National Institute for Health and Care Excellence

Final

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

Evidence review E: CPAP devices for the treatment of mild OSAHS

NICE guideline NG202

Intervention evidence review

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Final

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1.1 Review question: What is the clinical and cost effectiveness of CPAP devices for the treatment of mild obstructive sleep apnoea/hypopnoea syndrome (OSAHS)?

1.2 Introduction

Obstructive sleep apnoea is associated with long-term cardiovascular, cerebrovascular and neurocognitive consequences, particularly in the moderate to severe range. Continuous positive airway pressure (CPAP) has been regarded as first line treatment for these people, regardless of symptoms. However, the long-term implications for mild OSAHS are far less defined, the management of patients is far less clear cut, and there is a wide variation in practice nationally. In NICE technology appraisal guidance TA139 published in 2008 -CPAP for the treatment of mild OSAHS is only recommended if patients have symptoms that affect their quality of life and ability to go about their daily activities, and lifestyle advice and any other relevant treatment options have been unsuccessful or are considered inappropriate. This has led to difficulties in accessing treatment for those patients with significant symptoms despite only falling within the mild range for OSAHS based on the AHI. In clinical practice there are patients with mild OSAHS with significant symptoms who benefit from CPAP therapy and there has been an increased research focus on this subset, which has prompted this re-review of the evidence.

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 mild OSAHS Strata: Types of CPAP: Fixed CPAP, auto CPAP, bi level/ Non-invasive ventilation (NIV) Mild OSAHS: AHI >5 but <15 Exclusion: Children and young adults (under 16 years old), moderate or severe OSAHS
Intervention(s)	All types of CPAP: • fixed CPAP • auto CPAP • bi level/non-invasive ventilation (NIV) Treatment was of at least one week duration.
Comparison(s)	• usual care (including conservative intervention such as lifestyle advice regarding weight loss, alcohol consumption and sleep hygiene as well as sleep posture advice or treatment). Usual care as reported in the studies • placebo • oral devices.
Outcomes	**Critical** • generic or disease specific quality of life measures (continuous)

	• mortality (dichotomous) **Important** • sleepiness scores (continuous, e.g. Epworth) • apnoea-Hypopnoea index (continuous) • oxygen desaturation index (continuous) • CO_2 control (continuous) • hours of use (adherence measure, continuous) • patient preference (continuous) • minor adverse effects of treatment (rates or dichotomous) • driving outcomes (continuous) • neurocognitive outcomes (continuous) • blood pressure(continuous) • withdrawals (dichotomous) • impact on co-existing conditions: o HbA1c for diabetes (continuous) o cardiovascular events for cardiovascular disease (dichotomous) o systolic blood pressure for hypertension (continuous) Minimum follow up: 1 month Outcomes will be separated into short term (latest follow-up to 6 months) and long-term (latest follow-up beyond 6 months)
Study design	• RCTs • systematic review of RCTs Parallel or crossover to be included

1.4 Clinical evidence

1.4.1 Included studies

Six studies were included in the review;[21, 50, 61, 63, 206, 209] these are summarised in Table 2 below.

Three studies included a purely mild severity population (AHI 5 – 15). Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Three studies included a mixed severity population with range of means AHI (5-15). Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

All studies included in the review compared CPAP to placebo or standard care in a mild 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.

Two studies compared CPAP to standard care, three studies compared CPAP to oral placebo tablet, one study compared CPAP to sham (or placebo/inactive) CPAP. There was no evidence for CPAP compared to oral devices.

Follow-up of the studies ranged from 8 weeks to 6 months.

No evidence was available for the outcomes of CO2 control, disruption of partners sleep, impact on cardiovascular events for cardiovascular disease and impact on HbA1c for diabetes.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Barnes 2002[21] Cross over trial Australia	(n=28) CPAP: Patients received nasal CPAP (Sullivan Elite; ResMed, Sydney, Australia) for 8 weeks. (n=28) placebo: a placebo lactose tablet for 8 weeks. Patients were told that the tablet was intended to improve airway function during sleep and were instructed to take it immediately before going to bed.	Patients with mild OSAHS Age - 45.5 (10.7); Gender (M:F): 35:7 Mean AHI of 12.9 (6.3). Body mass index, kg/m2 30.2 (4.8) In general, they were middle-aged and overweight. Inclusion criteria: more than 18 years of age and if their overnight diagnostic sleep study showed an AHI of between 5 and 30/h. Each diagnostic polysomnographic study required at least 4 h of sleep, at least 30 min of sleep in the supine position, and at least 30 min of rapid eye movement (REM) sleep.	AHI ESS SF-36 FOSQ 24 hour systolic blood pressure 24 hour diastolic blood pressure Patient preference	Mixed severity population. Mild OSAHS based on mean AHI.
Craig 2012[50] RCT UK	Intervention – CPAP; Patients assigned to CPAP were instructed in the use of an auto-adjusting CPAP machine (Autoset S8, ResMed, Abingdon, UK). Induction was	All patients were diagnosed with OSA using overnight respiratory polygraphy as standard in the participating centres. Patients were eligible if they were aged	SF36 ESS SAQLI Systolic BP Adherence	

Study	Intervention and comparison	Population	Outcomes	Comments
	by trained staff who were not involved in outcome assessments or data analysis. Humidification and interface choices were made on an individual basis. All patients had one or more follow-up visits to download compliance data, check for residual apnoea/hypopnoeas and mask leakage, and to make any necessary adjustments. There were routine telephone calls at 2 and 4 months, and telephone advice and replacement parts if requested by the patient. Duration/follow up – 6 months N=154 Comparison – Standard care; The standard care (SC) group had an identical planned visit schedule to the CPAP group. Both groups were asked to continue on their normal medication and not given any specific advice regarding diet and exercise. Duration/follow up – 6 months N=156	between 45 and 75 years, had proven OSA on the diagnostic sleep study, with >7.5 per hour oxygen desaturations of >4% (oxygen desaturation index, ODI), but had insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This decision followed a detailed discussion between physician and patient about the evidence for possible benefits of CPAP versus the potentially lifelong nightly usage of a physical therapy. Thus patients with Epworth Sleepiness Scores (ESS) above the conventional upper normal limit (9) were included, when this was not accompanied by patient concerns. Baseline ESS - mean (SD) CPAP – 7.9 (4.4) Standard care – 8 (4.2) Baseline ODI – median (25^{th}, 75^{th} percentiles) CPAP – 10.2 (4.7; 17.5) Standard care – 9.4 (5.2; 15)	Preference EQ5D ODI	

Study	Intervention and comparison	Population	Outcomes	Comments
Engleman 1997[63] RCT UK	Intervention – CPAP; 16 patients with mild OSAHS spent four weeks on CPAP therapy (Sullivan APD-1 units, ResCare, Abingdon, UK) Duration/follow up – 1 month N=16 Comparison – Placebo; four weeks on an oral placebo (Ranitidine 300mg homologue, Glaxo, Greenford, UK) in a dose of two tablets at bedtime Duration/follow up – 1 month N=16	Subjects were prospectively recruited from consecutive outpatients referred to the Sleep Clinic for investigation of OSAHS. Entry criteria required two or more symptoms of OSAHS1 and an AHI in the range 5.0–14.9 per hour slept during clinical polysomnography, conducted and scored according to theusual methods Baseline ESS – mean (SE) – 14(1) (ESS score was available only in 9 out of 16 patients) Baseline AHI – mean (SE) – 11(1)	ESS IQ decrement score HADS depression HADS anxiety	
Engleman 1999[61] RCT UK	Intervention – CPAP for four weeks, At the start of the CPAP treatment limb, patients were issued with a Sullivan III CPAP unit and a heated CPAP humidifier (both ResMed Ltd., Abingdon, UK) and advised to use CPAP, with or without humidification, all night and every night and during any daytime naps during that treatment period. Patients were supplied with a contact telephone number in the event of problems or side effects with	A prospective series of patients were recruited from new attenders at the outpatient sleep clinic. Entry criteria specified an initial complaint of at least two symptoms of the OSAHS including significant sleepiness demonstrated by an Epworth sleepiness score of 8 or greater or admitted sleepiness while driving, and a demonstrated AHI on polysomnography	ESS Adherence Adverse effects SF 36 Driving outcomes Neurocognitive outcomes Patient preference	

Study	Intervention and comparison	Population	Outcomes	Comments
	CPAP, and any problems not prevented by humidification were actively sought in telephone contact made in the second week of treatment, so that these could be managed and compliance reinforced. Duration/follow up – 1 month N=34 Comparison – Placebo tablet, patients were told that the placebo treatment (Glaxo, Greenford, UK), prescribed in a dose of two tablets at bedtime, might improve upper airway muscle function in sleep. Duration/follow up – 1 month N=34	in the range 5.0 to 14.9 per hour slept. Baseline AHI – (5-15) Mean AHI not reported Baseline ESS – mean (SD) – 13 (3)		
Weaver 2012[206] RCT UK	Intervention – CPAP for 8 weeks. An unmasked polysomnographic technologist performed the CPAP set-ups (Philips Respironics, Monroeville, PA) and distributed CPAP data cards (Philips Respironics Encore SmartCard). Participants sent these cards weekly to the clinical centre.	Participants were recruited from consecutive patients. Eligibility criteria included patients with newly diagnosed milder OSA (AHI 5–30 events/h) who were naive to CPAP and had an Epworth Sleepiness Scale (ESS) score greater than 10 . Additionally, participants had a stable medical condition in the past 3 months; greater than fifth	FOSQ ESS Adherence Adverse events SF 36 POMS Systolic BP	

Study	Intervention and comparison	Population	Outcomes	Comments
	Duration/follow up – 2 months N=113 Comparison – The sham CPAP looked identical to active CPAP, but delivered less than 1.0 cm H2O of pressure for 8 weeks Duration/follow up – 2 months N=110	grade reading level; and no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident, or sleepiness sensitive occupation. Baseline AHI – mean (SD) CPAP group – 12.8(6.4) Sham CPAP – 12.5 (6.5) Baseline ESS – mean(SD) CPAP group – 15.21 (3.37) Sham CPAP – 14.66(3.05)		
Wimms 2020[209] RCT UK	Intervention – CPAP plus standard care followed up for 3 months Duration/follow up –3 months N=115 Comparison – Standard care followed up for 3 months Duration/follow up – 3 months N=118	Eligibility was assessed by a home sleep test (respiratory polygraphy; ApneaLink Air, ResMed Ltd, Oxfordshire, UK) with measurements of airflow, respiratory effort, pulse oxygen saturation, and pulse rate. Patients (≥18 years to ≤80 years) with an AHI of at least 5 events per h to 15 or fewer events per h (by either AASM 2007 or AASM 2012 scoring criteria) were eligible. The primary analysis population was patients with an AHI of at least 5 events per h to 15 or fewer events per h diagnosed using AASM 2012 scoring	SF 36 FOSQ EQ5D ESS FSS (fatigue severity score) HADS (hospital anxiety and depression score) Adherence	

