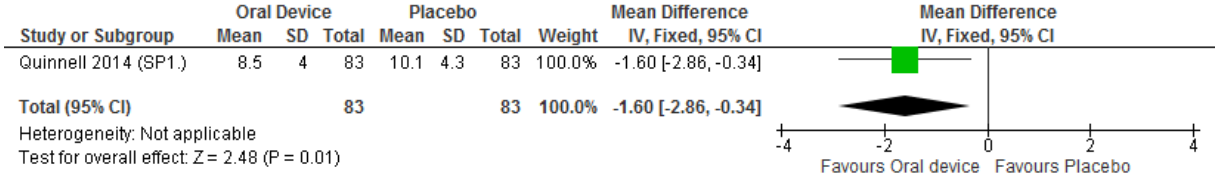


Figure 11: ESS (Epworth) – semi-bespoke (0-24, higher is worse)

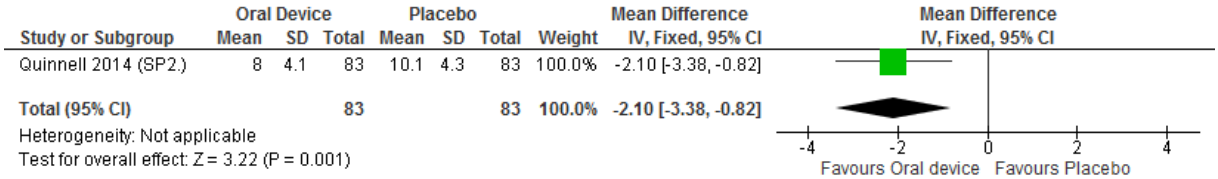


Figure 12: ESS (Epworth) – custom-made (0-24, higher is worse)

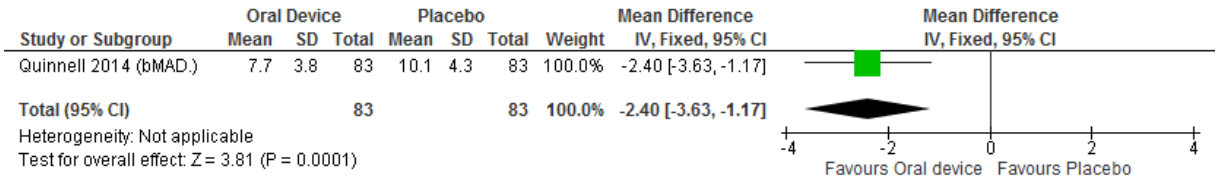


Figure 13: adverse events minor – boil and bite

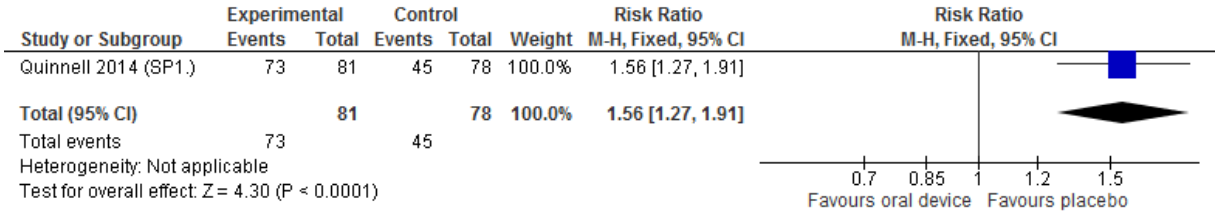


Figure 14: adverse events minor – semi-bespoke

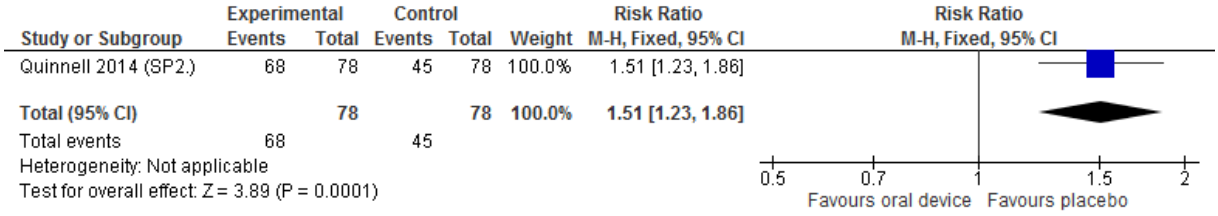
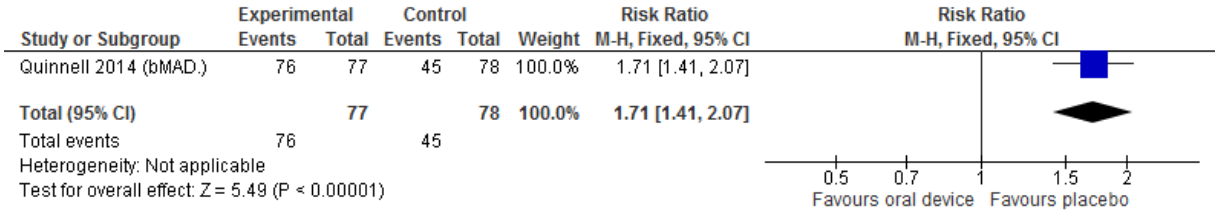


Figure 15: adverse events minor – custom-made



E.2 Oral devices (mandibular advancement splints) compared to Placebo (moderate OSAHS)

Figure 16: AHI – final value (lower is better)

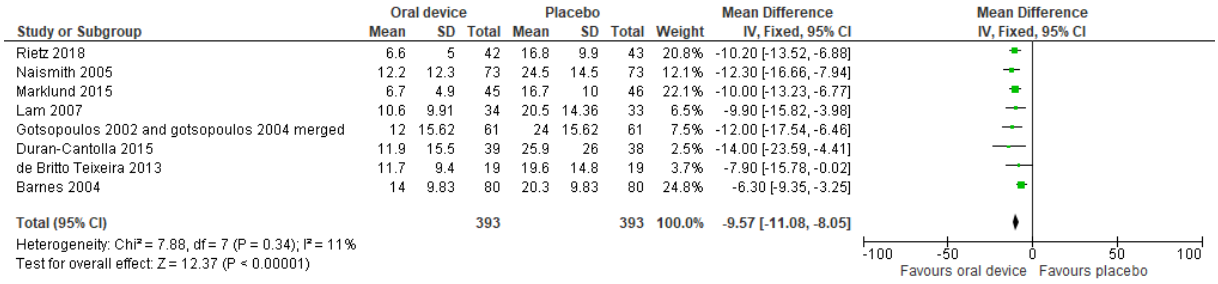


Figure 17: AHI – change score (lower is better)

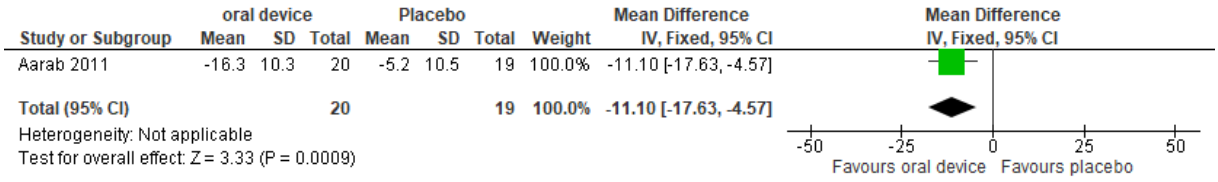


Figure 18: ESS (Epworth) (0-24, higher is worse)

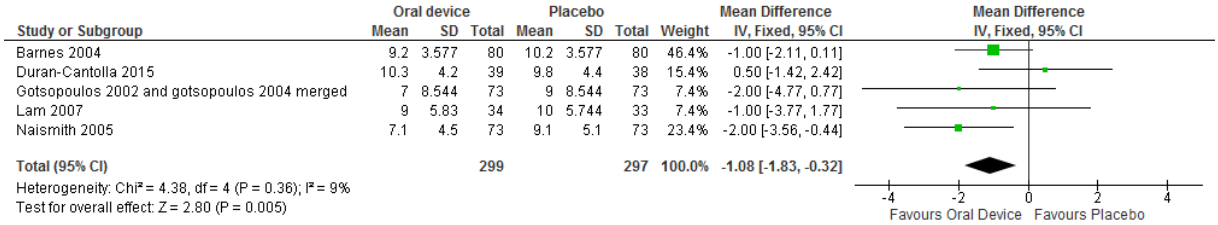


Figure 19: ODI (lower is better)

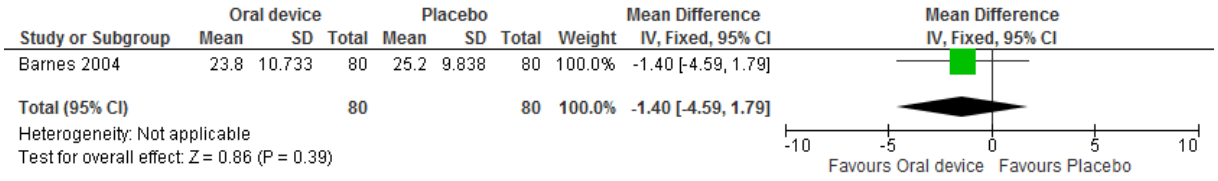


Figure 20: FOSQ (mean score) 5-20, lower is worse

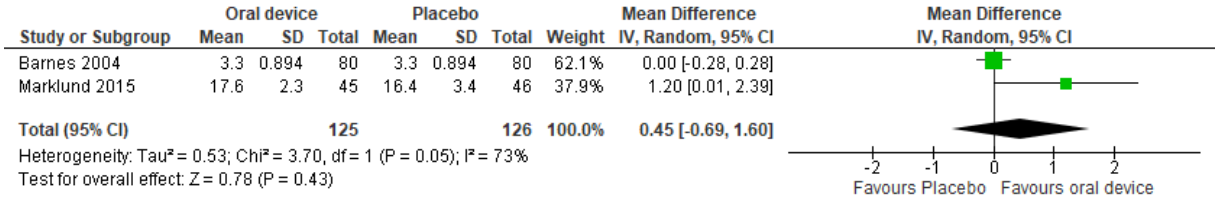


Figure 21: SF 36 – mental (0-100, higher is better)

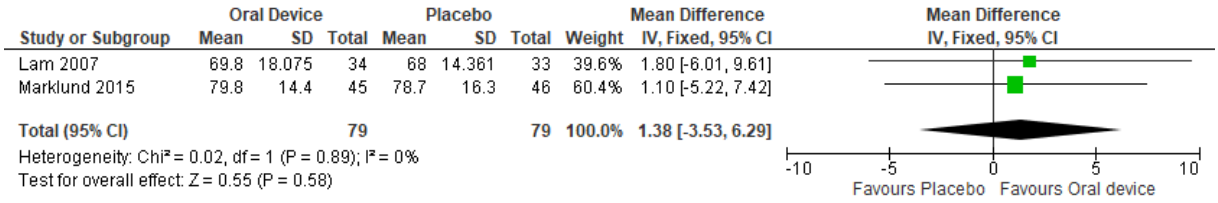


Figure 22: SF 36 – physical (0-100, higher is better)

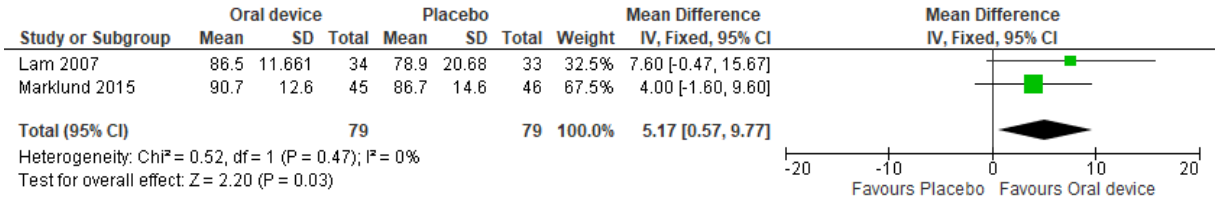


Figure 23: Adherence hours per night

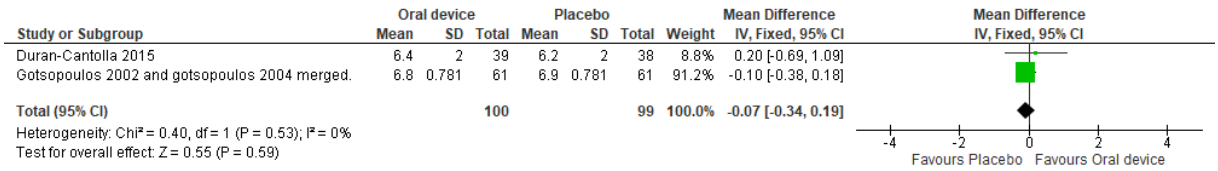


Figure 24: Systolic BP

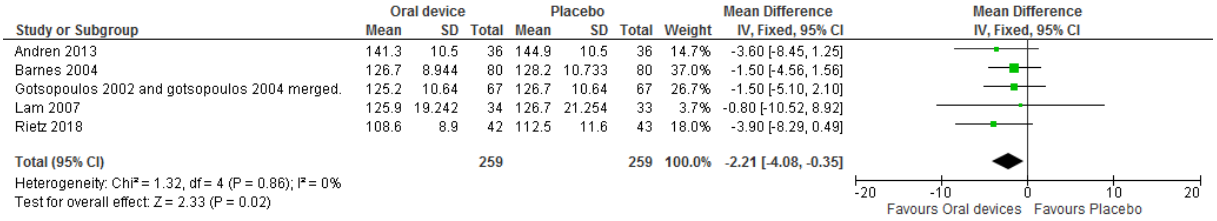


Figure 25: SAQLI (1-7, higher is better)

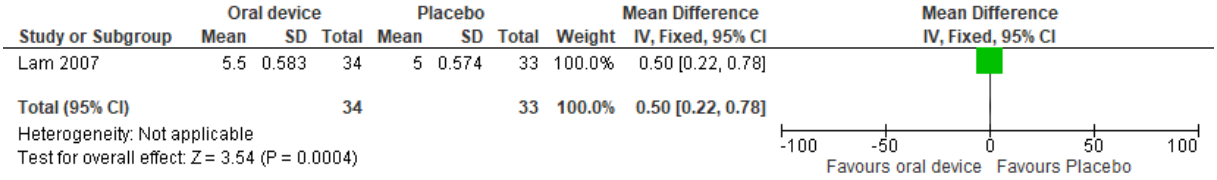


Figure 26: Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting) (lower is better)

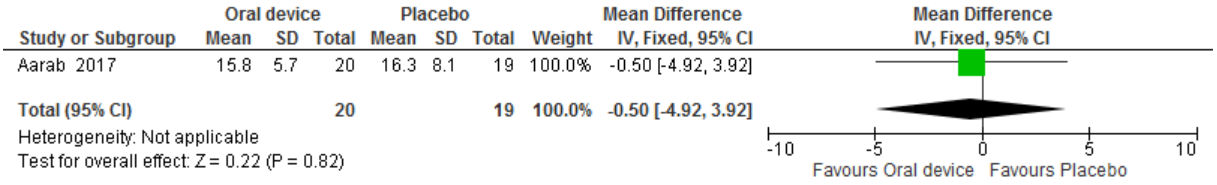


Figure 27: Adverse events – side effects (mild, moderate and severe side effects)