Study	Intervention and comparison	Population	Outcomes	Comments
		criteria. Patients diagnosed by the more widely used AASM 2007 scoring criteria were included in the secondary analysis. Baseline AHI – (5 – 15) Mean AHI not reported Baseline ESS – mean (SD CPAP group – 9.9(4.5) Standard care – 10.0(4.2)		

See sppendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: CPAP compared to Placebo/Standard care mild population (AHI 5 -15)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/standard care	Risk difference with CPAP (95% CI)
SF36 Physical (change score) Scale 0 -100. Higher is better	233 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean SF36 physical in the control groups was -0.6	The mean SF36 physical in the intervention groups was 1.6 higher (0.01 lower to 3.21 higher)
SF 36 Mental (change score) Scale 0 -100. Higher is better	233 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean SF36 mental in the control groups was -0.7	The mean SF36 mental in the intervention groups was 4.9 higher (2.94 to 6.86 higher)
SF 36 Energy/vitality (change score and follow up score combined) Scale 0 -100. Higher is better	267 (2 studies) 1-3 months	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean SF 36 energy/vitality in the control groups was 23	The mean SF36 energy/vitality in the intervention groups was 7.69 higher (5.63 to 9.74 higher)
EQ5D (Change score) Scale 0.59 – 1. Higher is better	233 (1 study) 3 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean EQ5D (change score) population in the control groups was 0	The mean EQ5D (change score) in the intervention groups was 0.03 higher (0.01 lower to 0.07 higher)
EQ5D (VAS change score) Scale 0 -100. Higher is better	233 (1 study) 3 months	⨁⨁⊖⊖ LOW[1] due to risk of bias		The mean eq5d (vas change score) ESS >9 in the control groups was -0.9	The mean eq5d (vas change score) ESS >9 in the intervention groups was 4 higher (0.08 to 7.92 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/standard care	Risk difference with CPAP (95% CI)
FOSQ (change score) Scale 5-20. Higher is better	233 (1 study) 3 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean FOSQ in the control groups was 0.1	The mean FOSQ in the intervention groups was 1.3 higher (0.88 to 1.72 higher)
FSS (fatigue severity score) – change score Scale 9-63 (≥36 significant fatigue) Lower is better	233 (1 study) 3 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean FSS (fatigue severity score) in the control groups was 1.4	The mean FSS (fatigue severity score) in the intervention groups was 8.6 lower (10.98 to 6.22 lower)
HADS (hospital anxiety and depression) - anxiety (change score and follow up score combined) Scale 0-21 (≥11 definite case). Lower is better.	283 (3 studies) 1-3 months	⨁⨁⨀⨀ LOW[1] due to risk of bias		The mean HADS (hospital anxiety and depression) - anxiety in the control groups was 3.96	The mean HADS (hospital anxiety and depression) - Anxiety in the intervention groups was 0.81 lower (1.44 to 0.18 lower)
HADS (hospital anxiety and depression) - depression (change score and follow up score combined Scale 0-21 (≥11 definite case). Lower is better.	283 (3 studies) 1-3 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision		The mean HADS (hospital anxiety and depression) - depression in the control groups was 3.7	The mean HADS (hospital anxiety and depression) - Depression in the intervention groups was 1.61 lower (2.24 to 0.99 lower)
Mortality	No studies	N/A		Not available	Not available
ESS (change score and follow up score combined) Scale 0-24.	283 (3 studies) 1-3 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision		The mean ESS in the placebo/ standard care groups was 7	The mean ESS in the intervention groups was 2.87 lower (3.62 to 2.11 lower)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/standard care	Risk difference with CPAP (95% CI)
Lower is better.					
Preference	50 (2 studies) 1 month	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision	RR 1.03 (0.44 to 2.4)	520 per 1000	16 more per 1000 (from 291 fewer to 728 more)
Adverse events[4]	34 (1 study) 1 month	⨁⨁⊖⊖ LOW[1] due to risk of bias	RR 2.88 (1.5 to 5.5)	235 per 1000	442 more per 1000 (from 118 more to 1000 more)
Driving outcomes - SteerClear (obstacles hit) – 30 minute test	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Driving outcomes - SteerClear (Obstacles hit) in the control groups was75.3	The mean Driving outcomes - SteerClear (Obstacles hit) in the intervention groups was 0.5 lower (23.69 lower to 22.69 higher)
Driving outcomes - SteerClear (obstacles hit) – 60 minute test	34 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Driving outcomes - SteerClear (Obstacles hit) in the control groups was 195	The mean Driving outcomes - SteerClear (Obstacles hit) in the intervention groups was 6 lower (80.63 lower to 68.63 higher)
Neurocognitive outcomes - Block design score	34 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - Block Design Score in the control groups was 32	The mean Neurocognitive outcomes - Block Design Score in the intervention groups was 1 lower (6.25 lower to 4.25 higher)
Neurocognitive outcomes - Trailmaking A (sec)	34 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2]		The mean Neurocognitive outcomes - Trailmaking A,s in the	The mean Neurocognitive outcomes - Trailmaking A,s in the intervention groups was

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/standard care	Risk difference with CPAP (95% CI)
		due to risk of bias, imprecision		control groups was 29	3 lower (8.23 lower to 2.23 higher)
Neurocognitive outcomes - Trailmaking B (sec)	50 (2 studies) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - Trailmaking B,s in the control groups was 71.35	The mean Neurocognitive outcomes - Trailmaking B,s in the intervention groups was 5.68 lower (17.52 lower to 6.16 higher)
Neurocognitive outcomes - Performance IQ score	34 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes – Performance IQ score in the control groups was 108	The mean Neurocognitive outcomes - Performance IQ score in the intervention groups was 1 higher (7.8 lower to 9.8 higher)
Neurocognitive outcomes - IQ decrement score	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - IQ decrement score in the control groups was 5.3	The mean neurocognitive outcomes - IQ decrement score pure mild in the intervention groups was 1.7 higher (7.46 lower to 10.86 higher)
Neurocognitive outcomes - PASAT (paced auditory serial addition test) 2 (sec) (Correct)	50 (2 studies) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - PASAT 2-s (correct) in the control groups was 71.3	The mean Neurocognitive outcomes - PASAT 2-s (correct) pure mild in the intervention groups was 3.5 higher (1.39 lower to 8.39 higher)
Neurocognitive outcomes RVIPT (Rapid visual information processing task) (correct)	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes RVIPT (Correct) in the control groups was 34.8	The mean Neurocognitve outcomes RVIPT (correct) pure mild in the intervention groups was 2.1 higher (6.77 lower to 10.97 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/standard care	Risk difference with CPAP (95% CI)
Neurocognitive outcomes - Median eight choice reaction time (ms)	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - Median eight choice reaction time (ms) in the control groups was 356	The mean neurocognitive outcomes - Median eight choice reaction time (ms)pure mild in the intervention groups was 9 higher (35.35 lower to 53.35 higher)
Neurocognitive outcomes - Verbal fluency (total words)	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes - Verbal fluency (total words) in the control groups was 39.2	The mean neurocognitive outcomes - verbal fluency (total words) pure mild in the intervention groups was 0.7 lower (9.86 lower to 8.46 higher)
Neurocognitive outcomes - BVRT (Benton visual retention test) (correct)	16 (1 study) 1 month	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean Neurocognitive outcomes – BVRT (correct) in the control groups was 7.3	The mean neurocognitive outcomes - BVRT (correct) pure mild in the intervention groups was 0 higher (1.66 lower to 1.66 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 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; FOSQ- 2 ; ESS -2.5; SAQLI – 2. GRADE default MID (0.5XSD) used for all other continuous outcomes.

3 Downgraded by 1 or 2 increments for heterogeneity, unexplained by sub-group analysis. Random effect analysis used.
4 CPAP group: Early awakening's from sleep (n=4), sleep disturbance to patient or partner caused by noise from CPAP generator or humidifier (n=8), mask or headgear problems (n=8), dry or open mouth during CPAP use (n=4), waking with the mask off (n=2), continued snoring on CPAP (n=1), Inability to fall asleep with prescribed pressure (n= 1). Placebo group: Muscle tightness (n=1), more frequent awakenings from sleep (n=1), paraesthesia in limbs (n=1) or throat (n= 1), headaches (n= 3), delayed sleep onset (n=1), stomach cramps (n=1), "hungover" and tired sensation in mornings (n=3), episode of chest and arm pain (n=1).

Table 4: Clinical evidence summary: CPAP compared to Placebo/Standard care mixed severity population (mean AHI 5 -15)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/Standard care	Risk difference with CPAP (95% CI)
SF 36 mental Scale 0 -100. Higher is better	323 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF 36 mental in the control groups was 48.5	The mean SF 36 mental in the intervention groups was 3.5 higher (1.22 to 5.78 higher)
SF 36 Energy/Vitality Scale 0 -100. Higher is better	339 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean SF 36 energy/vitality in the control groups was 53.9	The mean SF36 energy/vitality in the intervention groups was 6.7 higher (2.08 to 11.32 higher)
EQ5D (change score) Scale 0.59 – 1. Higher is better	217 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean EQ5D (ESS <9) in the control groups was 0.8	The mean EQ5D (ESS <9) in the intervention groups was 0.03 higher (0.02 lower to 0.08 higher)
EQ5D (VAS score) Scale 0 -100. Higher is better	218 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean EQ5D (VAS score) in the control groups was 70.3	The mean EQ5D (VAS score) in the intervention groups was 5.2 higher (0.68 to 9.72 higher)
SAQLI Higher is better	330 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness		The mean SAQLI in the control groups was 5	The mean SAQLI in the intervention groups was 0.6 higher (0.35 to 0.85 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/Standard care	Risk difference with CPAP (95% CI)
FOSQ (change score) Higher is better Scale 5-20	223 (1 study) 2 months	⨁⨁⨁⨀ MODERATE[2] due to indirectness		The mean FOSQ in the control groups was -0.14	The mean FOSQ in the intervention groups was 1.12 higher (0.4 to 1.84 higher)
Mortality	No studies	N/A		Not available	Not available
ESS (change score) Scale 0-24. Lower is better.	223 (1 study) 2 months	⨁⨁⨀⨀ LOW[2,3] due to indirectness, imprecision		The mean ESS in the control groups was -0.5	The mean ESS in the intervention groups was 2.1 lower (3.13 to 1.07 lower)
ODI Lower is better.	341 (1 study) 6 months	⨁⨀⨀⨀ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		The mean ODI in the control groups was 12.6	The mean ODI in the intervention groups was 7.4 lower (9.85 to 4.95 lower)
Adherence	223 (1 study) 2 months	⨁⨁⨀⨀ LOW[2,3] due to indirectness, imprecision		The mean Adherence in the control groups was 3.1 hours	The mean Adherence in the intervention groups was 0.9 higher (0.36 to 1.44 higher)
Adverse events (unspecified)	239 (1 study) 2 months	⨁⨁⨀⨀ LOW[2,3] due to indirectness, imprecision	RR 0.99 (0.86 to 1.13)	780 per 1000	8 fewer per 1000 (from 109 fewer to 101 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/Standard care	Risk difference with CPAP (95% CI)
Systolic blood pressure (24 hour)	310 (1 study) 2 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, indirectness		The mean Systolic Blood Pressure (24 hour) in the control groups was 129.8	The mean Systolic Blood Pressure (24 hour) in the intervention groups was 1.3 higher (1.68 lower to 4.28 higher)
24 hour systolic blood pressure (change value)	28 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		Mean 24 hour systolic blood pressure at baseline was 130.3 (10.5)	The mean 24 hour systolic blood pressure (change value) in the intervention groups was 0.5 higher (3.77 lower to 4.77 higher)
24 hour diastolic blood pressure (change value)	28 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		Mean 24 hour diastolic blood pressure at baseline was 81.6 (7.5)	The mean 24 hour diastolic blood pressure (change value) in the intervention groups was 0.9 lower (11.07 lower to 9.27 higher)
Patient preference	28 (1 study) 8 weeks	⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision		RR 0.75 (0.44 to 1.28)	143 fewer per 1000 (from 320 fewer to 160 more)

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 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..

1.4.5 Narrative results

Data has been presented narratively for studies where the data could not be analysed in GRADE. 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.

Craig 2012: CPAP vs Standard care (n=341) (very low quality)

Adherence data available only for CPAP group: median 2.39 (0.36 to 4.59).

Preference data presented only for CPAP group: 71 % wished to continue with CPAP.

Engleman 1999: CPAP vs placebo (n=34) (very low quality)

Adherence data available only for CPAP group: mean (SD) 3.2(2.4).

Engleman 1997: CPAP vs placebo (n=16) (very low quality)

Adherence data available only for CPAP group: mean (SE) 3.2(0.7).

Wimms 2020: CPAP vs standard care (n=233) (very low quality)

Preference data available only for CPAP group: 81 % wished to continue with CPAP.

Barnes 2002: CPAP vs placebo (n=28) (very low quality)

AHI data at 8 weeks available only for CPAP: mean 4.24 (SD 2.9)

SD not reported for the following outcomes:

FOSQ (change score) at 8 weeks; CPAP: mean +0.07 (no SD) n=28, placebo: mean +0.06 (no SD); n=28. Baseline mean overall score: mean 0.8 (SD 0.1)
Epworth Sleepiness Scale (change score) at 8 weeks; CPAP: mean -2.7 (no SD) n=28, Group 2: mean -2.1 (no SD); n=28. Baseline ESS: mean 11.2 (SD 5.0)

SF-36 physical functioning (change score) at 8 weeks;CPAP : mean +4.2 (no SD) n=28, placebo: mean +5.5 (no SD); n=28. Baseline score: mean 78.1 (SD 22.4)

SF-36 mental health (change score) at 8 weeks; CPAP: mean +6.4 (no SD) n=28, placebo: mean +6.3 (no SD); n=28. Baseline score: mean 72.5 (SD 19.1)
SF-36 vitality (change score) at 8 weeks; CPAP: mean +12.8 (no SD) n=28, placebo: mean +13.0 (no SD); n=28. Baseline score : mean 48.4 (SD 21.5).

The study reported that there was no significant difference between CPAP and placebo for the above outcomes of FOSQ, ESS and SF-36.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

Two health economic studies published in three papers were included in this review.[135, 178, 205] These are summarised in the health economic evidence profile below (Table 5) 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.[135, 205]

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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 5: Health economic evidence profile: CPAP (2) versus Conservative management (1)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Sharples 2014[178](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: £2191[(c)]	2−1: 0.304	2 vs 1: £7,207 per QALY gained	Results for this comparison were not sensitive
Weatherly 2009[135, 205](UK) TA139	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: £21[(f)]	2−1: 0.13	2 vs 1: £20,585 per QALY gained	Probability Intervention 2 cost effective (£20K/30K threshold): 43%/68%

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

Study	Applicability	Limitations	Other comments	Costs	Health Outcomes	Cost effectiveness	Uncertainty
Sharples 2014[178](UK)	Directly applicable (d)	Minor limitations (e)	• 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(f)	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[205](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: £504(f)	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.

(g) UK NHS perspective
(h) Authors have modelled cardiovascular risk using the Framingham risk calculator rather than the QRISK3 and also assume the entire model cohort drives.
(i) 2011 UK pounds
(j) UK NHS perspective
(k) 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.
(l) 2005 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 and the strategies compared were

- 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 QRISK and the latter were from Department of Transport statistics.

CPAP costs

- The costs of fixed-pressure CPAP devices and consumables were extracted from the NHS Supply Chain catalogue[149]. The unweighted mean of different devices

(excluding VAT) was used in the model base case - £207. 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)
  - 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 (excluding VAT) of 'boil and bite', semi-bespoke and custom-made mandibular advancement splints were £33, £118 and £296 respectively. Source was publically 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).
- The cost of a sleep study to assess treatment effectiveness was included in the first year (50% home respiratory polygraphy and 50% home oximetry).

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 7, Table 8 and Figure 1. The lowest cost strategy was conservative management followed by boil and bite MAS and the most costly was semi-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 7: 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 8: 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%

* at a threshold of £20,000 per QALY gained

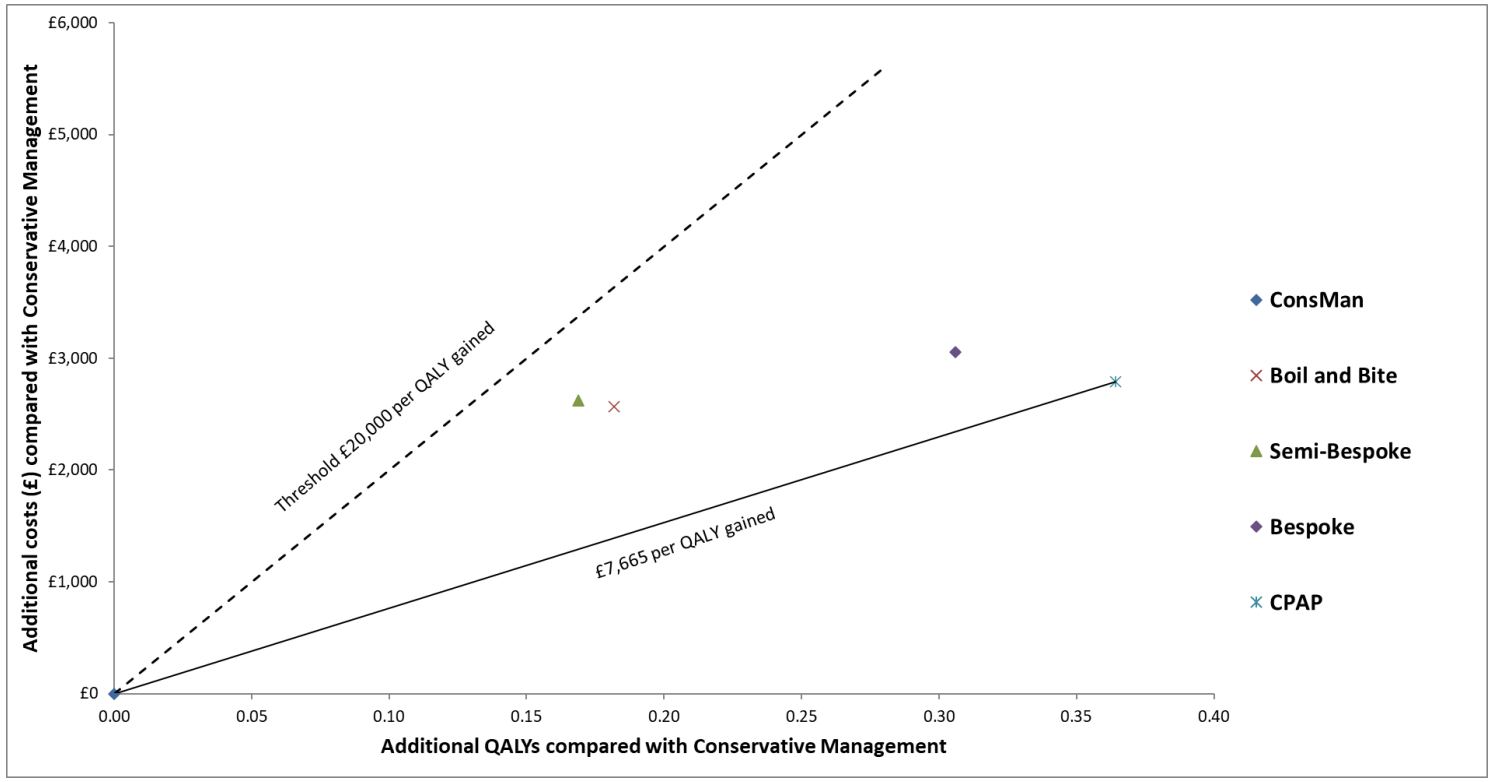

Figure 1: Base case cost effectiveness results (probabilistic)