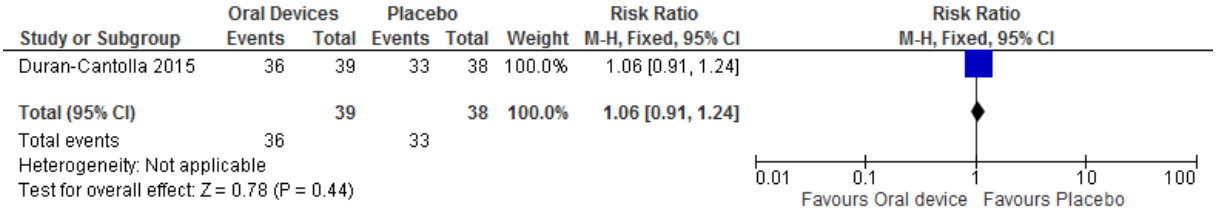
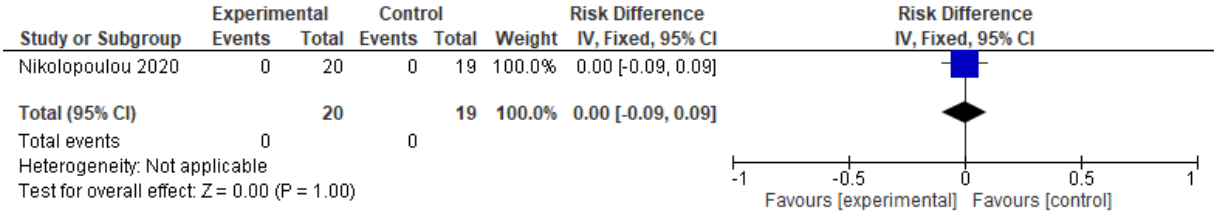


Figure 28: Adverse events – TMD pain



E.3 Oral Devices (mandibular advancement splints) compared to CPAP (moderate OSAHS)

Figure 29: AHI – final value (lower is better)

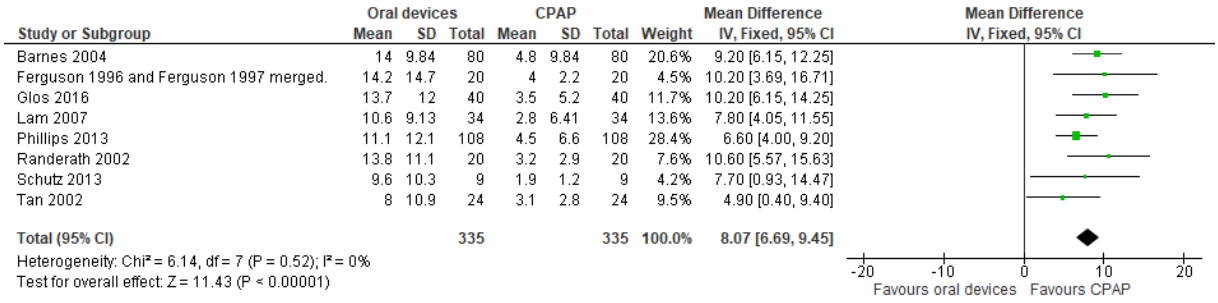


Figure 30: AHI – change score (lower is better)

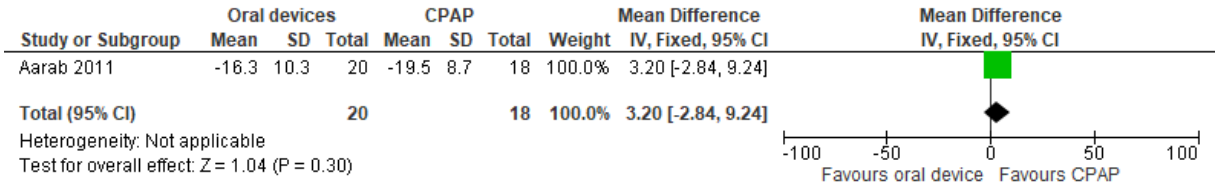


Figure 31: AHI 12 months after the intervention (lower is better)

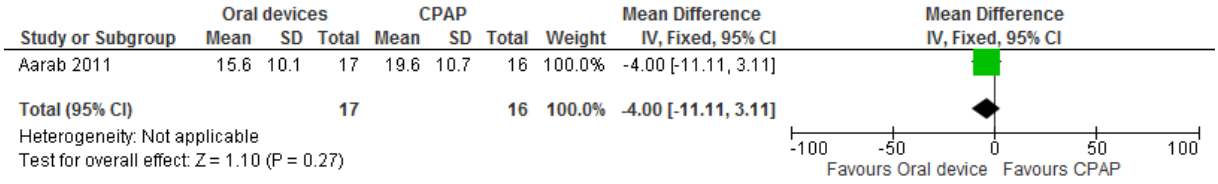


Figure 32: AHI 18 months after the intervention (lower is better)

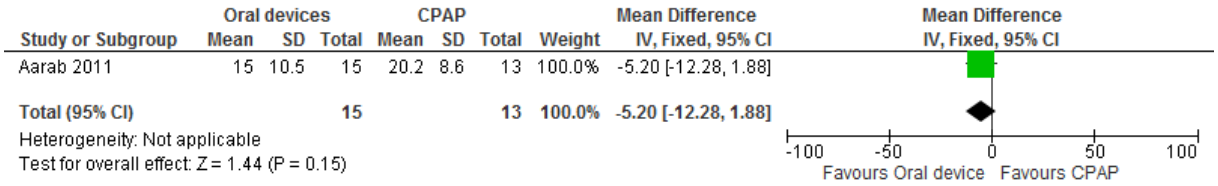


Figure 33: FOSQ (mean score) (5-20, lower is worse)

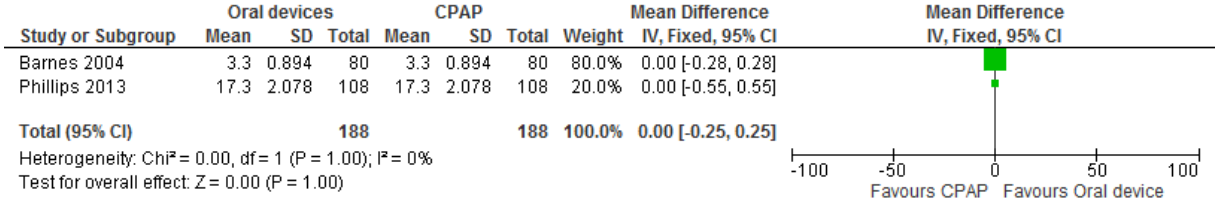


Figure 34: SF 36 (mental) (0-100, higher is better)

Study or Subgroup	Oral devices Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lam 2007	69.8	18.075	34	71.8	16.326	34	20.8%	-2.00 [-10.19, 6.19]
Phillips 2013	75.3	15.588	108	72.6	16.627	108	75.4%	2.70 [-1.60, 7.00]
Schutz 2013	68	16.2	9	68.6	24.3	9	3.8%	-0.60 [-19.68, 18.48]
Total (95% CI)			**151**			**151**	**100.0%**	**1.60 [-2.14, 5.33]**

Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

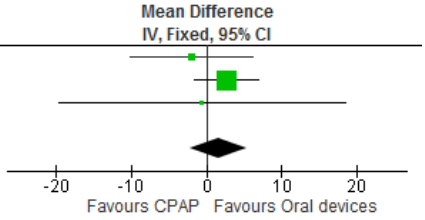


Figure 35:SF 36 (physical) (0-100, higher is better)

Study or Subgroup	Oral devices Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lam 2007	86.5	11.66	34	88.2	9.912	34	46.4%	-1.70 [-6.84, 3.44]
Phillips 2013	84.7	19.74	108	83.7	19.74	108	44.3%	1.00 [-4.26, 6.26]
Schutz 2013	85	13	9	82.1	11.9	9	9.3%	2.90 [-8.61, 14.41]
Total (95% CI)			**151**			**151**	**100.0%**	**-0.08 [-3.58, 3.43]**

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

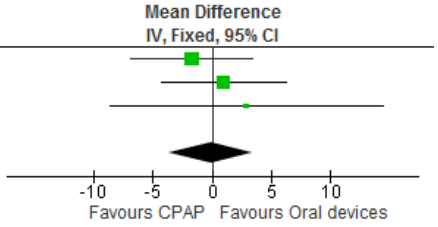


Figure 36: SF-36 (vitality) (0-100, higher is better)

Study or Subgroup	Oral devices Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
de Vries 2019	59.3	24.2	29	60.7	22.5	37	100.0%	-1.40 [-12.81, 10.01]
Total (95% CI)			**29**			**37**	**100.0%**	**-1.40 [-12.81, 10.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

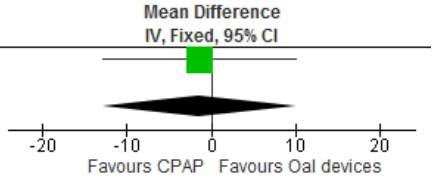


Figure 37: EQ5D (VAS) (0-100, higher is better)

Study or Subgroup	Oral devices Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
de Vries 2019	74.4	14.4	29	71.1	12.9	37	100.0%	3.30 [-3.39, 9.99]
Total (95% CI)			**29**			**37**	**100.0%**	**3.30 [-3.39, 9.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

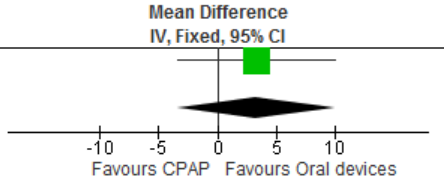


Figure 38: Systolic BP

Study or Subgroup	Oral devices Mean	SD	Total	CPAP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Barnes 2004	126.7	8.944	80	127.3	10.733	80	55.6%	-0.60 [-3.66, 2.46]
Glos 2016	119.6	12.6	40	119.6	10.5	40	20.2%	0.00 [-5.08, 5.08]
Lam 2007	125.9	19.242	34	123	14.577	34	7.9%	2.90 [-5.21, 11.01]
Yamamoto 2019	121.7	12.4	40	122.1	13.4	40	16.3%	-0.40 [-6.06, 5.26]
Total (95% CI)			**194**			**194**	**100.0%**	**-0.17 [-2.45, 2.11]**

Heterogeneity: Chi² = 0.64, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

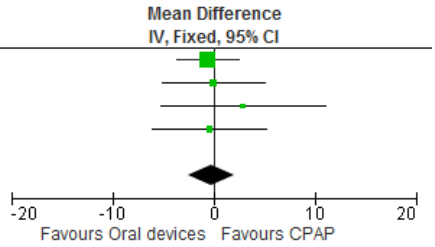


Figure 39: ODI (lower is better)

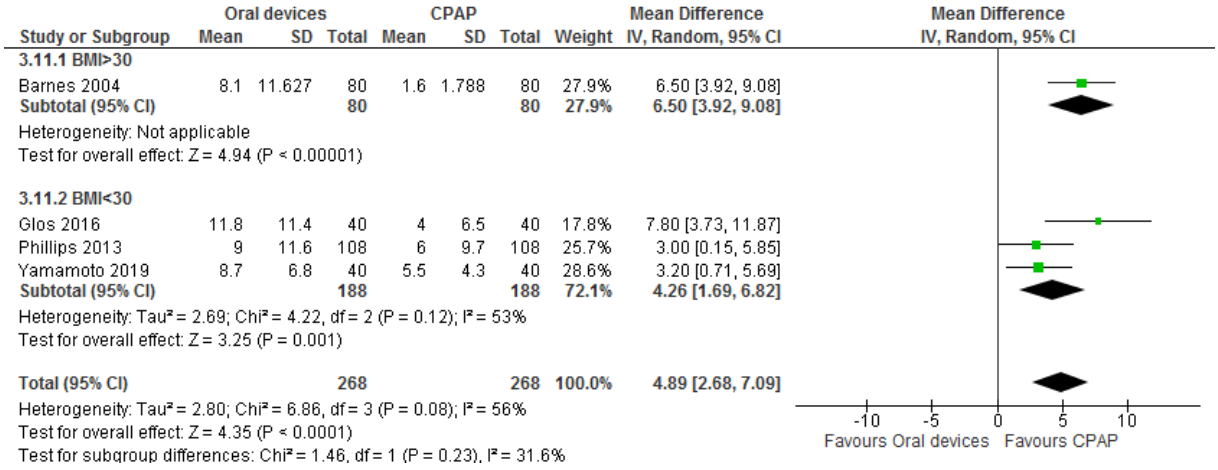


Figure 40: ESS (Epworth) (0-24, higher is worse)

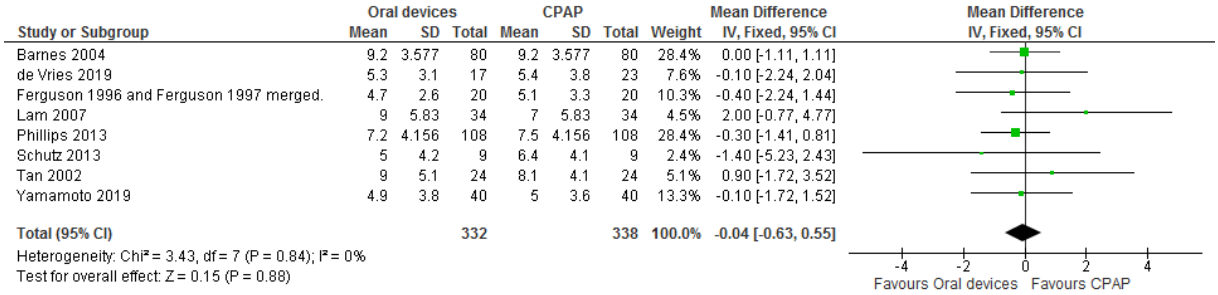


Figure 41: ESS (Epworth) 12 months (0-24, higher is worse)

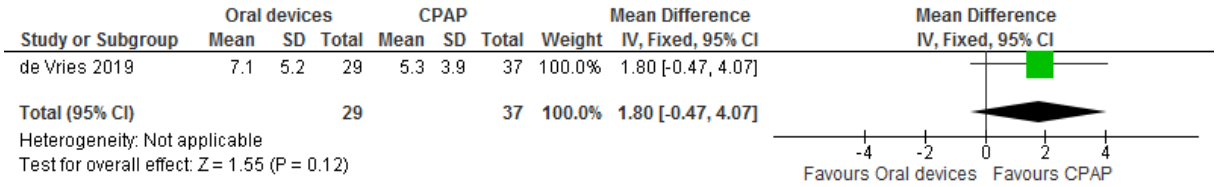


Figure 42: Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting (higher is worse)