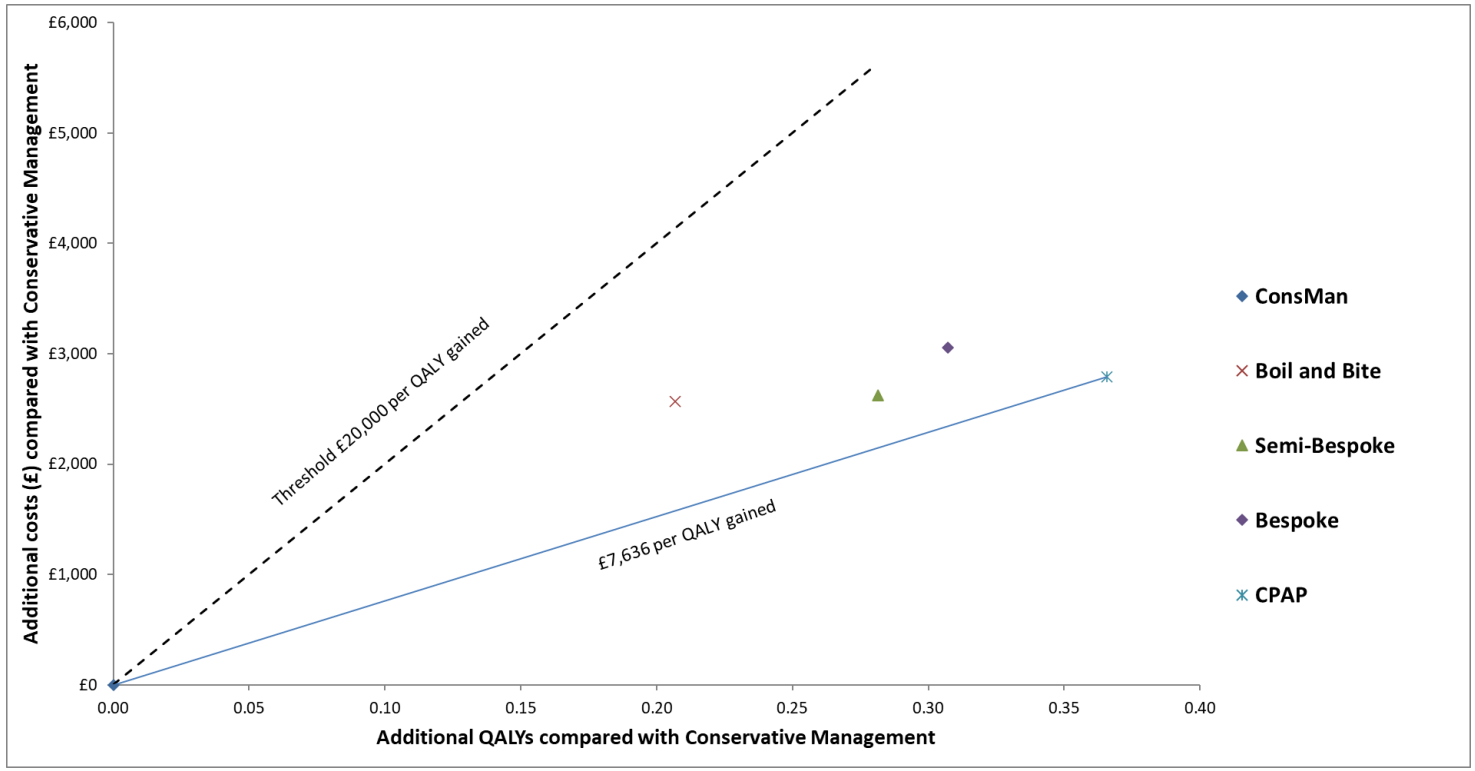

Figure 2: Cost effectiveness results when EQ-5D was mapped from ESS

Compared to conservative management the cost per QALY gained varied between £6,500 and £15,300 for CPAP and between £5,100 and £12,800 for custom-made MAS - Table 9. The ranking of treatments was quite stable across the analyses (Table 10). 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.

Table 9: 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
Lower risk profile	16,870	18,274	10,968	8,440
Other				

Analysis	Cost per QALY gained (versus Conservative Management)			
	Boil and Bite MAS	Semi-Bespoke MAS	Custom-made MAS	CPAP
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 10: 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
Longer durability for bespoke oral devices	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 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

- One cost-utility analyses found that CPAP was cost effective compared with conservative management for people with mild or moderate OSAHS (£7,200 per QALY gained). This study was assessed as directly applicable with minor limitations.

- One cost-utility analysis found that CPAP was cost effective at £30,000 per QALY but not at £20,000 per QALY compared with conservative management for people with mild OSAHS (£20,600 per QALY gained). This study was assessed as directly applicable with potentially serious limitations.
- One original cost-utility analyses found that CPAP was cost effective compared with conservative management for people with mild OSAHS (£7,700 per QALY gained). This study was assessed as directly applicable with minor limitations.

Compared with oral devices

- Two cost-utility analyses found that CPAP was cost effective compared with mandibular advancement splints for people with mild or moderate OSAHS (£3,900-£15,400 per QALY gained). These studies were assessed as directly 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.

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, oxygen desaturation index, CO2 control, adverse effects of treatment, disruption of partners 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. Outcomes were separated into short term (<6 months) follow up, and long-term (>6 months) follow up. The majority of outcomes were reported at < 6 months follow-up.

No evidence was identified for the outcomes of CO2 control, disruption of partners sleep, impact on cardiovascular events for cardiovascular disease and impact on HbA1c for diabetes.

1.6.1.2 The quality of the evidence

There was evidence from six studies comparing CPAP with placebo/standard care in mild severity populations. Three studies included purely mild populations (all patients with AHI 5 to 15) and three studies included mixed severity populations with mean AHI 5 to 15. Two studies compared CPAP to standard care, three studies compared CPAP to placebo, one study compared CPAP to sham CPAP. The committee noted that the low and very low quality of the evidence was in part because blinding of interventions which was not possible for CPAP, and the subjective nature of the main outcomes for quality of life and ESS score.

CPAP compared to placebo/standard care in mild severity population (AHI 5 to 15)

There was evidence from two studies comparing CPAP to placebo (tablet) and one study comparing CPAP to standard care in purely mild OSAHS. The populations recruited to the studies were predominately male with a diagnosis of OSAHS. At baseline the majority of the study populations had high BMI (over 24 kg/m^2) and ESS scores (>9). All three studies included a purely mild population with AHI 5 to 15 and therefore were not downgraded for indirectness.

The quality of the evidence varied from low to very low quality. The majority of evidence was downgraded due to risk of bias, inconsistency and imprecision. Risk of bias was most commonly due to selection bias and performance bias as there was a lack of blinding in the studies due to the nature of the interventions. Inconsistency for the outcome preference was due to point estimate varying widely across studies which was unexplained by subgroup analysis. Potential subgroups were: high risk occupational groups such as: heavy goods vehicle drivers compared to general population, coexisting conditions such as: type 2 diabetes vs atrial fibrillation vs hypertension; BMI – obese vs non-obese; sleepiness - Epworth >9 vs Epworth 9 or less; and age >65 and <65 years. Sub-group analysis could not be conducted for occupational status, coexisting conditions, BMI or ESS as these were not reported in the studies. Both studies included patients under 65 years old therefore subgroup analysis was not applicable. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

CPAP compared to placebo/standard care in a mixed severity population (mean AHI 5 to 15)

There was evidence from one study comparing CPAP to standard care, one study comparing CPAP to placebo (tablet) and one study comparing CPAP to sham CPAP device in a mixed severity population. The populations recruited to the studies were predominately male with a diagnosis of OSAHS. At baseline, the majority of the study populations had high BMI.

All three studies included mixed OSAHS severity populations 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 quality of the evidence varied from moderate to very low quality; majority of evidence was downgraded due to risk of bias, indirectness and imprecision. Risk of bias was most commonly due to selection bias and performance bias as there was a lack of blinding in the studies due to the nature of the interventions. Studies were downgraded for indirectness because they included mixed severity OSAHS. The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

CPAP compared to oral devices

There was no evidence available for CPAP compared to oral devices.

1.6.1.3 Benefits and harms

CPAP compared to placebo/standard care in mild severity population (AHI 5 to 15)

In the purely mild population, the evidence suggested that CPAP improved outcomes relating to sleepiness, fatigue, vitality and health related quality of life: ESS, FSS (fatigue severity score), SF 36 mental component score, SF36 energy/vitality score, EQ5D, but with an increase in adverse events such as early awakening's from sleep, sleep disturbance to patient or partner caused by noise from CPAP generator or humidifier, mask or headgear problems, dry or open mouth during CPAP use, waking with the mask off, continued snoring on CPAP and inability to fall asleep with prescribed pressure. The committee also noted that there was some uncertainty across the effect sizes seen within evidence with some confidence intervals crossing the MID thresholds or line of no effect for ESS, SF36 mental component score and EQ5D outcomes. The evidence suggested that there was no clinically important difference between CPAP and placebo/standard care for other measures: SF36 physical component, EQ5D (VAS change score), FOSQ change score, HADS both anxiety and depression components, preference, driving outcomes - steer clear (obstacles hit).

The committee noted that there were many outcomes in the included studies, many of which were exploratory. They discussed that the outcomes were not all comparable or of equal relevance. The committee noted that driving and neurocognitive outcomes were harder to interpret compared to ESS, FSS and quality of life measures. It was noteworthy that there were improvements in insomnia measures in the mild population, which is an increasingly common presenting symptom in patients referred for sleep apnoea assessment.

It might be expected that improvements in sleepiness or intermittent hypoxia would improve neurocognitive outcomes compared to placebo/ standard care to treat mild OSAHS, but this was not found to be the case for comprehensive testing of the following measures: block

design score, trail making A, trail making B, performance IQ score, Pasat 2-s (correct) – paced auditory serial addition test, RVIPT – rapid visual processing task, median eight choice reaction time (ms), verbal fluency, BVRT – Benton visual retention test. The committee noted that the impact of sleep apnoea on neurocognition is multifactorial; whereas CPAP treatment may benefit neurocognition through improvement in sleepiness, it is unlikely to have an impact on long-term hypoxic damage to the brain which is irreversible and will be determined by the duration of OSAHS.