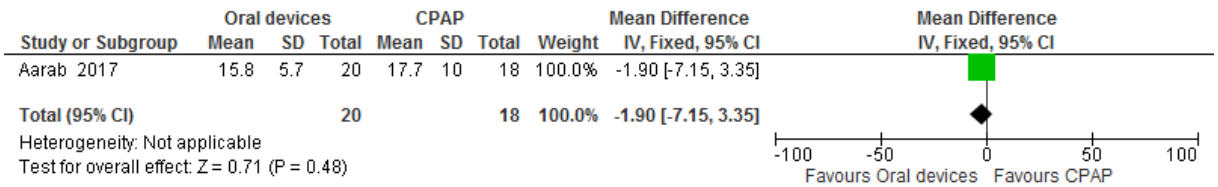


Figure 43: Preference number of patients %

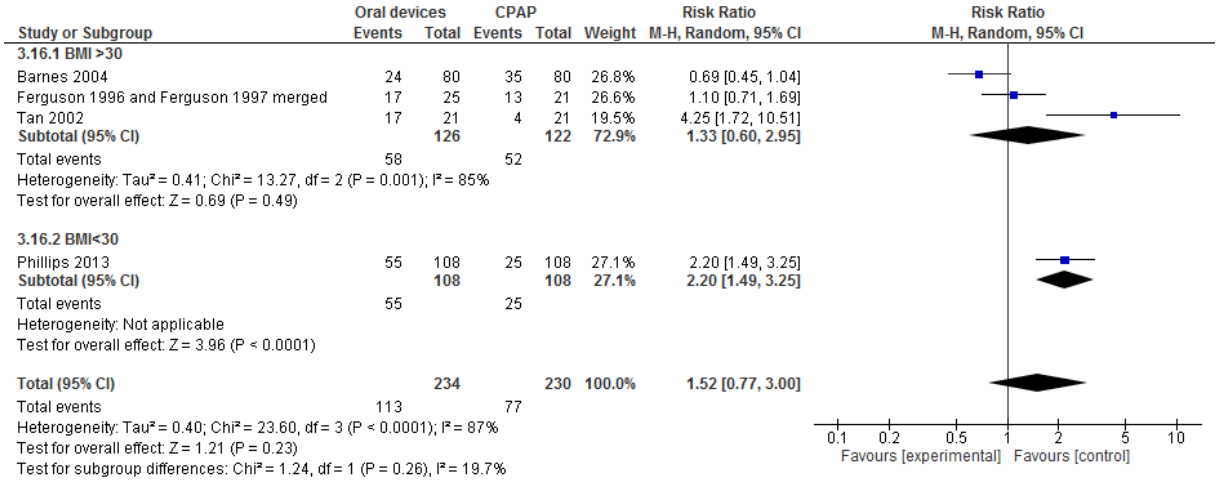


Figure 44: Adverse effects – side effects (dichotomous)

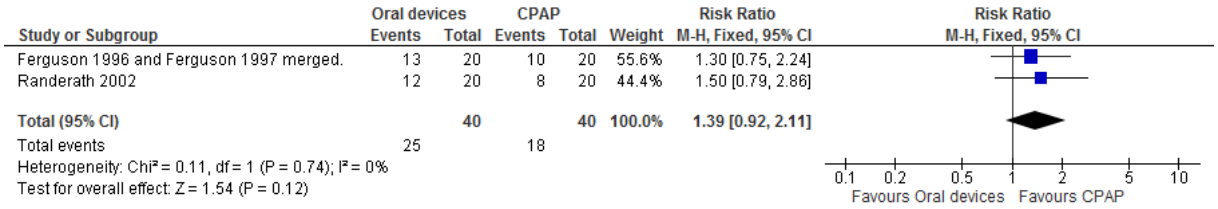


Figure 45: Adverse events – TMD pain

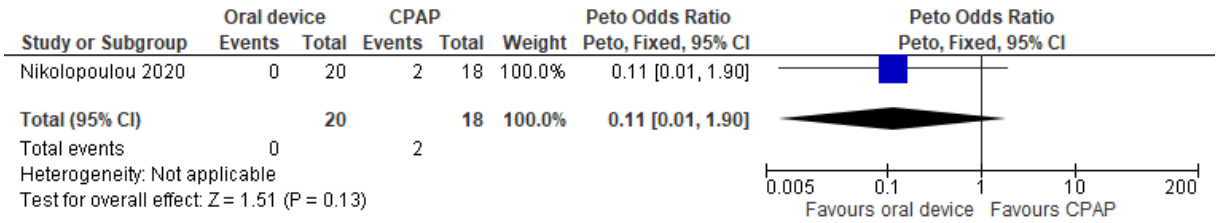


Figure 46: Adherence hours per night (self-reported for oral device)

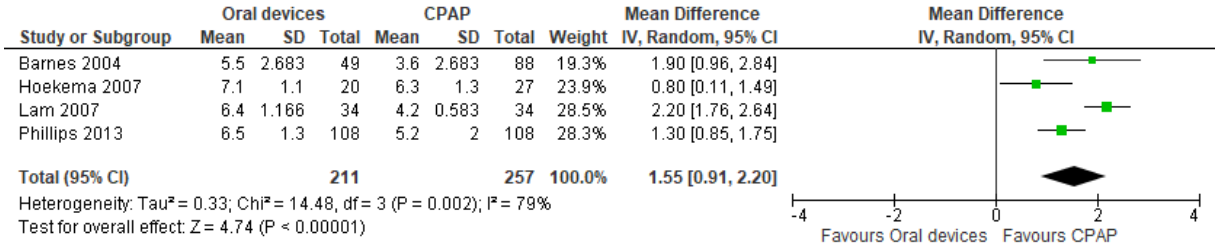


Figure 47: Adherence hours per night (objective)

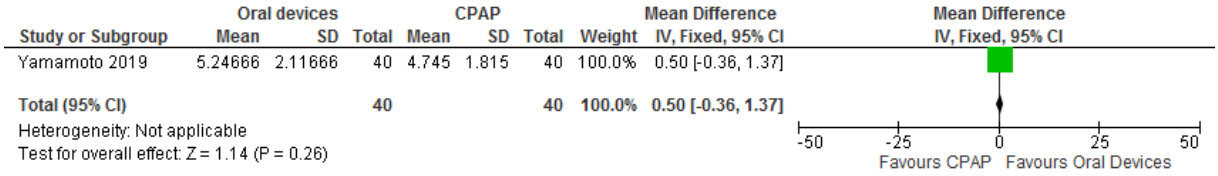
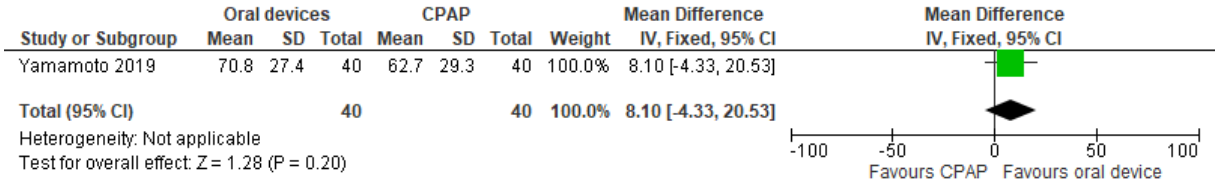


Figure 48: Adherence rate of use >4 h per night %



E.4 Oral devices (mandibular advancement splints) compared to surgery (moderate OSAHS)

Figure 49: AHI (lower is better)

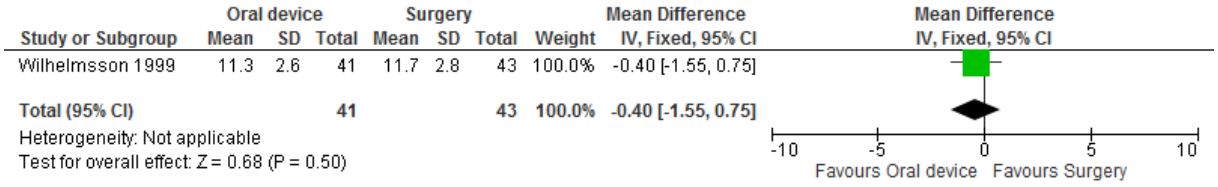


Figure 50: AHI 12 months (lower is better)

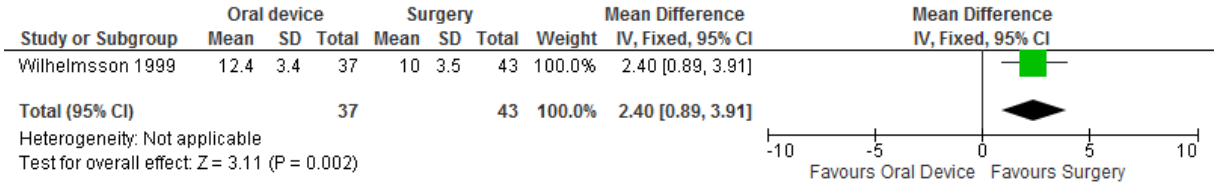


Figure 51: ODI (lower is better)

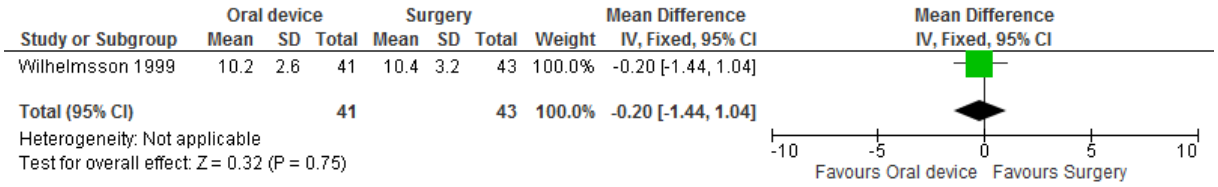
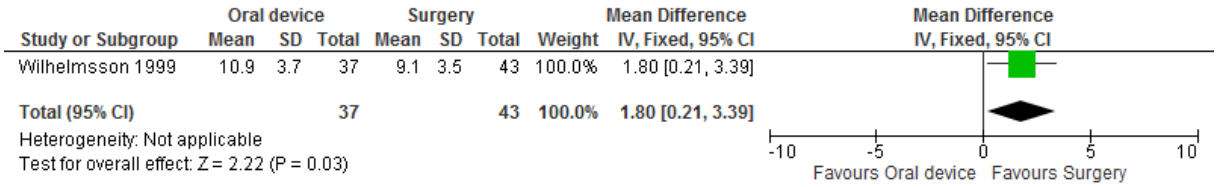


Figure 52: ODI 12 months (lower is better)



E.5 Oral devices (mandibular advancement splints) compared to each other

Boil and bite compared to custom-made (mild OSAHS)

Figure 53: AHI (lower is better)

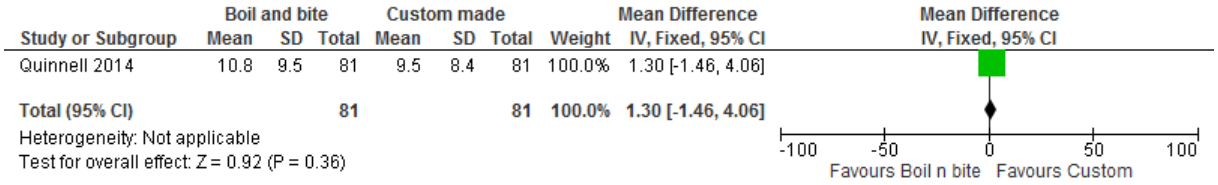


Figure 54: ESS (0-24, higher is worse)

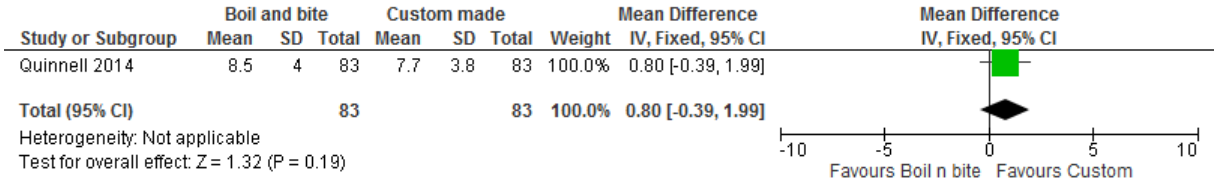


Figure 55: EQ5D – utility score (0-1, higher is better)

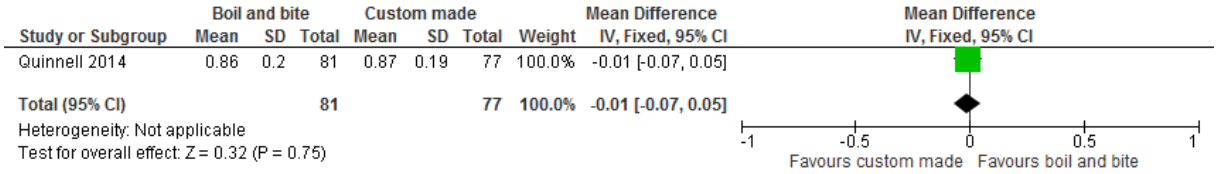


Figure 56: EQ5D – VAS (0-100, higher is better)

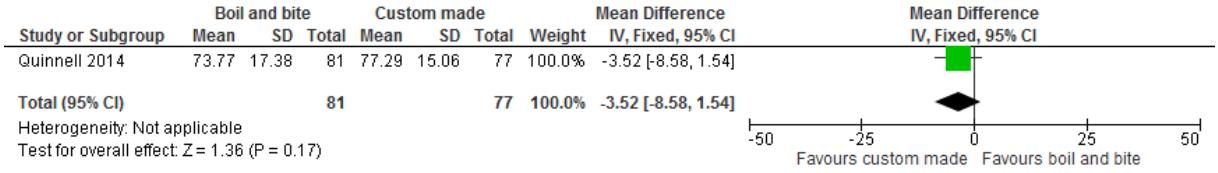


Figure 57: SF-36 – Vitality (0-100, higher is better)

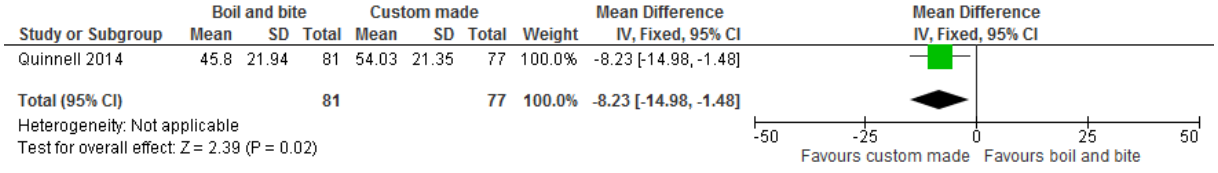


Figure 58: Minor adverse events

Figure 59: Preference

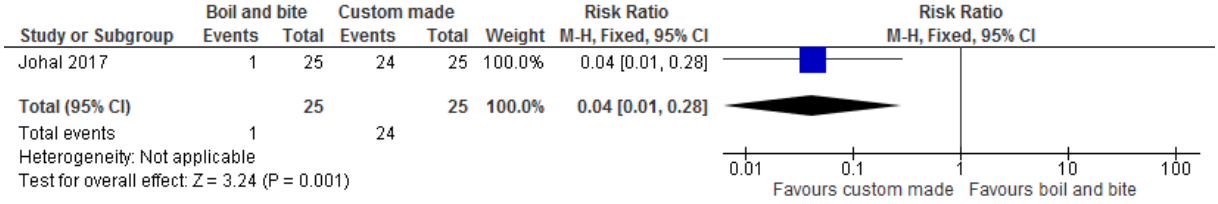
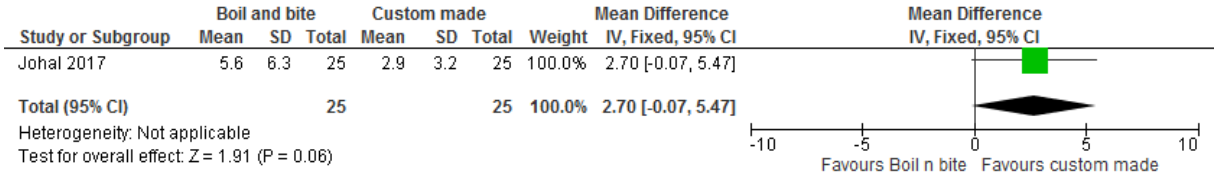