Narrative evidence from three studies reported adherence and preference only for CPAP group. The evidence was of a very low quality and included two small studies (n=16, and n=34) and one large study (n=233). The committee agreed that no conclusions could be drawn from it.

CPAP compared to placebo/standard care in a mixed severity population (mean AHI 5 to 15)

The evidence suggested that CPAP improved ODI, and outcomes relating to sleepiness, vitality and health related quality of life: ESS, SF36 mental component, SF36 energy/vitality, EQ5D, with better adherence to CPAP than placebo. The committee also noted that there was some uncertainty across the effect sizes seen within evidence with some confidence intervals crossing the MID thresholds or line of no effect. The evidence suggested that more people preferred placebo compared to CPAP. The evidence suggested that there was no clinically important difference between CPAP and placebo/standard care for 24 hour systolic blood pressure, 24 hour diastolic blood pressure, EQ5D (VAS score), SAQLI, FOSQ and adverse events.

Narrative evidence from one large study (n=233) reported adherence and preference only for CPAP group. The evidence was of a very low quality. The committee agreed that no conclusions could be drawn from it. Narrative evidence from one small cross-over study (n=28) reported there was no significant difference between CPAP and placebo for the outcomes of AHI, ESS, FOSQ, SF-36 (physical functioning, mental health and vitality). The evidence was of very low quality.

Treatment options for mild OSAHS

The committee agreed that in both pure mild and mixed severity population, CPAP was found to be beneficial in improving outcomes relating to quality of life and sleepiness, when compared to conservative management. Despite the uncertainty within some outcomes, the committee agreed that there was generally a benefit of CPAP for people with mild OSAHS whose symptoms affect their quality of life and usual daytime activities. The committee agreed that when considering treatment for mild OSAHS the severity of symptoms, AHI, oxygen saturation and patient preference should be all taken into consideration.

Asymptomatic mild OSAHS or mild OSAHS with symptoms that do not affect usual daytime activities:

Based on their experience the committee agreed that in people with asymptomatic mild OSAHS or mild OSAHS with symptoms that do not affect usual daytime activities, lifestyle changes alone can prevent OSAHS worsening and improve quality of life hence they should be offered appropriate conservative/lifestyle advice without other interventions as a first line treatment.

In line with current practice, the committee agreed that all people with OSAHS should also be offered lifestyle advice on weight loss, preventing excess weight gain, smoking cessation, and reduced alcohol intake as appropriate alongside the chosen treatment method as obesity increases the prevalence and severity of OSAHS, smoking causes upper airway inflammation which can exacerbate symptoms, and excess alcohol before sleep reduces upper airway tone increasing apnoeas, and reduces sleep quality. Sleep hygiene

recommendations include ensuring adequate sleep time, avoiding caffeine and stimulants that interfere with sleep prior to bedtime, exercising regularly, having a quiet, comfortable, darkened bedroom, and winding down before sleep. Lifestyle and sleep hygiene advice should be tailored to the person's circumstances.The committee noted that people without symptoms may come to the attention of a specialist because their partner has witnessed apnoeas and overt snoring.

For lifestyle advice the committee agreed to refer to NICE guidelines on stop smoking interventions and services, preventing excess weight gain, obesity (in particular the section on lifestyle changes), alcohol-use disorders: prevention (in particular the recommendations on screening, brief advice and extended brief interventions for adults).

Symptomatic mild OSAHS whose symptoms affect their usual daytime activities:

For people with symptomatic mild OSAHS whose symptoms affect their usual daytime activities, the evidence suggested that CPAP was more clinically and cost effective than conservative management, including lifestyle changes and sleep hygiene. However, the quality of the evidence means that there is some uncertainty about the cost effectiveness.

CPAP was found to be beneficial in improving sleepiness, fatigue, vitality and quality of life, which confirmed the committee's experience that there are benefits to giving CPAP to people with symptomatic mild OSAHS. While some people could try lifestyle modification first, they noted that these changes take time to work and may not always be effective. Delaying offering CPAP to people with any of the priority factors for rapid referral (listed in recommendation 1.2.1) could adversely affect quality of life, associated medical conditions, or the person's ability to carry out their work, by failing to control their symptoms. The committee agreed that in their experience offering CPAP to these groups helped control their symptoms and reduced the risks described in the committee discussion of the evidence report for prioritisation (Evidence report C). Therefore, the committee agreed that for these people, CPAP should be offered as a first-line treatment alongside lifestyle changes, as soon as mild OSAHS is diagnosed. They also agreed that CPAP would be beneficial to control symptoms in people for whom lifestyle changes alone are unsuccessful or are not appropriate (further information about priority factors is in the Evidence report C Prioritisation review).

The evidence showed fixed-level CPAP and auto CPAP to be equally effective, and auto-CPAP to be more costly. Therefore, the committee agreed to recommended fixed-level CPAP as the first-choice treatment. However, some people, particularly those in whom high pressures are only needed part of the time, find auto-CPAP more comfortable and effective than fixed-level CPAP. For others, telemonitoring may not be possible because of technological constraints such as the lack of availability of internet or poor internet connection, auto-CPAP should be an option in these cases. The committee were also aware that some hospitals get significant discount on auto-CPAP devices which might make them more cost effective. Therefore, the committee agreed that if auto-CPAP is available at the same or lower cost than fixed-level CPAP, auto-CPAP could be considered. This is discussed in more detail in Evidence report F on PA variants for discussion of the evidence on types of CPAP.

The committee also discussed the benefits of telemonitoring. These include early night-by-night access to data which can lead to early detection of problems such as mask leaks or persistent respiratory events of sleep apnoea, and the ability to monitor that OSAHS so that it continues to be effectively controlled and the individual is adherent to therapy. Telemonitoring makes managing a person's OSAHS more efficient for clinicians as they have ready access to the data should they need it. For example, if contacted by a person with an issue they can use the data to help identify the problem (for example, mask leak or inadequate pressure) and take appropriate action without the need for a scheduled appointment. The committee agreed that video and telephone consultations along with telemonitoring is also advantageous to people with OSAHS as it can reduce the number of

in-person visits needed to the sleep service. This can be particularly beneficial to patients who have difficulty in getting to clinics, for example, people who live in remote places or people with poor mobility, there would be fewer clinic visits in such cases. The reduction in the number of face-to-face consultations will also help reduce the risk of infection during the COVID-19 pandemic. Telemonitoring has facilitated remote assessment of patients during the coronavirus pandemic and has become a standard follow-up option in most sleep services. This use is likely to continue long term, because it is convenient for patients, enables them to assess progress themselves and allows access to efficacy and adherence data whenever needed, for example, for problem solving, routine follow-up and to complete DVLA reports.

The costs of telemonitoring were also discussed and the committee noted that in their experience, telemonitoring is included in the price of the machine for 12 months. Based on this they agreed that telemonitoring should be offered alongside CPAP for the first 12 months of treatment, and considered beyond 12 months where optimal control of symptoms and AHI has not been achieved, or to help with solving problems that people with OSAHS might experience. However, some people, particularly those in whom high pressures are only needed part of the time, find auto-CPAP significantly more comfortable and effective than fixed level CPAP. For others, telemonitoring may not be possible for technological reasons such as a lack of availability of internet or poor internet connection. The committee agreed that auto-CPAP should be available in these cases. The committee were also aware that some hospitals get significant discount on auto-CPAP devices and that this might make them cost-effective.

Given the low quality evidence and uncertainty about the cost-effectiveness between auto and fixed-level CPAP the committee made a research recommendation to help inform future guidelines (see **Error! Reference source not found.** of Evidence report F: PA variants). The c ommittee did not make a research recommendation for long term use of telemonitoring as they believe telemonitoring is already becoming common practice and will remain so in the future. They agreed it is more convenient for CPAP users and clinicians. It also saves time as users do not need to download data and post or take it in to the sleep service.

Based on their experience of current practice, the committee agreed that using humidification with CPAP in people with nasal symptoms can reduce side effects associated with upper airway dryness (see Evidence report F on PA variants for discussion of evidence on addition of humidification).

The committee noted that some people with mild symptomatic OSAHS cannot tolerate CPAP. The committee noted that a mandibular advancement splint (MAS), a type of oral device, may be an alternative in some of these (see Evidence report G).

1.6.2 Cost effectiveness and resource use

The use of CPAP incurs the cost of a device, consumables, such as masks and filters and follow up or monitoring. 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 were identified that evaluated CPAP in a mild or mild/moderate OSAHS population. One of them was the analysis from TA139. However, neither of these studies contained the most recent randomised trial evidence. Therefore, an original decision model was developed to assess the cost effectiveness of CPAP compared with both conservative management and oral devices 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 either customised or semi-bespoke mandibular advancement splint. CPAP cost £8,500 per QALY gained compared with conservative management. 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.

Another model was developed that compared different strategies for people suspected of having OSAHS. These strategies were combinations of a diagnostic tool and a treatment strategy – see Evidence report D: Diagnostic tests. This model allows the comparison of CPAP with conservative management in mild OSAHS under conditions where the population is diluted due to being diagnosed with real world but imperfect diagnostic tests. In the base case and every sensitivity analysis, regardless of the diagnostic test used, the mild OSAHS intervention strategies (where a proportion of the people with mild OSAHS had CPAP and others had custom-made MAS or conservative management) were cost effective compared with conservative management at a threshold of £20,000 per QALY gained.

These models were based on the guideline's systematic review of the clinical effectiveness evidence. The GRADE weighting for this evidence was Low or Very Low. Currently some people with mild OSAHS are already using CPAP either because they have tried lifestyle modification and this has been unsuccessful but also if their symptoms are particularly severe. Since, the use of CPAP is thought to vary considerably by area, offering CPAP to everyone diagnosed with mild OSAHS could lead to a large number of additional CPAP users and potentially a substantial cost impact for the NHS. Given the low quality of the evidence, there is still some uncertainty about the effectiveness and cost effectiveness of CPAP in mild OSAHS. Therefore, the committee were cautious in their recommendations and discussed prioritising CPAP for those that would benefit the most.