Figure 60: ODI (lower is better)



Boil and bite compared to semi-bespoke (mild OSAHS)

Figure 61: AHI (lower is better)

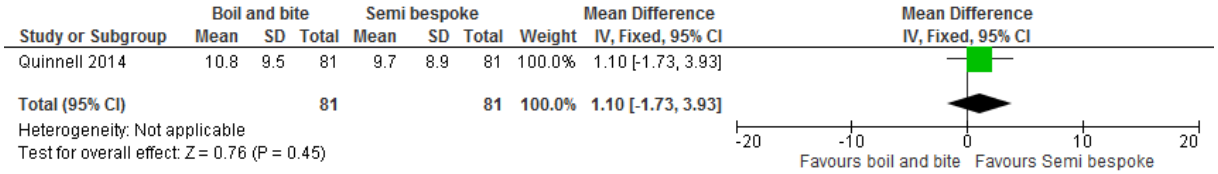


Figure 62: ESS (0-24, higher is worse)

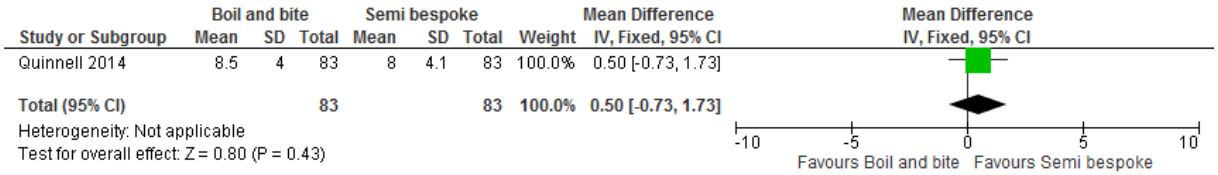


Figure 63: EQ5D – Utility score (0-1, higher is better)

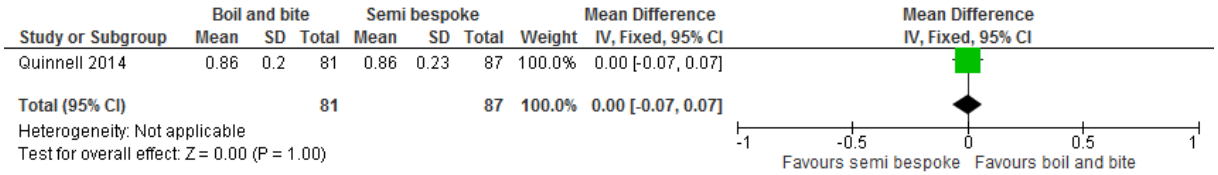


Figure 64: EQ5D – VAS (0-100, higher is better)

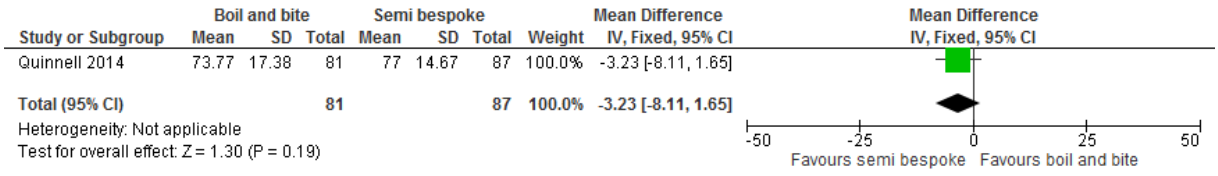


Figure 65: SF-36 – Vitality (0-100, higher is better)

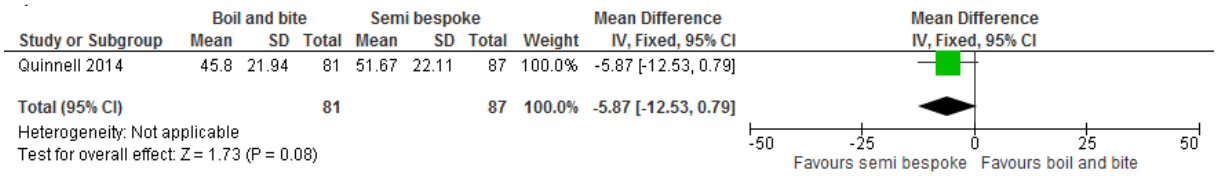
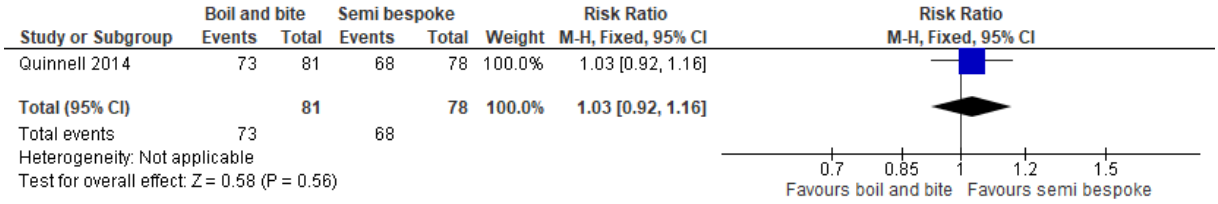


Figure 66: Minor adverse events



Semi-bespoke compared to custom-made (mild OSAHS)

Figure 67: AHI (lower is better)

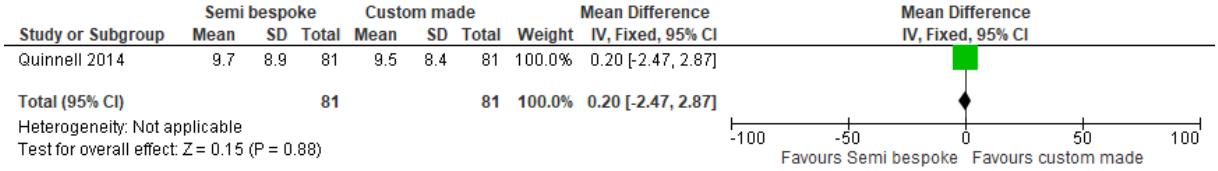


Figure 68: ESS (0-24, higher is worse)

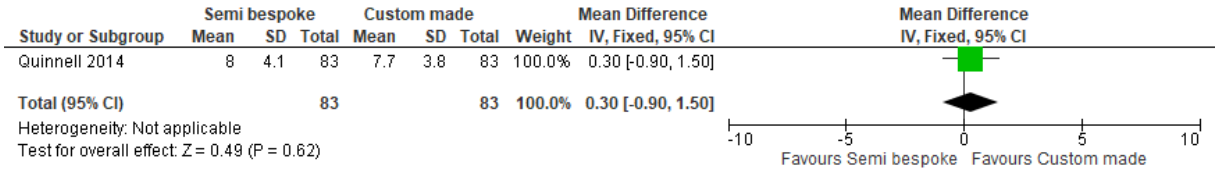


Figure 69: EQ5D – Utility score (0-1, higher is better)

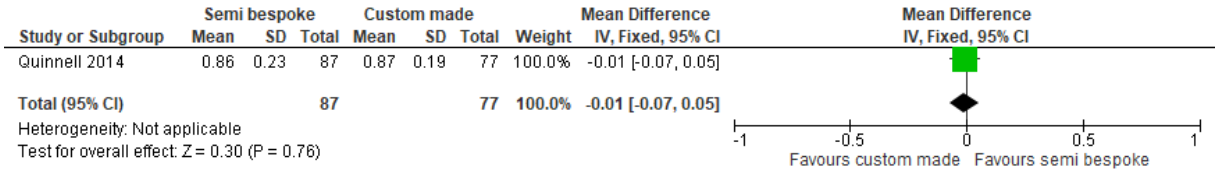


Figure 70: EQ5D – VAS (0-100, higher is better)

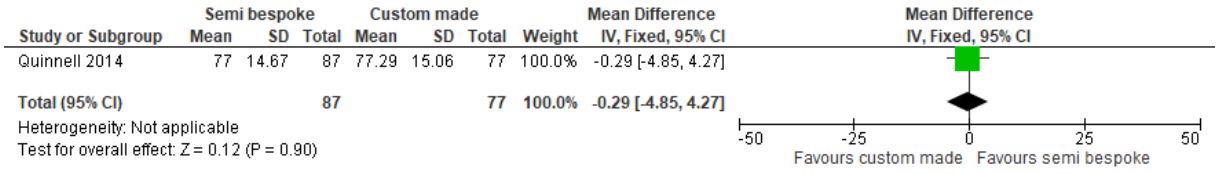


Figure 71: SF-36 – Vitality (0-100, higher is better)

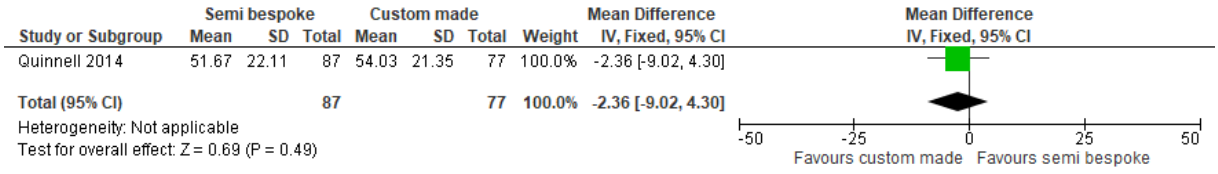


Figure 72: minor adverse events

Heat moulded (Semi-bespoke) compared to custom-made (moderate OSAHS)

Figure 73: AHI – change score (lower is better)

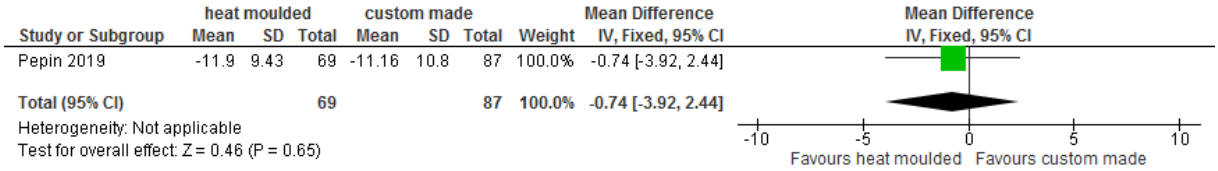


Figure 74: ESS – change score (0-24, higher is worse)

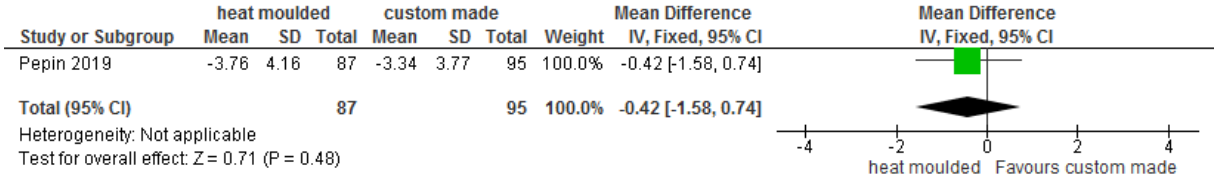


Figure 75: SF-12 Mental – change score (0-100, higher is better)

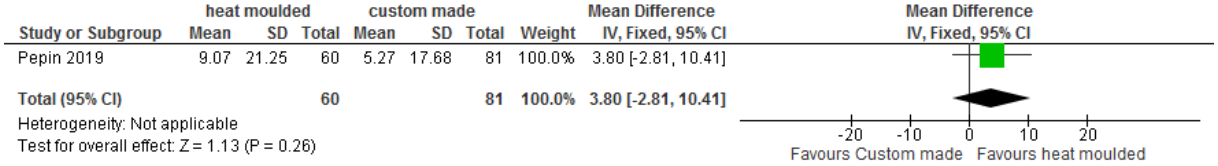


Figure 76: SF-12 Physical - change score (0-100, higher is better)

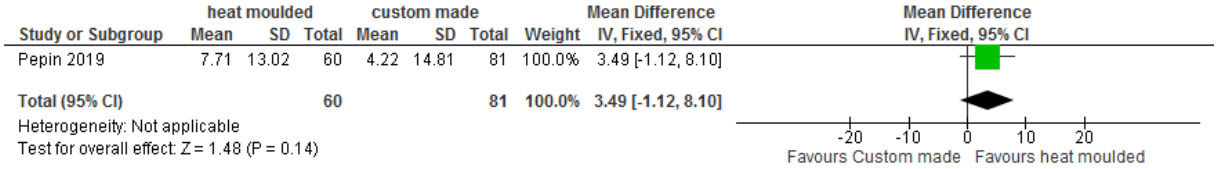


Figure 77: Systolic BP– change score

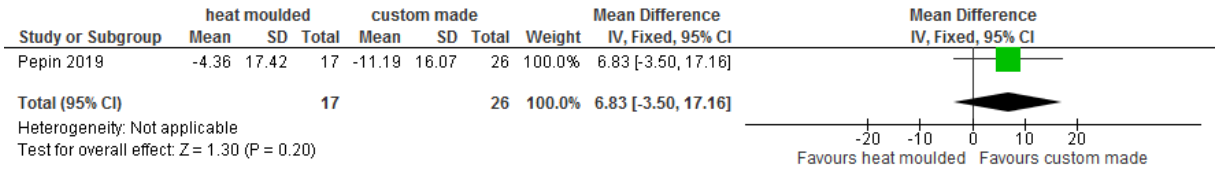


Figure 78: Adherence hours per night

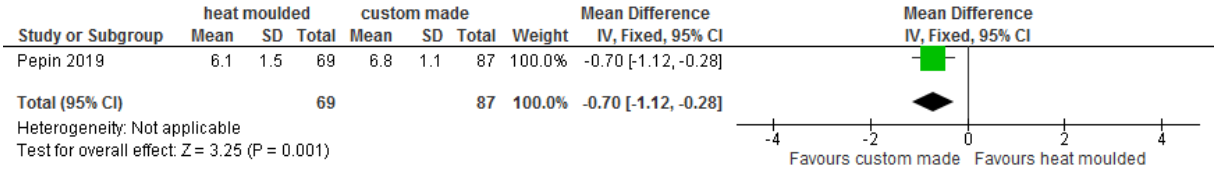
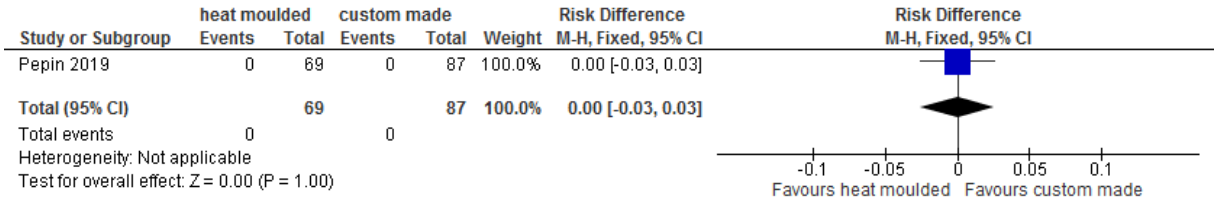


Figure 79: Serious adverse events



Appendix F: GRADE tables

Table 24: Clinical evidence profile: Mandibular advancement splints versus Placebo - mild OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mandibular advancemnet splints	Placebo	Relative (95% CI)	Absolute		
AHI - boil and bite (follow-up mean 6 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	81	81	-	MD 3.8 lower (6.88 to 0.72 lower)	⊕OOO VERY LOW	IMPORTANT
AHI- semi-bespoke (follow-up mean 6 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	81	81	-	MD 4.9 lower (7.9 to 1.9 lower)	⊕OOO VERY LOW	IMPORTANT
AHI- custom-made (follow-up mean 6 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	81	81	-	MD 5.1 lower (8.03 to 2.17 lower)	⊕OOO VERY LOW	IMPORTANT
EQ5D VAS score - boil and bite (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	78	-	MD 0.55 lower (5.9 lower to 4.8 higher)	⊕⊕OO LOW	CRITICAL
EQ5D VAS score - semi-bespoke (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	78	78	-	MD 2.68 higher (2.31 lower to 7.67 higher)	⊕⊕OO LOW	CRITICAL
EQ5D VAS score - custom-made (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	77	78	-	MD 2.03 lower (7.09 lower to 3.03 higher)	⊕⊕OO LOW	CRITICAL
SF36 vitality - boil and bite (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	78	-	MD 2.85 higher (4.28 lower to 9.98 higher)	⊕⊕OO LOW	CRITICAL
SF36 vitality - semi-bespoke (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	Serious[2]	Serious[3]	None	87	78	-	MD 8.72 higher (1.68 to 15.76 higher)	⊕OOO VERY LOW	CRITICAL
SF36 vitality - custom-made (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	77	78	-	MD 11.08 higher (3.95 to 18.21 higher)	⊕OOO VERY LOW	CRITICAL
ESS (Epworth) - boil and bite (follow-up mean 6 weeks; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	83	83	-	MD 1.6 lower (2.86 to 0.34 lower)	⊕OOO VERY LOW	IMPORTANT
ESS (Epworth) - semi-bespoke (follow-up mean 6 weeks; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	83	83	-	MD 2.1 lower (3.38 to 0.82 lower)	⊕OOO VERY LOW	IMPORTANT

ESS (Epworth) - custom-made (follow-up mean 6 weeks; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	83	83	-	MD 2.4 lower (3.63 to 1.17 lower)	⊕OOO VERY LOW	IMPORTANT
Adverse events minor - boil and bite (follow-up mean 6 weeks)[9]												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	73/81 (90.1%)	57.7%	RR 1.56 (1.27 to 1.91)	323 more per 1000 (from 156 more to 525 more)	⊕⊕OO LOW	IMPORTANT
Adverse events minor - semi-bespoke (follow-up mean 6 weeks)[9]												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	68/78 (87.2%)	57.7%	RR 1.51 (1.23 to 1.86)	294 more per 1000 (from 133 more to 496 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events minor - custom-made (follow-up mean 6 weeks)[9]												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	76/77 (98.7%)	57.7%	RR 1.71 (1.41 to 2.07)	410 more per 1000 (from 237 more to 617 more)	⊕⊕OO LOW	IMPORTANT
Mortality												
No outcome available												

1 · Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 · Downgraded by 1 or 2 increments because: The majority of the evidence included an indirect population of mild to moderate severity patients based on the AHI of included population (downgrade by one increment) or a very indirect population (downgrade by two increments)
3 · Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.; Established MIDs for EQ5D- 10; ESS -2.5GRADE default MID (0.5XSD) used for all other continuous outcomes.

5 Results for each MAD comparison are presented in separate analysis to avoid double counting the control arm due to the cross over design of the study.

6 A thermoplastic 'boil and bite' device fitted by the patient. Can be self-customised by remoulding.

7 A semi-bespoke device formed from a dental impression mould self-fitted by the patient. Can involve re-fitting with the assistance of a dentist when necessary

8 A custom-made mandibular advancement device professionally fitted by specialists

9. minor adverse events included; dryness/bad taste/numbness, discomfort/ mouth problems, excessive salivation, cold related, infection.

Table 25: Clinical evidence profile: Mandibular advancement splits versus Placebo - moderate OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mandibular advancement splits	Placebo	Relative (95% CI)	Absolute		
AHI (follow-up mean 6 months; Better indicated by lower values)												
8	randomised trials	serious[1]	no serious inconsistency	serious[2]	No serious imprecision	None	393	393	-	MD 9.66 lower (11.31 to 8.01 lower)	⊕⊕OO LOW	IMPORTANT
AHI change score (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	20	19	-	MD 11.10 higher (4.57 to 17.63 higher)	⊕OOO VERY LOW	IMPORTANT
ESS (Epworth) (follow-up mean 6 months; range of scores 0-24; Better indicated by lower values)												
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	299	297	-	MD -1.08 lower (-1.83 to -0.32 lower)	⊕⊕OO LOW	IMPORTANT
ODI (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	80	80	-	MD 1.4 lower (4.59 lower to 1.79 higher)	⊕⊕OO LOW	IMPORTANT
FOSQ (mean score) (follow-up mean 6 months; range of scores 5-20; Better indicated by higher values)												

2	randomised trials	serious[1]	Serious[4]	serious[2]	no serious imprecision	None	125	126	-	MD 0.45 higher (0.69 lower to 1.6 higher)	⊕OOO VERY LOW	IMPORTANT
SF36 mental (follow-up mean 6 months; range of scores 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	79	79	-	MD 1.38 higher (3.53 lower to 6.29 higher)	⊕OOO VERY LOW	IMPORTANT
SF36 Physical (follow-up mean 6 months; range of scores 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	79	79	-	MD 5.17 higher (0.57 to 9.77 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence hours per night (follow-up mean 6 months; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	100	99	-	MD 0.07 lower (0.34 lower to 0.19 higher)	⊕⊕OO LOW	IMPORTANT
Systolic blood pressure (follow-up mean 6 months; Better indicated by lower values)												
6	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	294	295	-	MD 2.27 lower (4.09 lower to 0.46 higher)	⊕⊕OO LOW	IMPORTANT
SAQLI (follow-up mean 6 months; range of scores 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	34	33	-	MD 0.5 higher (0.22 to 0.78 higher)	⊕⊕OO LOW	IMPORTANT
Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting (follow-up mean 6 months; Better indicated by lower values)[6]												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	20	19	-	MD 0.5 lower (4.92 lower to 3.92 higher)	⊕OOO VERY LOW	IMPORTANT

Adverse events-side effects (i.e. pain, hypersalivation, dryness, damage to dental restorations) (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	none	None	36/39 (92.3%)	33/38 (86.8%)	RR 1.06 (0.91 to 1.24)	52 more per 1000 (from 78 fewer to 208 more)	⊕⊕⊕O MODERATE	IMPORTANT
TMD (Temporomandibular disease) pain (follow-up mean 6 months)												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	serious[2]	none	None	20	19	Not estimable	-	⊕⊕OO LOW	IMPORTANT
Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)-1 hour; MID for Systolic and Diastolic BP – 5 mm hg. Established MIDs for SF-36 physical/mental- 2/3; FOSQ- 2; ESS -2.5; SAQLI – 2GRADE default MID (0.5XSD) used for all other continuous outcomes.

4. Downgraded by 1 or 2 increments for heterogeneity, unexplained by subgroup- analysis. . Random effects analysis used
5 Systolic BP values differed at baseline for Andren 2013 (mean oral device basal value = 143.6 (8.8), placebo = 145.4 (9.4))

6 For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information

Table 26: Clinical evidence profile: Mandibular advancement splits versus CPAP - moderate OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mandibular advancement splits**	**CPAP/APAP -**	**Relative (95% CI)**	**Absolute**		

AHI final value (follow-up mean 6 months; Better indicated by lower values)												
8	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	335	335	-	MD 8.07 higher (6.69 to 9.45 higher)	⊕⊕OO LOW	IMPORTANT
AHI - change score (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	20	18	-	MD 3.20 lower (9.24 lower to 2.84 higher)	⊕OOO VERY LOW	IMPORTANT
AHI (12 months after intervention) (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	17	16	-	MD 4 lower (11.11 lower to 3.11 higher)	⊕OOO VERY LOW	IMPORTANT
AHI (18 months after intervention) (follow-up mean 18 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	15	13	-	MD 5.2 lower (12.28 lower to 1.88 higher)	⊕OOO VERY LOW	IMPORTANT
FOSQ (mean score) (follow-up mean 6 months; range of scores 5-20; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	188	188	-	MD 0.06 lower (0.25 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
SF36 Mental (follow-up mean 6 months; range of scores: 0-100; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	151	151	-	MD 1.6 higher (2.14 lower to 5.33 higher)	⊕OOO VERY LOW	CRITICAL
SF36 Physical (follow-up mean 6 months; range of scores: 0-100; Better indicated by higher values)												

3	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	151	151	-	MD 0.08 lower (3.58 lower to 3.43 higher)	⊕OOO VERY LOW	CRITICAL
SF36 vitality (follow-up mean 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	None	29	37	-	MD 1.4 lower (12.81 lower to 10.01 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D (follow-up mean 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	29	37	-	MD 3.3 higher (3.39 lower to 9.99 higher)	⊕⊕OO LOW	CRITICAL
Systolic BP (follow-up mean 6 months; Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	194	194	-	MD 0.17 lower (2.45 lower to 2.11 higher)	⊕⊕OO LOW	IMPORTANT
ODI (follow-up mean 6 months; Better indicated by lower values)												
4	randomised trials	serious[1]	Serious[4]	serious[2]	serious [3]	None	268	268	-	MD 4.89 higher (2.68 to 7.09 higher)	⊕OOO VERY LOW	IMPORTANT
ESS (Epworth) (follow-up mean 6 months; range of scores: 0-24; Better indicated by lower values)												
8	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	332	338	-	MD 0.04 lower (0.63 lower to 0.55 higher)	⊕⊕OO LOW	IMPORTANT
ESS (Epworth) 12 months (follow-up mean 12 months; range of scores: 0-24; Better indicated by lower values)												

1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	None	29	37	-	MD 1.8 higher (0.47 lower to 4.07 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes (SCL-90-R) insufficiency of thinking and acting (Better indicated by lower values)[6]												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	20	18	-	MD 1.9 lower (7.15 lower to 3.35 higher)	⊕OOO VERY LOW	IMPORTANT
Preference number of patients (Barnes and Ferguson worked out from%) % of patients (follow-up mean 6 months)												
4	randomised trials	serious[1]	very serious[4]	serious[2]	very serious[3]	None	113/234 (48.3%)	77/230 (33.5%)	RR 1.52 (0.77 to 3)	174 more per 1000 (from 77 fewer to 670 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects - Side effects dichotomous (follow-up mean 6 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	25/40 (62.5%)	50%	RR 1.39 (0.92 to 2.11)	195 more per 1000 (from 40 fewer to 555 more)	⊕OOO VERY LOW	IMPORTANT
Adherence hours per night (self-reported in oral devices) (follow-up mean 6 months; Better indicated by higher values)												
4	randomised trials	serious[1]	very serious[4]	serious[2]	no serious imprecision	None	211	257	-	MD 1.63 higher (1.35 to 1.89 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence hours per night (objective) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	40	40	-	MD 0.50 higher (0.36 lower to 1.37 higher)	⊕OOO VERY LOW	IMPORTANT

adherence rate of use >4h per night % (follow-up mean 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	40	40	-	MD 8.1 higher (4.33 lower to 20.53 higher)	⊕OOO VERY LOW	IMPORTANT
TMD (Temporomandibular disease) pain (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	20	19	Peto OR 0.11 (0.01 to 1.9)	94 fewer per 1000 (from 104 fewer to 95 more)	⊕OOO VERY LOW	IMPORTANT
Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)- 1 hour; MID for Systolic and Diastolic BP – 5 mm hg; Established MIDs for SF-36 physical/mental- 2/3; FOSQ- 2; EQ5D VAS- 10; ESS -2.5.. GRADE default MID (0.5XSD) used for all other continuous outcomes.

4 Downgraded by 1 or 2 increments for heterogeneity, unexplained by subgroup analysis (BMI). Random effects analysis used

5 Adverse effects: Randerath 2002 study reported feeling of pressure in the mouth and on the face and early morning discomfort in the mouth and TMJ. Fergusson 1996 and 1997 study reported nasal congestion, sore teeth and jaw, excessive salivation, rhinorrhoea, eye irritation and a sense of suffocation.

6 For neurocognitive outcomes the scale was missing, however the committee still wanted to include these outcomes despite this missing information

Table 27: Clinical evidence profile: Mandibular advancement splits versus surgery - moderate OSAHS

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mandibular advancement splits	Surgery	Relative (95% CI)	Absolute		
AHI (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	None	41	43	-	MD 0.4 lower (1.55 lower to 0.75 higher)	⊕⊕OO LOW	IMPORTANT
AHI 12 months (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	37	43	-	MD 2.4 higher (0.89 to 3.91 higher)	⊕⊕OO LOW	IMPORTANT
ODI (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	None	41	43	-	MD 0.2 lower (1.44 lower to 1.04 higher)	⊕⊕⊕O MODERATE	IMPORTANT
ODI - 12 months (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	37	43	-	MD 1.8 higher (0.21 to 3.39 higher)	⊕⊕OO LOW	IMPORTANT
Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by one increment if the confidence interval crossed one MID and downgraded by two increments if the confidence interval crossed both MIDs. GRADE default MID(0.5XSD) used for AHI and ODI outcomes.