The committee agreed that in people with mild OSAHS who have symptoms that affect their quality of life and usual daytime activities AND have a significant comorbidity or a job for which vigilance is critical for safety (including vocational drivers), CPAP should be offered as first-line treatment. This is because it is most likely to be effective and cost-effective in this population. For other patients, CPAP might still be cost effective but the uncertainty is greater. For them, the committee recommended that CPAP be offered if lifestyle advice alone has been unsuccessful or is considered inappropriate.

Some people with mild OSAHS currently use CPAP, for example people with symptoms that affect their ability to do daily activities, and when other treatment options and lifestyle advice have been unsuccessful or are considered inappropriate. It is expected that there will be increased uptake of CPAP for mild OSAHS, and therefore a resource increase to the NHS from this recommendation especially as the estimate of prevalence of mild OSAHS has increased, and more patients people are referred and diagnosed.

The cost effectiveness of telemonitoring with CPAP is discussed in Evidence report F: Positive Airway Pressure therapy variants.

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Appendices

Appendix A: Review protocols

Table 11: Review protocol: CPAP in people with mild OSAHS

Field	Content
PROSPERO registration number	Not registered
Review title	CPAP devices for the treatment of mild OSAHS
Review question	What is the clinical and cost-effectiveness of CPAP devices for the treatment of mild OSAHS?
Objective	To determine the clinical effectiveness and cost-effectiveness of CPAP devices for the treatment of mild OSAHS.
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language 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.
Condition or domain being studied	Obstructive sleep apnoea/hypopnoea syndrome is the most common form of sleep disordered breathing. The guideline will also cover obesity hypoventilation syndrome and COPD-OSAHS overlap syndrome (the coexistence of obstructive sleep apnoea/hypopnoea syndrome and chronic obstructive pulmonary disease).
Population	Inclusion: People (16 and older) with mild OSAHS Strata: Types of CPAP: Fixed CPAP, auto CPAP, bi level Mild OSAHS: AHI >5 but <15 Exclusion: Children and young adults (under 16 years old) Moderate or severe OSAHS
Intervention/Exposure/Test	All types of CPAP: • Fixed CPAP

	• Auto CPAP • Bi level Treatment was of at least one week duration.
Comparator/Reference standard/Confounding factors	• Usual care (including conservative intervention such as lifestyle advice regarding weight loss, alcohol consumption and sleep hygiene as well as sleep posture advice or treatment). Usual care as reported in the studies. • Placebo • Oral devices
Types of study to be included	Published NMAs and IPDs will be considered for inclusion. • RCTs • Systematic review of RCTs • Parallel or crossover to be included
Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	–
Primary outcomes (critical outcomes)	• Generic or disease specific quality of life measures (continuous) • Mortality (dichotomous)
Secondary outcomes (important outcomes)	• Sleepiness scores (continuous, e.g. Epworth) • Apnoea-Hypopnoea index (continuous) • Oxygen desaturation index (continuous) • CO_2 control (continuous) • Hours of use (adherence measure, continuous) • Patient preference (continuous) • Minor adverse effects of treatment (rates or dichotomous) • Driving outcomes (continuous) • Neurocognitive outcomes (continuous) • Blood pressure(continuous) • Withdrawals (dichotomous) • 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)
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.

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.
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.
Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • High risk occupational groups (for example heavy goods vehicle drivers) vs general population • Coexisting conditions – type 2 diabetes vs atrial fibrillation vs hypertension vs none • BMI – obese vs non-obese • Sleepiness – Epworth >9 vs Epworth 9 or less

	• Age >65 and <65 years (sleep less consolidated in older people and aetiology for the condition is different in older people)	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	NA – not registered on PROSPERO	
Anticipated completion date	NA – not registered on PROSPERO	
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	
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	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
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.
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
Other registration details	NA – not registered
Reference/URL for published protocol	NA – not registered
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.
Keywords	-
Details of existing review of same topic by same authors	NA
Additional information	None
Details of final publication	www.nice.org.uk

Table 12: 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).[146]

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 8 positive airway pressure device

This literature search strategy was used for the following review;

- What is the clinical and cost-effectiveness of CPAP devices for the treatment of mild OSAHS?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[146]

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 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 6 July 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 6 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.	Continuous Positive Airway Pressure/
29.	positive airway* pressure.ti,ab.
30.	Continuous Positive Airway* Pressure.kw.
31.	Positive-Pressure Respiration/
32.	(positive adj3 pressure adj (therapy or device* or ventilat*)).ti,ab.
33.	(PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP).ti,ab.
34.	(biPAP or BPAP or NBiPAP or NBPAP or NIV).ti,ab.
35.	((noninvasive or non-invasive) adj3 ventilat*).ti,ab.
36.	or/28-35
37.	27 and 36
38.	randomized controlled trial.pt.
39.	controlled clinical trial.pt.
40.	randomi#ed.ti,ab.
41.	placebo.ab.
42.	randomly.ti,ab.
43.	Clinical Trials as topic.sh.
44.	trial.ti.
45.	or/38-44
46.	Meta-Analysis/
47.	exp Meta-Analysis as Topic/
48.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
49.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
50.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
51.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
52.	(search* adj4 literature).ab.
53.	(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.
54.	cochrane.jw.
55.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

56.	or/46-55
57.	37 and (45 or 56)

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.	positive end expiratory pressure/
27.	positive airway pressure.ti,ab.
28.	Continuous Positive Airway Pressure.kw.
29.	(positive pressure adj2 (therapy or device* or ventilation)).ti,ab.
30.	(PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP).ti,ab.
31.	(biPAP or BPAP or NBiPAP or NBPAP or NIV).ti,ab.
32.	((noninvasive or non-invasive) adj3 ventilation).ti,ab.
33.	or/26-32
34.	25 and 33
35.	random*.ti,ab.
36.	factorial*.ti,ab.
37.	(crossover* or cross over*).ti,ab.
38.	((doubl* or singl*) adj blind*).ti,ab.
39.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
40.	crossover procedure/
41.	single blind procedure/
42.	randomized controlled trial/

43.	double blind procedure/
44.	or/35-43
45.	systematic review/
46.	meta-analysis/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(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.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	34 and (44 or 55)

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: [Continuous Positive Airway Pressure] explode all trees
#9.	positive airway* pressure:ti,ab
#10.	Continuous Positive Airway* Pressure:kw
#11.	(positive near/3 pressure near/3 (therapy or device* or ventilat*)):ti,ab
#12.	(PAP or CPAP or aPAP or nCPAP or autoCPAP or auto-CPAP):ti,ab
#13.	(biPAP or BPAP or NBiPAP or NBPAP or NIV):ti,ab
#14.	((noninvasive or non-invasive) near/3 ventilat*):ti,ab
#15.	MeSH descriptor: [Positive-Pressure Respiration] this term only
#16.	(or #8-#15)
#17.	#7 and #16

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 14: 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 15: 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

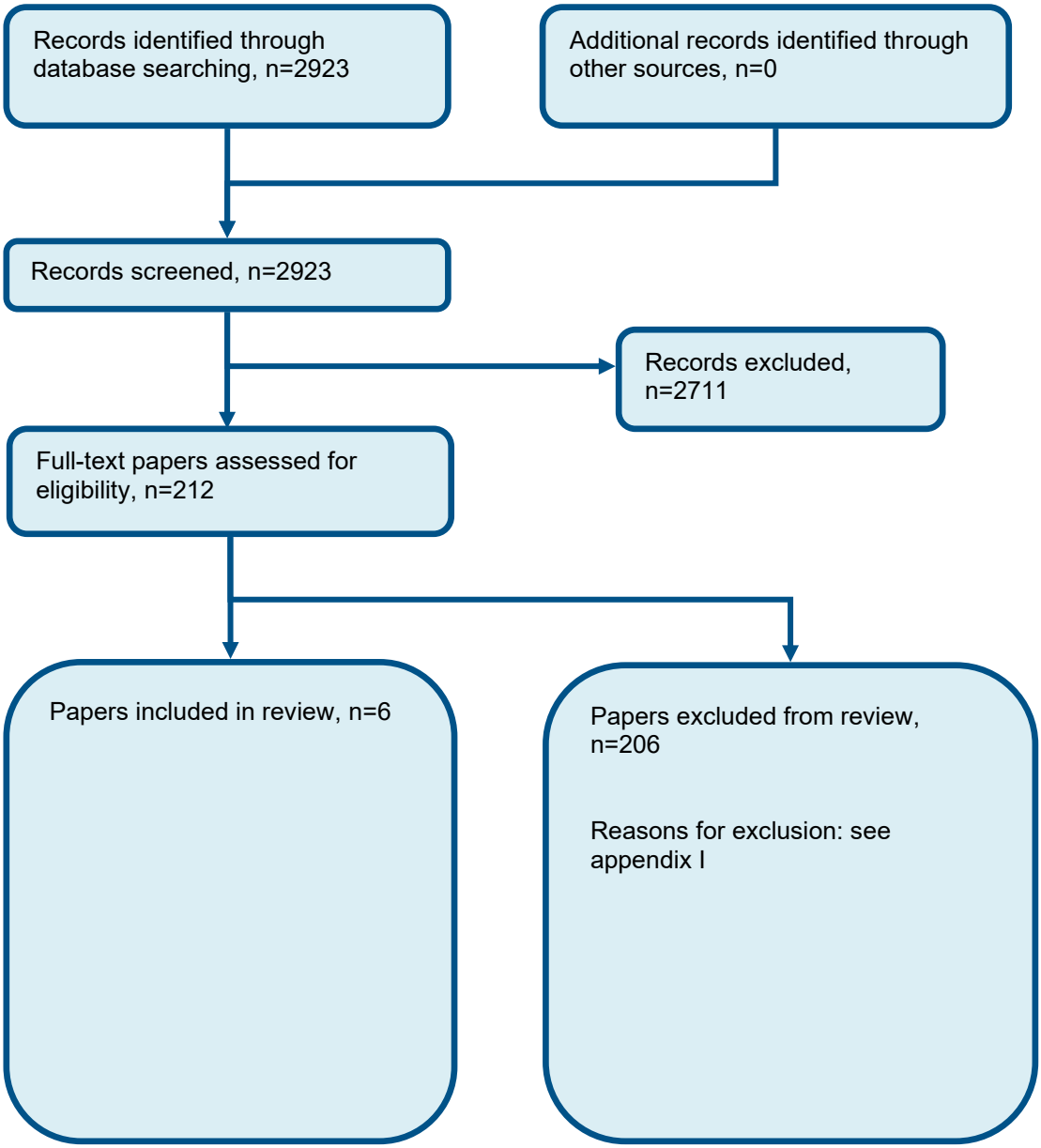
Embase (Ovid) search terms

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 CPAP in people with mild OSAH