Grade tables for Mandibular advancement splits compared to each other

Table 28: Clinical evidence profile: Boil and bite compared to custom-made - mild OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	boil and bite	Custom-made	Relative (95% CI)	Absolute		
AHI (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	81	-	MD 1.3 higher (1.46 lower to 4.06 higher)	⊕⊕OO LOW	IMPORTANT
ESS (follow-up mean 1 months; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	83	83	-	MD 0.8 higher (0.39 lower to 1.99 higher)	⊕⊕OO LOW	IMPORTANT
EQ5D - utility score (follow-up mean 6 weeks; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	81	77	-	MD 0.01 lower (0.07 lower to 0.05 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D- VAS (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	77	-	MD 3.52 lower (8.58 lower to 1.54 higher)	⊕⊕OO LOW	CRITICAL
SF-36 Vitality (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	81	77	-	MD 8.23 lower (14.98 to 1.48 lower)	⊕OOO VERY LOW	CRITICAL
minor adverse events (follow-up mean 6 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	72/81 (90.1%)	98.7%	RR 0.91 (0.85 to 0.99)	89 fewer per 1000 (from 10 fewer to 148 fewer)	⊕⊕OO LOW	IMPORTANT
Preference (follow-up mean 3 months)												
1	randomised trials	Very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	1/25 (4%)	24/25 (96%)	RR 0.04 (00.1 to 0.28)	922 fewer per 1000 (from 691 fewer to 864 fewer)	⊕OOO VERY LOW	NOT IMPORTANT
ODI (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	Very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	25	25	-	MD 2.7 higher (0.07 lower to 5.47 higher)	⊕OOO VERY LOW	IMPORTANT
Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for EQ5D – 0.03; EQ5D VAS- 10; ESS -2.5.. GRADE default MID (0.5XSD) used for all othercontinous outcomes.

Table 29: Clinical evidence profile: Boil and bite compared to semi-bespoke - mild OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Boil and bite**	**Semi-bespoke**	**Relative (95% CI)**	**Absolute**		
AHI (follow-up mean 1 months; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	81	-	MD 1.1 higher (1.73 lower to 3.93 higher)	⊕⊕OO LOW	IMPORTANT
ESS (follow-up mean 1 months; range of scores: 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	83	83	-	MD 0.5 higher (0.73 lower to 1.73 higher)	⊕⊕OO LOW	IMPORTANT
EQ5D- utility score (follow-up mean 6 weeks; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	81	87	-	MD 0 higher (0.07 lower to 0.07 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D - VAS (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	87	-	MD 3.23 lower (8.11 lower to 1.65 higher)	⊕⊕OO LOW	CRITICAL
SF-36 Vitality (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	None	81	87	-	MD 5.87 lower (12.53 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL
minor adverse events (follow-up mean 6 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	73/81 (90.1%)	87.2%	RR 1.03 (0.92 to 1.16)	26 more per 1000 (from 70 fewer to 140 more)	⊕⊕OO LOW	IMPORTANT
Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for; EQ5D – 0.03; EQ5D VAS- 10; ESS -2.5GRADE default MID (0.5XSD) used for all other continuous outcomes.

Table 30: Clinical evidence profile: semi-bespoke compared to custom-made - mild OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Semi-bespoke	Bespoke	Relative (95% CI)	Absolute		
AHI (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	81	81	-	MD 0.2 higher (2.47 lower to 2.87 higher)	⊕⊕OO LOW	IMPORTANT
ESS (follow-up mean 1 months; range of scores 0-24; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	83	83	-	MD 0.3 higher (0.9 lower to 1.5 higher)	⊕⊕OO LOW	IMPORTANT
EQ5D - utility score (follow-up mean 6 weeks; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	None	87	77	-	MD 0.01 lower (0.07 lower to 0.05 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D- VAS (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	87	77	-	MD 0.29 lower (4.85 lower to 4.27 higher)	⊕⊕OO LOW	CRITICAL
SF-36 Vitality (follow-up mean 6 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	87	77	-	MD 2.36 lower (9.02 lower to 4.3 higher)	⊕⊕OO LOW	CRITICAL
minor adverse events (follow-up mean 6 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	68/78 (87.2%)	98.7%	RR 0.88 (0.81 to 0.97)	118 fewer per 1000 (from 30 fewer to 188 fewer)	⊕⊕OO LOW	IMPORTANT

Mortality												
Not available												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Established MIDs for EQ5D – 0.03; EQ5D VAS- 10; ESS -2.5. GRADE default MID (0.5XSD) used for all other continuous outcomes.

Table 25: Clinical evidence profile: heat moulded semi-bespoke compared to custom-made - moderate OSAHS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Heat moulded (semi-bespoke)**	**Custom-made**	**Relative (95% CI)**	**Absolute**		
AHI (follow-up mean 2 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	69	87	-	MD 0.74 lower (3.92 lower to 2.44 higher)	⊕⊕OO LOW	IMPORTANT
ESS (follow-up mean 2 months; range of scores 0-24: Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	87	95	-	MD 0.42 lower (1.58 lower to 0.74 higher)	⊕OOO VERY LOW	IMPORTANT
SF-12 Mental score (follow-up mean 2 months; range of scores 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	81	-	MD 3.8 higher (2.81 lower to 10.41 higher)	⊕OOO VERY LOW	CRITICAL
SF-12 physical score (follow-up mean 2 months; range of scores 0-100; Better indicated by higher values)												

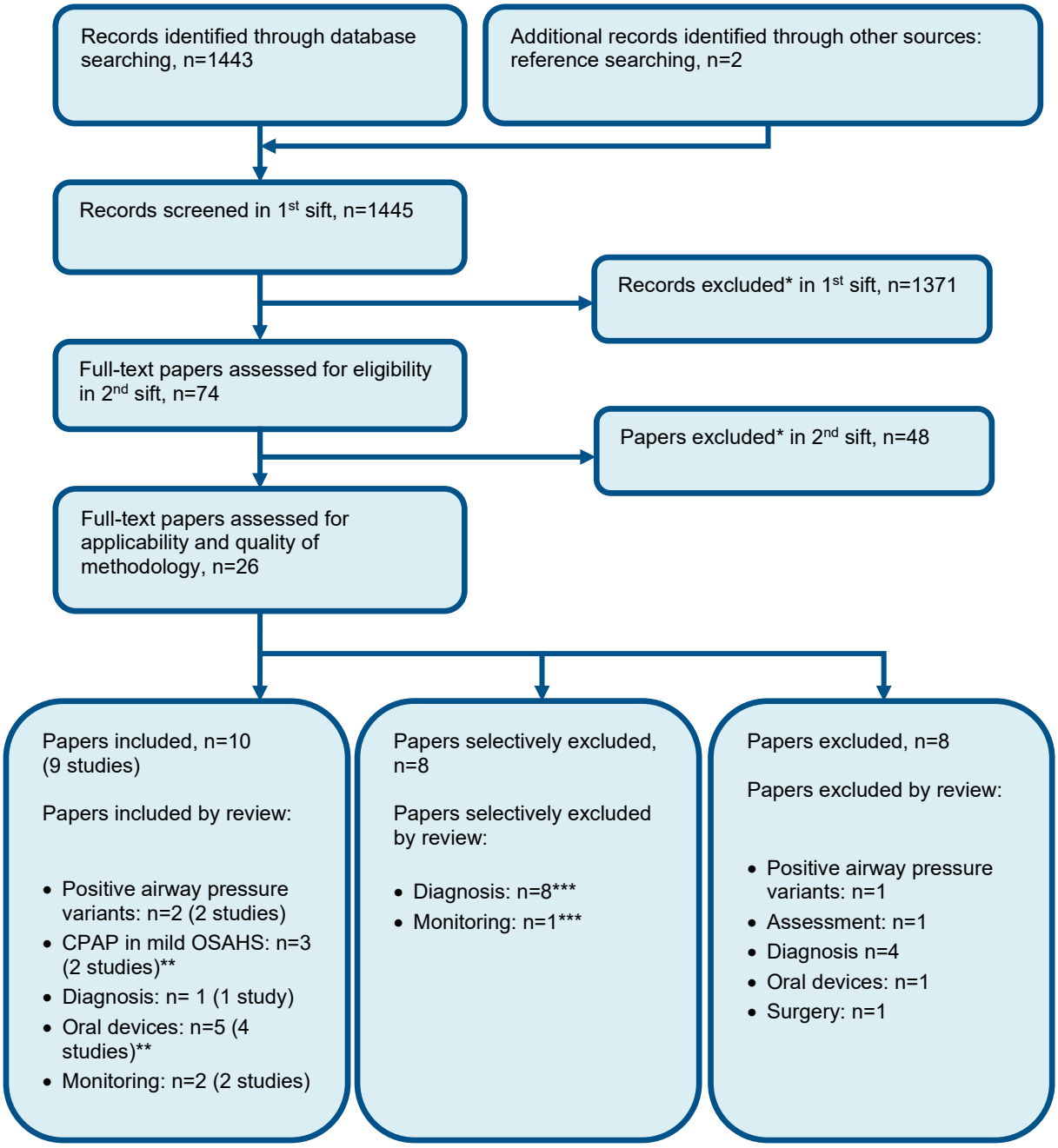
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	60	81	-	MD 3.49 higher (1.12 lower to 8.1 higher)	⊕OOO VERY LOW	CRITICAL
Systolic BP (follow-up mean 2 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	17	26	-	MD 6.83 higher (3.5 lower to 17.16 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence - hours per night (follow-up mean 2 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	69	87	-	MD 0.7 lower (1.12 to 0.28 lower)	⊕OOO VERY LOW	IMPORTANT
serious adverse events (follow-up mean 2 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	0/69 (0%)	0%	RR 0 (-0.03 to 0.03)	-	⊕OOO VERY LOW	IMPORTANT
Mortality												
Not available												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect or very indirect population respectively
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. MID for machine usage (adherence)-1 hour; MID for Systolic and Diastolic BP – 5 mm hg. Established MIDs for SF-36 physical/mental- 2/3; ESS -2.5 GRADE default MID (0.5XSD) used for all other continuous outcomes.

[4] Risk Difference analysis used as there were zero events. Imprecision calculated as follows - No imprecision (sample size >350), Serious imprecision (sample size >70<350), Very serious imprecision (sample size <70)

Appendix G: Health economic evidence selection

Figure80 : Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Two studies (in three papers) were included for two different questions
*** One study was considered for two different questions

Appendix H: Health economic evidence tables

Study	De Vries 2019[38]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis; health outcome = QALYs **Study design:** Within-trial analysis (RCT) **Approach to analysis:** **Perspective:** Netherlands societal **Time horizon**: 12 months **Treatment effect duration:** 12 months[(a)] **Discounting:** Costs = N/A Outcomes = N/A	**Population:** All consecutive patients aged 18 years or older with an AHI of 15 to 30 events per hour based on PSG (primarily of the obstructive type) and fulfilling the inclusion and exclusion criteria were invited to take part in a parallel multicentre randomised controlled trial and scheduled for a baseline visit. **Cohort settings:** N: 85 Mean age: 50.7 Male %: 82% **Intervention 1:** CPAP – patients were treated with auto-adjusting CPAP (Philips Respironics REMstar Auto A-flex, provided by VitalAire BV The Netherlands) for 3 weeks, after which the appropriate fixed CPAP pressure for each individual patient was set by a skilled, specialised nurse (i.e. highest pressure derived from the	**Direct medical costs (mean per patient):** Intervention 1: £1,761 Intervention 2: £3,916 Incremental (2−1): £2,155 (95% CI: NR; p=NR) **Currency & cost year:** Dutch 2015 presented here as 2015 UK pounds **Cost components incorporated:** Direct medical costs, costs of treatment, outpatient hospital visits, visits to GP, and other health care providers and hospital stay. Indirect costs were included such a travel costs and income loss.	**QALYs (mean per patient):** Intervention 1: N/A Intervention 2: N/A Incremental (2−1): 0.028 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** [(b)] £77,725 per QALY gained 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 20%/17% **Analysis of uncertainty:**

	Hoffstein formula of the auto-adjusting CPAP) during the study patients were allowed to change their max and to use chin straps or a humidifier if desired. **Intervention 2:** Oral devices – patients were treated with a custom-made titratable biblock MAD (SomnomedDent MAD SomnoMed Australia/Europe AG) to start the mandible was set at approximately 60-70% of the patient's maximum advancement.			

Data sources
Clinical trial: NCT01588275. **Health outcomes:** Health-related quality of life (EQ-5D-3L). **Cost sources:** Costs were primarily sourced from the Dutch healthcare authority, the units of health care consumption, such as visits to outpatient's clinic and hospitals were measured at patient level and cost was calculated based on standard prices according to care insurance board. The productivity loss was calculated according to the human capital method with the Dutch salary costs. **Quality-of-life weights:** EQ-5D-3L scores were obtained from the patients and converted into single index value between 0-1. Different algorithms to calculate the utility values have been obtained using representative samples of the general population to get a societal perspective.
Comments
Source of funding: SomnoMed Goedegebuure and VitalAire Nederland BV. **Limitations:** One trial. The study only had a 12 month follow-up period and which might not be long enough to assess cost-effectiveness, especially in terms of cost as cost of MAD therapy are made in the first month as device is custom-made but the maintenance cost was lower compared to CPAP after the first year, which can influence cost-effectiveness in the longer-term therapy. The authors reported that there may be selective bias as patients selected on having moderate OSA willing to be randomised to either MAD or CPAP therapy, and the results cannot be generalised to all other patients. The entire cohort is able to drive which would is not an accurate representation of real life.
Overall applicability: Partially Applicable[(c)] **Overall quality:** Potentially Serious Limitations[(d)]

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) The duration of treatment during the included trials was 12 months.

(b) ICER calculated by NGC with direct medical costs only
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Quinnel 2014[175]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis; health outcome = QALYs **Study design:** Within trial analysis **Approach to analysis:** Analysis of individual level data of EQ5D and resource use. Unit costs applied. **Perspective:** UK NHS **Time horizon**: 4 weeks **Treatment effect duration:**4 weeks **Discounting:** Costs = n/a Outcomes = n/a	**Population:** Patients diagnosed with mild-moderate OSA (AHI = 5 events/hour to <30 events/hour). These patients did not require CPAP (as defined by TA139), refused CPAP or chose inclusion in this within trial instead. **Patient characteristics:** N: 90 Mean age: 50.9 Drop out: 17.8% **Intervention 1:** No treatment **Intervention 2:** SleepPro 1 (SP1): A thermoplastic 'boil and bite' device fitted by the patient following the manufacturers printed instructions. Patient softens the device in hot water	**Total costs (mean per patient):** Intervention 1: £78.50 Intervention 2: £74.64 Intervention 3: £63.43 Intervention 4: £104.89 Incremental (2−1): -£3.87 (95% CI: NR; p=NR) Incremental (3−1): -£15.08 (95% CI: NR; p=NR) Incremental (4−1): £26.39 (95% CI: NR; p=NR) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Staff time for fitting devices, GP and dentist visits, hospital admissions,	**QALYs (mean per patient):** Intervention 1: 0.0649 Intervention 2: 0.0658 Intervention 3: 0.0658 Intervention 4: 0.0667 Incremental (2−1): 0.00094 (95% CI: NR; p=NR) Incremental (3−1): 0.00088 (95% CI: NR; p=NR) Incremental (4−1): 0.0667 (95% CI: NR; p=NR)	Cost-effectiveness of all interventions compared to each other: **Intervention 1:** Dominated by intervention 3 **Intervention 2:** Dominated by intervention 3 **ICER (Intervention 4 versus Intervention 3):** £46,067 Above a willingness to pay of £20,000, intervention 3 had a probability of being cost-effective in excess of 95% compared with SP1, bMAD or no-treatment alternatives

	and moulds the device so that it causes advancement of the mandible according to an individual determined comfortable position. Rewarming, allows remoulding. **Intervention 3:** SleepPro 2 (SP2): A semi-bespoke device, formed from a dental impression used by a patient. Patients are provided with an impression kit to mould their device at home and then they send this to the manufacturer so that the SP2 can be made. Impression kit includes an SP1 with holes to allow injection of dental putty. Patient instructed to mould the device (same way as SP1) and wear the device for two nights to ensure optimum position (remould if necessary). Patient then made up the putty and injected it into the SP1 and sends the resulting impression to manufacturer. The manufacturer produces the SP2 mould using this impression and is designed to grip the entire dentition. Thinner walls than SP1 intended to result in a more comfortable fit.	telephone calls and other healthcare related costs incurred by patients within trial		

	Intervention 4: Bespoke device: A custom-made MAD device fitted by specialist NHS oral-maxillofacial laboratory. Position 'wax-bite' taken from patient and degree of mandibular advancement was determined. Upper and lower full dental impressions were taken in alginate by suitably qualified dental professional and cast in dental stone. Casts were trimmed and articulated using the positional wax bite. Patient returns 2 weeks later for the fitting to allow optimal balance between advancing the mandible sufficiently to bring tongue base off the posterior pharyngeal wall and patient comfort.			
Data sources				
Health outcomes: Health-related quality of life (EQ-5D-3L) reported directly from patients. **Quality-of-life weights:** EQ-5D, UK tariff **Cost sources:** Costs were primarily sourced from PSSRU and NHS reference costs.				
Comments				
Source of funding: National Institute for Health (NIHR) Health Technology Assessment Programme **Limitations:** While the aim of the economic evaluation is to establish the cost-effectiveness of dental devices in the short term, the 4-week time horizon may be too brief to capture costs appropriately. The activities of a patient immediately after receiving an intervention may not be an accurate representation of their behaviours or resource uptake over a longer time horizon.				
Overall applicability: Directly Applicable[(c)] **Overall quality:** Potentially Serious Limitations[(d)]				

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ESS = Epworth sleepiness score; ICER= incremental cost-effectiveness ratio; n/a NR= not reported; QALYs= quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Sharples 2014[194]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis; Health outcome = QALYs **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model based on four health states using yearly cycles **Perspective:** UK NHS **Time horizon**: Lifetime **Treatment effect duration[(a)]:** Lifetime **Discounting:** Costs = 3.5% Outcomes = 3.5%	**Population:** Patients diagnosed with mild to moderate obstructive sleep apnoea **Cohort settings:** Start age: 50 Sex: Male **Intervention 1:** Conservative management: Provision of lifestyle advice to encourage weight loss, avoidance of alcohol or sedative medication, improved sleep hygiene and use of a lateral sleeping position **Intervention 2:** SleepPro 2 (SP2): A semi-bespoke device, formed from a dental impression used by a patient. Patients are provided with an impression kit to mould their device at home and then they send this to the manufacturer so that the SP2 can be made.	**Total costs (mean per patient):** Intervention 1: £6,116 Intervention 2: £8,022 Intervention 3: £8,307 Incremental (2−1): £1,906 (95% CI: NR; p=NR) Incremental (3−2): £285 (95% CI: NR; p=NR) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Staff time for fitting dental devices, CPAP machine costs, GP and dentist visits, hospital admissions, telephone calls and other healthcare related costs incurred by patients for dental devices, treatment for coronary heart disease and stroke, road traffic	**QALYs (mean per patient):** Intervention 1: 14.336 Intervention 2: 14.621 Intervention 3: 14.640 Incremental (2−1): 0.285 (95% CI: NR; p=NR) Incremental (3−2): 0.019 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £6,687 per QALY gained 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 47%/52% **ICER (Intervention 3 versus Intervention 2):** £15,367 per QALY gained 95% CI:NR Probability Intervention 2 cost effective (£20K/30K threshold): 52%/55% **Analysis of uncertainty:** Deterministic sensitivity analyses: Dental device costs reduced to that of thermoplastic device (£128): ICER (CPAP versus dental device) = £89,182 per QALY gained Dental device costs increased to that of bespoke devices (£558): ICER (CPAP versus dental device) =

	Impression kit includes an SP1 with holes to allow injection of dental putty. Patient instructed to mould the device (same way as SP1) and wear the device for two nights to ensure optimum position (remould if necessary). Patient then made up the putty and injected it into the SP1 and sends the resulting impression to manufacturer. The manufacturer produces the SP2 mould using this impression and is designed to grip the entire dentition. Thinner walls than SP1 intended to result in a more comfortable fit. **Intervention 3:** CPAP: A small, electric pump that deliver air to the nose or mouth via a hose and soft plastic mask during sleep. The air pressure opens up the airway, particularly at pharyngeal level, preventing the soft tissue from collapsing.	accidents, ongoing intervention management		Dominant (CPAP more effective and less costly) CPAP compliance reduced by 5%: ICER (CPAP versus dental device) = £40,668 per QALY gained CPAP compliance reduced by 10%: ICER (CPAP versus dental device) = (Dental device more effective and less costly)
Data sources				
Health outcomes: The authors conducted a systematic review to identify the clinical effectiveness of dental devices and CPAP compared with conservative management (or placebo). The baseline characteristics of the patients in the within trial analysis was used to determine the baseline risks. **Quality-of-life weights:** EQ-5D UK tariff was used in the model. These were calculated by using an algorithm to map the Epworth score to the EQ-5D **Cost sources:** Device costs were sourced from ResMed (one of the many CPAP manufacturers), sources also included NHS reference costs, PSSRU and in some cases clinical expertise. The authors also frequently references the economic model developed by the evidence review group for TA139 as their source.				

Comments
Source of funding: NIHR Health Technology Assessment Programme**. Limitations:** The authors modelled cardiovascular risk according to the Framingham risk model; however as this is not based on a UK population, the results may differ if the model was re-run with NICE's preferred cardiovascular risk calculator, the QRISK3. Model also assumes that the entire cohort is able to drive which is not an accurate representation of real life.
Overall applicability: Directly Applicable[c] **Overall quality:** Minor Limitations[d]

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ESS = Epworth sleepiness score; ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) Treatment effect was sourced from a meta-analysis conducted by the authors as part of this economic analysis. The duration of treatment during the included trials was generally short, with 60 of the 75 trials reporting a treatment period of ≤12 weeks. The authors made an assumption that these treatment effects would remain constant over a lifetime horizon.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Weatherly 2009[223] with full health technology assessment report in McDaid 2009[139]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis; health outcome = QALYs **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model based on four health states using yearly cycles. **Perspective:** UK NHS **Time horizon**: Lifetime **Treatment effect duration:** Lifetime[(a)] **Discounting:** Costs = 3.5% Outcomes = 3.5%	**Population:** Patients diagnosed with obstructive sleep apnoea **Cohort settings:** M age: 50 Sex: Male **Intervention 1:** Conservative management: Provision of lifestyle advice to encourage weight loss, avoidance of alcohol or sedative medication, improved sleep hygiene and use of a lateral sleeping position **Intervention 2:** Dental device: to maintain the patency of the pharyngeal airway and prevent the lumen from collapsing during sleep by holding the tongue or mandible forward, thereby enlarging the posterior airspace. **Intervention 3:** CPAP: A small, electric pump that deliver air to the nose or mouth via a hose and soft plastic mask during sleep. The air pressure opens up the	**Total costs (mean per patient):** Intervention 1: £8,140 Intervention 2: £8,797 Intervention 3: £9,301 Incremental (2−1): £657 (95% CI: NR; p=NR) Incremental (3−2): £504 (95% CI: NR; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** CPAP machine, staff time for CPAP/dental device setup, treatment for coronary heart disease and stroke, road traffic accidents, and ongoing intervention management	**QALYs (mean per patient):** Intervention 1: 11.93 Intervention 2: 12.26 Intervention 3: 12.39 Incremental (2−1): 0.33 (95% CI: NR; p=NR) Incremental (3−2): 0.13 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £2,000 per QALY gained 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 20%/17% **ICER (Intervention 3 versus Intervention 2):** £3,899 per QALY gained 95% CI: NR Probability Intervention 3 cost effective (£20K/30K threshold): 80%/83% **Subgroup Analysis[(b)]:** Sensitivity analysis conducted at different OSA severities. **Mild**: Insufficient clinical evidence to compare CPAP with dental devices **Moderate**: CPAP was cost-effective compared with conservative management (ICER: £9,391 per QALY gained). Probability that CPAP is cost-effective at the 20K/30K threshold: 70%/78%. Dental

	airway, particularly at pharyngeal level, preventing the soft tissue from collapsing.			devices were subject to extended dominance. **Severe**: Insufficient clinical evidence to compare CPAP with dental devices.
Data sources				
Health outcomes: The authors conducted a systematic review to identify the clinical effectiveness of dental devices and CPAP compared with conservative management (or placebo). The pre-intervention arms of these trials were utilised to identify the baseline risks. **Quality-of-life weights:** EQ-5D, UK tariff. These were calculated by using an algorithm to map the Epworth score to the EQ-5D. **Cost sources:** Device costs were sourced from ResMed (one of the many CPAP manufacturers), sources also included NHS reference costs, PSSRU and in some cases clinical expertise.				
Comments				
Source of funding: NIHR Health Technology Assessment Programme. **Limitations:** Translation of health benefits in terms of ESS utility was based on simple regression models derived from three sets of patient level data which contained predominantly individuals receiving CPAP rather than oral devices. When the authors presented subgroup analysis, they have classified severity with respect to their ESS rather than their AHI. The ESS is very subjective and there is more recent evidence in the literature that indicates that certain individuals may not complain of sleepiness symptoms but still have OSA which would suggest the ESS would not be an appropriate tool to determine severity. The authors modelled cardiovascular risk according to the Framingham risk model however as this is not based on a UK population. Therefore, the results may differ if the model was re-run with NICE's preferred cardiovascular risk calculator, the QRISK3. Costs associated with cardiovascular events may not be accurate as this depends on the type of cardiovascular event. Model also assumes that the entire cohort is able to drive which would is not an accurate representation of real life.				
Overall applicability: Directly Applicable[(c)] **Overall quality:** Potentially Serious Limitations[(d)]				

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ESS = Epworth sleepiness score; ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) Treatment effect was sourced from a meta-analysis conducted by the authors as part of this economic analysis. The duration of treatment during the included trials was generally short, with the majority of studies between four and 12-week duration. The authors made an assumption that these treatment effects would remain constant over a lifetime horizon.

(b) Severity was determined according to the Epworth score. The committee for the sleep apnoea guideline prefer to classify severity according to the number of AHI events/hour.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 31: Studies excluded from the clinical review- oral devices compared to other interventions/no interventions

Reference	Reason for exclusion
Aarab 2020[1]	Inappropriate study design- patients were randomised to polysomnography with MAA in situ vs polysomnography without MAA in situ
Abdullatif 2016[5]	systematic review - references checked
Acar 2014[6]	inappropriate comparison/no usable outcomes
Ahrens 2011[7]	systematic review - references checked
Arya 2019[10]	No details of baseline AHI provided
Arya 2010[11]	No useable outcomes reported and no details of baseline AHI provided
Bacon 2000[12]	not in English
Banhiran 2018[13]	severe OSA ahi 39, crossover; first line
Banhiran 2020[14]	Inappropriate population - this crossover study included severe population, all patients underwent 3 weeks with tongue retention device and 3 weeks with CPAP
Bartolucci 2019[17]	systematic review - references checked
Berg 2020[18]	Inappropriate study design/no relevant outcomes - observational study, Associations between Friedman score,treatment compliance, and AHI improvement were
Blanco 2005[20]	Inappropriate comparison oral device compared to oral device
Borrie 2013[21]	Inappropriate comparison oral device compared to oral device
Bratton, 2015[22]	systematic review - references checked
Bratton 2015[23]	systematic review - references checked
Bridgman 2000[24]	systematic review - references checked
Burr 2015[25]	abstract only
Camacho 2019[27]	systematic review - references checked
Cammaroto 2017[28]	systematic review - references checked
Cartwright 1985[31]	inappropriate study design, non-randomised observational study
Cartwright 1988[30]	Inappropriate study design non randomised study
Chang 2017[33]	systematic review - references checked
Chen 2008[36]	Unavailable
Clarke 199[37]	first line severe OSA crossover
Dal-Fabbro 2009[40]	Abstract only
Dal-Fabbro 2014[39]	crossover severe AHI 42.3(4.5); first line
de Vries 2018[44]	systematic review - references checked
Dieltjens 2015[46]	incorrect study design no comparison group, non RCT
Doff 2010[48]	severe AHI >30, first line
Doff 2012[50]	severe AHI >30, first line
Doff 2013[47]	severe AHI >30, first line
Doff 2013[49]	severe AHI >30, first line

Reference	Reason for exclusion
Dubey 2017[53]	Inappropriate study design article
Duran 2002[55]	Conference abstract
El-Solh 2017[56]	severe crossover; first line
Engleman 2001[57]	abstract only
Engleman 2002[58]	severe >30AHI first line
Esilva 2014[59]	abstract only
Fleetham 1998[63]	unavailable posters
Ftikhar 2017[99]	Systematic review- references checked
Flemons 1998[64]	Abstract only
Gagnadoux 2009[66]	severe AHI (34) crossover; first line
Garcia-Campos 2016[70]	Inappropriate study design, before and after study
Garner 2020[71]	Inappropriate population/inappropriate study design - study included healthy, physically fit subjects were included, respiratory parameters while exercising were
Gauthier 2011[75]	crossover Inappropriate comparison oral vs oral
Gotsopoulos 2001[81]	Conference abstract
Han 2014[84]	not in English
Health Quality 2009[86]	Systematic review - references checked
Higurashi 2002[88]	non RCT
Hoekema 2004[91]	systematic review - references checked
Hoekema 2007[90]	Severe AHI (49.1); first line
Hoekema 2008[94]	severe AHI 52.2(24.1); first line
Hoekema 2008[92]	severe population Oral group - 39.4 ± 30.8; CPAP group - 40.3 ± 27.6; first line
Hoffstein 2007[95]	systematic review - references checked
Holty 2010[96]	systematic review - references checked
Hsieh 2013[97]	systematic review - references checked
Iftikhar 2017[99]	systematic review - references checked
Isacsson 2019[104]	inappropriate study design non randomised study/ retrospective study
Jacq 2017[105]	Inappropriate study design no oral device (osteopathic manipulation vs sham manipulation of sphenopalatine ganglion.
Johnston 2001[111]	inappropriate population - patients with severe snoring, non-sleep apnoea
Johnston 2002[110]	crossover severe ahi 31.93; first line
JPRN 2019[212]	citation only
Kingshott 2002[115]	crossover 1 night study, inappropriate population patients with SDB)
Koretsi 2018[116]	systematic review - references checked
Kuhn 2017[117]	systematic review - references checked
Leotard 2019[124]	inappropriate comparison MAD+ nasal mask CPAP vs oro-nasal mask CPAP
L'Estrange 1999[118]	unavailable posters
Levendowski 2012[125]	oral device vs oral device
Li 2013[127]	systematic review - references checked
Li 2020[126]	systematic review references checked
Lim 2006[128]	systematic review - references checked
Pitarch 2018[170]	inappropriate study design non randomised
Marklund 2012[134]	systematic review - references checked