Appendix D: Clinical evidence tables

Study	Barnes 2002 [21]
Study type	RCT (Patient randomised; cross over)
Number of studies (number of participants)	1 (n=42)
Countries and setting	Two Australian centres (Austin and Repatriation Medical Centre, Heidelberg, Victoria and Repatriation General Hospital, Daw Park, South Australia)
Line of therapy	1st line
Duration of study	Intervention + follow up: 8 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients were diagnosed using overnight respiratory polygraphy
Stratum	Mild OSAHS (Mixed severity population)
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	More than 18 years of age and if their overnight diagnostic sleep study showed an AHI of between 5 and 30/h. Each diagnostic polysomnographic study required at least 4 h of sleep, at least 30 min of sleep in the supine position, and at least 30 min of rapid eye movement (REM) sleep.
Exclusion criteria	Patients with minimum blood oxygen saturation less than 75% in REM and 80% in non-REM were excluded, as were patients with clinically significant coexisting disease (e.g., diabetes, unstable ischemic heart disease) or sleepiness deemed to be unsafe and requiring urgent treatment, for example, history of falling asleep while driving or working, or in some other unsafe situation. To ensure valid interpretation of the neurobehavioral tests patients were required to be fluent in the English language and to have no history of cerebrovascular disease, closed head injury associated with loss of consciousness greater than 15 min in duration, psychiatric illness, or alcohol or drug abuse.
Recruitment/selection of patients	Patients were recruited from two Australian centres (Austin and Repatriation Medical Centre, Heidelberg, Victoria and Repatriation General Hospital, Daw Park, South Australia) to investigate daytime sleepiness, neurobehavioral

	function, and 24-h systemic blood pressure in patients with mild obstructive sleep apnoea (OSA) and to assess the response to 8 weeks of treatment with nasal CPAP and a placebo tablet. Patients recruited into the study were referred for investigation of symptomatic sleep-disordered breathing (snoring, observed breathing pauses in sleep, and daytime sleepiness).
Age, gender and ethnicity	Age - 45.5 (10.7); Gender (M:F): 35:7
Further population details	In general, they were middle-aged and overweight. Mean AHI of 12.9 (6.3). Body mass index, kg/m2 30.2 (4.8)
Indirectness of population	Serious indirectness: severity of the population judged by mean AHI
Interventions	(n=28) Intervention 1: Patients received CPAP (Sullivan Elite; ResMed, Sydney, Australia) for 8 weeks. (n=28) Intervention 2: a placebo lactose tablet for 8 weeks. Patients were told that the tablet was intended to improve airway function during sleep and were instructed to take it immediately before going to bed. There was no intervening washout period, as the onset and offset of benefits from CPAP occurs within 1 or 2 days.
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CPAP versus placebo

Protocol outcome 1: AHI >1 month
- Actual outcome: AHI at 8 weeks; Group 1: mean 4.24 (SD 2.9); n=28, Group 2: NR; n=28
Risk of bias: All domain - high, Selection - High, Blinding - low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Indirectness of outcome: No indirectness; n=14 not completed study.

Protocol outcome 2: 24 hr Systolic blood pressure for hypertension at >1 month
- Actual outcome : Systolic blood pressure at 8 weeks; Group 1: mean -0.7 mmHg (SD 8.1); n=28, Group 2: mean -1.2 mmHg (SD 8.2); n=28
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 ; n=14 not completed study.

Protocol outcome 3: 24 hr Diastolic blood pressure for hypertension at >1 month
- Actual outcome : Diastolic blood pressure at 8 weeks; Group 1: mean -2.1 mmHg (SD 25.5); n=28, Group 2: mean -1.2 mmHg (SD 10.3); n=28
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 ; n=14 not completed study.

Protocol outcome 4: Quality of life at >1 month - Actual outcome: FOSQ (change score) at 8 weeks; Group 1: mean +0.07 (no SD) n=28, Group 2: mean +0.06 (no SD); n=28. Baseline mean overall score: mean 0.8 (SD 0.1) 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 ; n=14 not completed study. Protocol outcome 5: Epworth Sleepiness Scale at >1 month - Actual outcome: Epworth Sleepiness Scale (change score) at 8 weeks; Group 1: mean -2.7 (no SD) n=28, Group 2: mean -2.1 (no SD); n=28. Baseline ESS: mean 11.2 (SD 5.0) 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 ; n=14 not completed study. Protocol outcome 6: Quality of life at >1 month - Actual outcome : SF-36 physical functioning (change score) at 8 weeks; Group 1: mean +4.2 (no SD) n=28, Group 2: mean +5.5 (no SD); n=28. Baseline score: mean 78.1 (SD 22.4) 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 ; n=14 not completed study. - Actual outcome: SF-36 mental health (change score) at 8 weeks; Group 1: mean +6.4 (no SD) n=28, Group 2: mean +6.3 (no SD); n=28. Baseline score: mean 72.5 (SD 19.1) 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 ; n=14 not completed study. - Actual outcome: SF-36 vitality (change score) at 8 weeks; Group 1: mean +12.8 (no SD) n=28, Group 2: mean +13.0 (no SD); n=28. Baseline score : mean 48.4 (SD 21.5) 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 ; n=14 not completed study. Protocol outcome 4: Patient preference at >1 month - Actual outcome: Patient preference at 8 weeks; Group 1: 12/28; n=28, Group 2: 16/28; n=28. 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; n=14 not completed study. Note: SD not reported for ESS, FOSQ, SF-36 outcomes.	
Protocol outcomes not reported by the study	Mortality at >1 month; AHI/RDI 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; HbA1c for diabetes at >1 month; Cardiovascular events at >1 month

Study	Craig 2012[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=391)
Countries and setting	Conducted in sleep clinics in United Kingdom
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients were diagnosed using overnight respiratory polygraphy
Stratum	Auto CPAP: Autoset S8, ResMed, Abington, UK
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Patients referred to sleep clinics, usually due to snoring, witnessed apnoea's or daytime sleepiness, were assessed for eligibility and a screening log was kept. All patients were diagnosed with OSA using overnight respiratory polygraphy as standard in the participating centres. Patients were eligible if they were aged between 45 and 75 years, had proven OSA on the diagnostic sleep study, with >7.5 per hour oxygen desaturations of >4% (oxygen desaturation index, ODI), but had insufficient daytime symptoms associated with OSA to warrant CPAP therapy. This decision followed a detailed discussion between physician and patient about the evidence for possible benefits of CPAP versus the potentially lifelong nightly usage of a physical therapy. Thus patients with Epworth Sleepiness Scores (ESS) above the conventional upper normal limit (9) were included, when this was not accompanied by patient concerns. In addition, to ensure technical uniformity of the ODI across centres, a second domiciliary, overnight, pulse-oximetry recording (Konica-Minolta Inc, Osaka, Japan) was performed in all patients at baseline and at 6 months. This was used as the trial ODI value, which could therefore be different from the entry ODI. All patients who gave informed consent did so in accordance with Good Clinical Practice standards.
Exclusion criteria	not stated
Recruitment/selection of patients	The Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial (MOSAIC) was a randomised, parallel, 6-month controlled trial that was conducted between May 2006 and February 2010. There were 10 recruiting centres in the UK and Canada, with Oxford as the coordinating centre. All centres are designated sleep units with facilities for diagnosis, treatment and follow-up of patients with OSA, and have healthcare professionals specifically trained in CPAP set-up and usage.
Age, gender and ethnicity	Age - Range: 45 - 75 years old. Gender (M:F): Define. Ethnicity: N/A

Further population details	1. Age: Age <65 (CPAP group - 57.9 (7.2); standard - 57.6 (7.5)). 2. BMI: BMI >/=30 (CPAP group 32.2 (5.6); Standard care - 32.5 (5.6). 3. Co-existing conditions: Not applicable 4. High risk occupation group: Not stated / Unclear
Indirectness of population	Serious indirectness: severity of the population judged by mean ODI
Interventions	(n=195) Intervention 1: CPAP - auto CPAP. Patients assigned to CPAP were instructed in the use of an auto-adjusting CPAP machine (Autoset S8, ResMed, Abingdon, UK). Induction was by trained staff who were not involved in outcome assessments or data analysis. Humidification and interface choices were made on an individual basis. All patients had one or more follow-up visits to download compliance data, check for residual apnoea/hypopnoeas and mask leakage, and to make any necessary adjustments. There were routine telephone calls at 2 and 4 months, and telephone advice and replacement parts if requested by the patient. Duration 6 months. Concurrent medication/care: N/A. Indirectness: No indirectness (n=196) Intervention 2: usual care. The standard care (SC) group had an identical planned visit schedule to the CPAP group. Both groups were asked to continue on their normal medication and not given any specific advice regarding diet and exercise. Duration 6 months. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Academic or government funding (The British Heart Foundation—unrestricted project grant, Oxford Health Services Research Committee paid for research salaries. ResMed UK made an unrestricted charitable donation to support research work in the Oxford Sleep Unit in 1998 and 2006, and supplied the CPAP machines for this trial. We would like to acknowledge the support of the NIHR Biomedical Research Centre Oxford.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AUTO CPAP versus USUAL CARE