Reference	Reason for exclusion
Marklund 2016[131]	inappropriate study design non randomised (before and after)
Martins 2018[135]	systematic review - references checked
Matsumoto 2018[138]	inappropriate population SDB patients (sleep disordered breathing)
Mehta 2001[141]	Unclear only 2 week intervention. Crossover
Nagasaka 1997[145]	Conference abstract
NCT 2012[148]	citation only
Neill 2002[149]	inappropriate study design - 1 night study
Ng 2003[150]	First line
Nikolopoulou 2013[153]	exclude less than 1 month intervention
Nikolopoulou 2017[154]	no usable outcomes sleep disorders questionnaire results only (SDQ)
Nizankowska-Jedrzejczyk 2014[155]	inappropriate comparison - osa patients vs control non osa patients
Noller 2017[156]	systematic review - references checked
Okuno 2014[159]	systematic review - references checked
Olson 2008[160]	Conference abstract
Patel 2019[162]	systematic review - references checked
Petri 2008[165]	parallel design patients were offered cpap but preferred MAS
Phillips 2013[166]	abstract only
Pirklbauer 2011[168]	systematic review - references checked
Portier 2010[172]	unavailable posters
Prado 2013[173]	Abstract only
Prado 2014[174]	Abstract only
Ramar 2015[180]	Inappropriate study design- American sleep apnoea guideline
Recoquillon 2019[183]	severe ahi 41 first line
Ringqvist 2003[186]	no usable outcomes (mandibular changes)
Schwartz 2018[191]	systematic review - references checked
Serra-Torres 2016[193]	systematic review - references checked
Sharples 2014[194]	systematic review - references checked
Sharples 2016[195]	systematic review - references checked
Sher 1996[196]	systematic review - references checked
Sjoholm 1994[198]	no usable outcomes (cephalometric measurements and night movements)
Tan 1998[202]	Conference abstract
Tegelberg 1999[206]	first line no usable outcomes only outcomes of oral device group presented
Tegelberg 2020[205]	Inappropriate comparison - custom-made oral device compared to custom-made oral device
Tong 2020[209]	Inappropriate study design - all patients underwent oral appliance therapy then were randomised to polysomnography with oral device vs polysomnography
Trzepizur 2009[210]	severe population 40 (31-49), CPAP vs MAD; first line
Uniken Venema 2020[216]	Inappropriate population/inappropriate study design - study included severe population, cross-sectional study
Uniken Venema 2020[215]	Inappropriate population - study included severe population ahi= 31.7(20.6), patients were randomised to MAD and CPAP treatments
Vanderveken 2004[217]	incorrect study design - non RCT
Walker-Engstrom 2001[221]	abstract only

Reference	Reason for exclusion
Yang 2015[226]	first line severe OSAHS
Yilmazer 2011[227]	unavailable posters
Younis 2015[228]	Inappropriate study design non randomised study. Unclear severity all patients AHI >5 but all severe cases excluded
Zhang 2019[229]	systematic review - references checked

I.2 Excluded clinical studies from oral devices compared to each other

Table 32: Studies excluded from the clinical review

Reference	Reason for exclusion
Alebraheem 2018[8]	Full text not available
Barnes 2012[15]	PDF (citation only or conference abstract)
Bishop 2010[19]	PDF (citation only or conference abstract)
Blanco 2005[20]	severe population ahi =33 in one arm and AHI=24 in another
Borrie 2013[21]	Abstract only
Buyse 2003[26]	Full text not available
Campbell 2009[29]	inappropriate comparison
Castello Branco 2017[32]	PDF (citation only or conference abstract)
Chang 2016[34]	PDF (citation only or conference abstract)
Chen 2018[35]	references checked
Cohen-Levy 2009[38]	inappropriate study design/literature review
Deane 2009[45]	Inappropriate comparison
Doff 2015[51]	inappropriate comparison
Dort 2008[52]	inappropriate comparison - tongue retaining device with suction vs tongue retention device appliance no suction
Ferguson 2006[60]	references checked
Flynn 2013[65]	Full text not available
Gagnadoux 2017[67]	Inappropriate study design non randomised study
Gao 2005[68]	Not in English
Gao 2019[69]	references checked
Gauthier 2009[74]	inappropriate comparison/Klearway vs silencer both custom-made
Gauthier 2010[72]	citation only
Gauthier 2010[73]	citation only
Gauthier 2011[75]	inappropriate comparison
Geoghegan 2015[76]	Severe population median AHI=34.4
Ghazal 2009[77]	Severe population AHI 32 and 37, both custom-made
Gupta 2012[83]	no comparison/ all patients followed
Gupta 2016[82]	Inappropriate comparison
Hans 1997[85]	Wrong population severe population mean RDI=35.6 and 36.5dental vs placebo?

Reference	Reason for exclusion
Heidsieck 2016[87]	references checked
Hoekema 2006[89]	references checked
Hukins 2001[98]	Full text not available
Iftikhar 2013[100]	references checked
Igelstrom 2012[101]	Full text not available
Isacsson 2017[103]	citation only
Isacsson, 2017[102]	Inappropriate study design non randomised study
Johal 2015[107]	references checked
Johal 2018[106]	references checked
John 2018[109]	references checked
JPRN 2013[213]	unavailable pdf trials site
JPRN 2017[214]	unavailable pdf trials site
Kastoer 2016[112]	references checked
Kato 2000[113]	Inappropriate comparison patients with sleep disordered breathing
Kerbrat 2018[114]	citation only
La Mantia 2018[119]	Inappropriate comparison custom-made compared to custom-made
Lai 2018[120]	citation only
Lavery 2018[122]	citation only
Lawton 2005[123]	severe population median AHI 45.5 (29.9 - 68)
Levandowski 2012[125]	inappropriate comparison
Maguire 2010[129]	custom-oral vs placebo
Marina 2019[130]	references checked
Marklund 2010[133]	Inappropriate comparison-OA monoblock vs orthodontic OA monoblock elastomeric appliance (SR-Ivocap Elastomer, Ivoclar, Schaan, Liechtenstein)
Masa 2019[136]	Full text not available
Massie 1999[137]	Full text not available
McNicholas 1997[140]	Full text not available
Ming 2018[142]	references checked
Mohsenin 2003[143]	references checked
Muñoz 2009[144]	Full text not available
Norrhem 2016[157]	Inappropriate comparison-adjustable with elastic band vs adjustable without elastic band
Norrhem 2017[158]	inappropriate study design - retrospective cohort study /inappropriate comparison-OA rigid (Somnodent) custom-fitted vs OA flex the narval appliance Resmed (custom-made)
PACTR 2018[161]	unavailable pdf trials site
Pepin 2018[163]	citation only
Piskin 2015[169]	inappropriate study design
Pitarch 2018[170]	Full text not available
Pitsis 2002[171]	Inappropriate comparison-OA rigid (Somnodent) custom-fitted vs OA flex the narval appliance Resmed (custom-made)

Reference	Reason for exclusion
Prado 2013[173]	abstract only
Prado 2014[174]	abstract only
Quinnell 2014[176]	inappropriate study design
Quinnell 2014[177]	citation only
Quintela 2009[178]	citation only
Rains 1995[179]	Full text not available
Ranieri 2018[182]	references checked
Remmers 2013[184]	inappropriate comparison
Rose 2002[187]	Inappropriate comparison custom-made vs custom-made
Saffer 2015[188]	references checked
Sakakibara 2005[189]	Not in English
Senn 2001[192]	references checked
Sivaramakrishnan 2017[197]	references checked
Spiegel 2004[199]	abstract only
Sutherland 2009[200]	citation only
Sutherland 2011[201]	inappropriate study design- cohort study
Tanoue 2009[204]	inappropriate study design cohort study
Teng 2017[207]	citation only
To 2006[208]	Full text not available
Turk 2005[211]	Not available
Vanderveken 2008[218]	Inappropriate population patients with sleep disordered breathing
Vincent 2017[219]	citation only
Walker-Engstrom 2003[220]	severe population mean AHI 47 and 50.4
Wang 2014[222]	Not in English
Zhou 2012[230]	Inappropriate comparison custom-made vs custom-made

I.3 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 33: Studies excluded from the health economic review

Reference	Reason for exclusion
Isacsson 2017[102]	This costing analysis was rated as having very serious limitations because it did not use randomised evidence.

Appendix J: Research recommendations

J.1 Mandibular advancement splints (MAS) for severe OSAHS

Research question: What is the clinical and cost effectiveness of mandibular advancement splint for managing severe OSAHS?

Why this is important:

There is now randomised controlled trial data from separate studies to support the use of bespoke MAS in mild and moderate OSAHS. What is not clear is whether a bespoke MAS would be of benefit in people with severe OSAHS – offering improvements over CPAP or more importantly as an alternative treatment option in those people who are CPAP intolerant. Reductions in OSAHS severity with a MAS may improve symptoms. This would allow best practice, cost effective treatment decisions. Research is therefore needed on this topic.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Inclusion: People (18 and older) with severe OSAHS (AHI>30) Including those people who have tried CPAP but been unable to adjust to this therapy. Exclusion: Children and young people (under 18) Anyone with potential ventilatory failure with oxygen saturations <92% (OHS, COPD-OSAHS overlap syndrome) Anyone with excessive daytime sleepiness affecting work or driving which needs urgent treatment People with dental/gingival problems, jaw joint problems or edentulous Intervention: Mandibular advancement splints Fully customised/fully bespoke only devices should be considered comparison: Surgery Other non-surgical intervention (positive airway pressure variants, positional modifiers) Combination therapy (combination of oral devices and any non-surgical/surgical interventions) No intervention (placebo, inactive control therapy)/ usual care as defined in the studies (including lifestyle advice etc) Outcomes: • Generic or disease specific quality of life measures • Sleepiness scores (e.g. Epworth sleepiness scale) • Apnoea-Hypopnoea index or respiratory disturbance index • Oxygen desaturation index • CO2 control • Adverse effects of treatment • disruption of partner's sleep

	• Driving outcomes • Neurocognitive outcomes • Adherence in hours of use • Patient preference • Impact on co-existing conditions: o HbA1c for diabetes o Cardiovascular events for cardiovascular disease
Importance to patients or the population	In mild and moderate OSAHS, there is evidence for symptomatic improvement with both CPAP and customised MAS treatments. These studies excluded people with severe OSAHS, as they went on to have CPAP as first line therapy. Whether a dental device offers effective or partial treatment for people with severe OSAHS in terms of reducing OSA severity and improvement of symptoms is important to know, in order for people to make an informed choice regarding their treatment, and health care providers to give accurate advice. This is also important for people with severe CPAP who are unable to adjust to or tolerate CPAP.
Relevance to NICE guidance	This research will enable future guidelines to clearly recommend an evidence based approach regarding which patients with severe OSAHS would benefit from CPAP and which from a customised MAS.
Relevance to the NHS	A clear recommendation will offer clinicians clearer guidance on use of CPAP or MAS in people with severe OSAHS and would be cost effective as the appropriate most effective treatment would be selected initially, minimising failure rate from a less effective treatment and potentially needing to try both therapies.
National priorities	No
Current evidence base	There is evidence for the effectiveness of oral devices in mild and moderate OSA but not in severe OSAHS, nor in people who are CPAP intolerant.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Randomised controlled trial of CPAP vs customised MAS In those intolerant of CPAP – randomised to customised dental device vs control
Feasibility	The trial is feasible and should be straightforward to carry out. There are many people diagnosed with severe OSAHS in all sleep centres, and many people attending sleep clinics who are unable to adjust to CPAP despite expert involvement of the sleep team. The follow up will need to be for at least 6 months to ensure adequate time for patient titration of MAS to optimised OSAHS therapy and thus compare differences in outcomes between the groups and establish which patient factors correlate with treatment success.
Other comments	-
Importance	High: the research is essential to inform future updates of key recommendations in the guideline and maximise resource allocation.

J.2 Treatment of mild and moderate OSAHS

Research question:

In mild and moderate OSAHS, which clinical and physiological phenotypes predict treatment response to customised mandibular advancement splints (MAS)?

Why this is important:

There is now randomised controlled trial data from studies to support the use of bespoke MAS in mild and moderate OSAHS. What is not clear is whether any clinical and physiological phenotypes predict

treatment response to customised MAS. This would allow best practice, cost effective treatment decisions. Research is therefore needed on this topic.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People (18 and older) with mild symptomatic OSAHS (AHI ≤15) and moderate OSAHS (AHI >/= 15 but <30), using customised MAS Predictors: Phenotypes that could predict treatment success: • Excessive daytime sleepiness • Insomnia • Gender • Surface facial phenotypes (Mandibular length, maxillary-mandibular relationship, etc.) • Skeletal phenotypes (Mandibular length, maxillary- mandibular relationship, etc.) • Supine-related OSA phenotype • Respiratory polygraphy with frequent pulse rate rise (suggesting arousals, sleep fragmentation) • Ethnicity Any of the above, alone or in combination Comparator: Any of the above vs an absence of phenotypes Outcome(s): Critical • Generic specific quality of life measures (continuous), such as SF36 vitality score and EQ-5D Important • Sleepiness scores (continuous, e.g. Epworth) • Apnoea-Hypopnoea index or Oxygen desaturation index • Pulse rate rises on respiratory polygraphy • Sleep apnoea quality of life score • Insomnia /sleep fragmentation score or measure • Patient preference • Adverse effects of treatment • Objective measures of adherence
Importance to patients or the population	In mild symptomatic OSAHS and moderate OSAHS, there is evidence for symptomatic improvement with customised MAS treatments. However, the patient factors which influence MAS treatment and give rise to maximum improvement of symptoms remain unclear.
Relevance to NICE guidance	This research will enable future guidelines to clearly recommend an evidence-based approach regarding which patients with mild or moderate OSAHS would benefit from customised MAS.
Relevance to the NHS	A clear recommendation will offer clinicians clearer guidance on selection of MAS in patients with mild or moderate OSAHS.
National priorities	No
Current evidence base	The current evidence is reviewed in Evidence report E of the full guideline. There was limited evidence supporting the use of customised MAS in mild to moderate OSHAS. Specific criteria for the selection of patients for MAS

	remain unclear, with no high-quality evidence available. The identification of clinical and physiological patient factors in predicting response to MAS offer significant potential benefits exist in terms of optimising treatment outcomes, permitting patients to make a more informed choice and importantly improving treatment adherence and for health care providers to give accurate advice.
Equality	The recommendation is unlikely to impact on equality issues.
Study design	Prospective cohort studies
Feasibility	The trial is readily feasible and straightforward to undertake. The follow up will need to be a minimum of 6 months to ensure adequate time for patient titration of MAS to optimise OSAHS therapy.
Other comments	-
Importance	High: the research is essential to inform future updates of key recommendations in the guideline and maximise resource allocation.