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for auto CPAP: SF36 Vitality at 6 months; Group 1: mean 60.6 (SD 20.9); n=171, Group 2: mean 53.9 (SD 22.5); n=168
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28
- Actual outcome for auto CPAP: SF36 Mental component at 6 months; Group 1: mean 52 (SD 9.8); n=165, Group 2: mean 48.5 (SD 11); n=158
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28
- Actual outcome for auto CPAP: SAQLI at 6 months; Group 1: mean 5.6 (SD 1); n=167, Group 2: mean 5 (SD 1.3); n=163
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28
- Actual outcome for auto CPAP: EQ5D (VAS) at 6 months; Group 1: mean 0.83 (SD 0.19); n=110, Group 2: mean 0.8 (SD 0.22); n=107
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28 - Actual outcome for auto CPAP: EQ5D Change score at 6 months; Group 1: mean 0.83 (SD 0.19); n=110, Group 2: mean 0.8 (SD 0.22); n=107 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28 Protocol outcome 2: Sleepiness score at >1 month - Actual outcome for auto CPAP: ESS (adjusted treatment effect) at 6 months; Adjusted mean difference. Mean difference (SE) = -2(0.3061) Total number of patients CPAP - 170; Placebo 171; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28 Protocol outcome 3: ODI at >1 month - Actual outcome for auto CPAP: ODI at 6 months; Group 1: mean 5.2 (SD 9); n=171, Group 2: mean 12.6 (SD 13.6); n=170 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: 24; Group 2 Number missing: 28 Protocol outcome 4: Adherence in hours of use at >1 month - Actual outcome for auto CPAP: Adherence at 6 months; Adherence only reported in the CPAP group Median 2.39(0.36 to 4.59); 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: 24; Group 2 Number missing: 28 - Actual outcome for auto CPAP: Preference at 6 months; Preference only reported in CPAP group 71 % of the patients wished to continue with CPAP; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 24; Group 2 Number missing: 28 Protocol outcome 5: Systolic blood pressure for hypertension at >1 month - Actual outcome for auto CPAP: Systolic blood pressure at 6 months; Group 1: mean 131.1 mmHg (SD 13.4); n=154, Group 2: mean 129.8 mmHg (SD 13.4); n=156 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: 24; Group 2 Number missing: 28	
Protocol outcomes not reported by the study	Mortality at >1 month; AHI/RDI 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; HbA1c for diabetes at >1 month; Patient preference at >1 month; Cardiovascular events at >1 month

Study	Engleman 1997[63]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in United Kingdom; Setting: Sleep clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: polysomnography
Stratum	Fixed CPAP: Sullivan APD-1 units, ResCare, Abington, UK
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Entry criteria required two or more symptoms of SAHS1 and an AHI in the range 5.0–14.9 per hour slept during clinical polysomnography, conducted and scored according to our usual methods. Polysomnography included electroencephalographic (EEG), electro-oculographic (EOG), and electromyographic (EMG) monitoring to facilitate the evaluation of sleep quality and microarousals (defined by increases in EEG frequency of 1.5 seconds or longer, coincident with any duration of increased EMG activity2). Breathing pauses were monitored by inductance plethysmography of abdominal and respiratory movement and by thermistor assessment of oronasal airflow Hypopnoeas were defined as 10 seconds or longer 50% reduction in respiratory movement and apnoeas as 10 seconds or longer of absent airflow. Arterial oxygen saturation was monitored using pulse oximetry
Exclusion criteria	Patients with coexisting neurological or sleep disorders, or residence outwith a 50 mile radius of the laboratory, were excluded.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Other: mean(SE) - 52(2). Gender (M:F): 12/4. Ethnicity: N/A
Further population details	1. age: Age <65 (mean 52). 2. BMI: Not stated / Unclear 3. Co-existing conditions: Not stated / Unclear 4. High risk occupation group: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: CPAP - Fixed CPAP . CPAP - patients spent 4 weeks on CPAP therapy (Sullivan APD-1 units, ResCare, Abington, UK) Patients were educated in the mechanisms of action of CPAP therapy and

	were asked to use CPAP units all night, most especially on the night before assessment. Duration 4 weeks. Concurrent medication/care: N/A. Indirectness: No indirectness (n=16) Intervention 2: placebo. Placebo tablet - Ranitidine 300 mg homologue, Glaxo, Greenford UK in a dose of 2 tablets at bedtime. with the permission of the local ethics committee, patients were told that the placebo tablet might improve upper airway pressure.. Duration 4 weeks. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (The authors thank Glaxo for their provision of placebo tablets and ResCare for their donation of CPAP units for use in this study. We gratefully acknowledge the contributions of the nursing, technical, and administrative staff of the Scottish National Sleep Laboratory to this project. Dr H M Engleman is supported by a grant from the British Lung Foundation.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIXED CPAP versus PLACEBO

Protocol outcome 1: Sleepiness score at >1 month
- Actual outcome for Fixed CPAP: ESS at 4 weeks; Group 1: mean 10.1 (SD 5.6); n=16, Group 2: mean 10 (SD 4.8); n=16
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Driving outcomes at >1 month
- Actual outcome for Fixed CPAP: Trail making B (secs) at 4 weeks; Group 1: mean 64.1 (SD 22); n=16, Group 2: mean 77.7 (SD 36.8); n=16
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Fixed CPAP: Steer clear (obstacles hit) at 4 weeks; Group 1: mean 74.8 (SD 31.2); n=16, Group 2: mean 75.3 (SD 35.6); n=16
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Neurocognitive outcomes at >1 month
- Actual outcome for Fixed CPAP: HADS depression at 4 weeks; Group 1: mean 3.4 (SD 3.6); n=16, Group 2: mean 5 (SD 4); n=16
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Fixed CPAP: HADS anxiety at 4 weeks; Group 1: mean 4.5 (SD 4.8); n=16, Group 2: mean 5.1 (SD 4.4); n=16
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for Fixed CPAP: PASAT 2-s (correct) at 4 weeks; Group 1: mean 37.8 (SD 13.2); n=16, Group 2: mean 35.3 (SD 11); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Fixed CPAP: RVIPT (correct at 4 weeks; Group 1: mean 36.9 (SD 12.8); n=16, Group 2: mean 34.8 (SD 12.8); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Fixed CPAP: Median eight choice reaction (ms) at 4 weeks; Group 1: mean 365 (SD 64); n=16, Group 2: mean 356 (SD 64); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Fixed CPAP: Verbal fluency (total word count) at 4 weeks; Group 1: mean 38.5 (SD 14); n=16, Group 2: mean 39.2 (SD 12.4); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Fixed CPAP: BVRT (correct) at 4 weeks; Group 1: mean 7.3 (SD 2.4); n=16, Group 2: mean 7.3 (SD 2.4); n=16 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: ; Group 2 Number missing: - Actual outcome for Fixed CPAP: IQ decrement score at 4 weeks; Group 1: mean 7 (SD 3.1); n=16, Group 2: mean 5.3 (SD 3.5); n=16 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Adherence in hours of use at >1 month - Actual outcome for Fixed CPAP: Adherence at 4 weeks; Reported only in CPAP group mean(SE) - 3.2 (0.7); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Patient preference at >1 month - Actual outcome for Fixed CPAP: Preference at 4 weeks; Group 1: 10/16, Group 2: 6/16 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Quality of life at >1 month; 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; 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	**Engleman 1999[61]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=34)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ESS, polysomnography
Stratum	Fixed CPAP: N/A
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Entry criteria specified an initial complaint of at least two symptoms of the SAHS (14), including significant sleepiness demonstrated by an Epworth sleepiness score of 8 or greater or admitted sleepiness while driving, and a demonstrated AHI on polysomnography in the range 5.0 to 14.9 per hour slept. Apnoeas were scored when thermistor airflow was absent for 10 s or longer, and hypopneas scored when abdominal or thoracic respiratory movement amplitude was reduced to 50% or less of the preceding stable baseline value for 10 s or longer, during sleep (15). Microarousals were defined by 1.5 s or longer of increased electroencephalogram (EEG) frequency accompanied by a rise in electromyogram (EMG) amplitude (1).
Exclusion criteria	Patients residing more than 50 miles from the laboratory, shift workers, and those with other coexisting sleep disorders, neurological or lung disease were excluded.
Age, gender and ethnicity	Age - Mean (SD): 44(8). Gender (M:F): 21/13. Ethnicity: N/A
Further population details	1. Age <65 (44(8)). 2. BMI: Not stated / Unclear 3. Co-existing conditions: Not stated / Unclear 4. High risk occupation group: Not stated / Unclear

Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: CPAP - Fixed CPAP. At the start of the CPAP treatment limb, patients were issued with a Sullivan III CPAP unit and a heated CPAP humidifier (both ResMed Ltd., Abingdon, UK) and advised to use CPAP, with or without humidification, all night and every night and during any daytime naps during that treatment period. Patients were supplied with a contact telephone number in the event of problems or side effects with CPAP, and any problems not prevented by humidification were actively sought in telephone contact made in the second week of treatment, so that these could be managed and compliance reinforced . Duration 4 weeks. Concurrent medication/care: Before the commencement of treatment, patients underwent a day of familiarisation and baseline assessment with all daytime function tests except the maintenance of wakefulness test, and were fitted with a nasal mask and educated in the mechanisms and technique of CPAP treatment. All underwent an overnight CPAP titration study to establish an optimal pressure to abolish breathing irregularities and arousals from sleep. Indirectness: No indirectness (n=34) Intervention 2: placebo. With the permission of the local ethics subcommittee, patients were told that the placebo treatment (Glaxo, Greenford, UK), prescribed in a dose of two tablets at bedtime, might improve upper airway muscle function in sleep. Duration 4 weeks. Concurrent medication/care: Before the commencement of treatment, patients underwent a day of familiarisation and baseline assessment with all daytime function tests except the maintenance of wakefulness test, and were fitted with a nasal mask and educated in the mechanisms and technique of CPAP treatment. All underwent an overnight CPAP titration study to establish an optimal pressure to abolish breathing irregularities and arousals from sleep. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIXED CPAP versus PLACEBO

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Fixed CPAP: SF36 Vitality at 4 weeks; Group 1: mean 58 (SD 19); n=34, Group 2: mean 46 (SD 23); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Sleepiness score at >1 month

- Actual outcome for Fixed CPAP: ESS at 4 weeks; Group 1: mean 8 (SD 4); n=34, Group 2: mean 11 (SD 4); n=34; Comments: baseline ESS: 13(SD3)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse effects of treatment at >1 month
- Actual outcome for Fixed CPAP: adverse effects at 4 weeks; Group 1: 23/34, Group 2: 8/34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Driving outcomes at >1 month
- Actual outcome for Fixed CPAP: SteerClear (obstacles hit) at 4 weeks; Group 1: mean 189 (SD 156); n=34, Group 2: mean 195 (SD 158); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Neurocognitive outcomes at >1 month
- Actual outcome for Fixed CPAP: TrailMaking A,s at 4 weeks; Group 1: mean 26 (SD 11); n=34, Group 2: mean 29 (SD 11); n=34; Comments: The Trail Making Test (TMT) is an evaluation tool that has two parts that are referred to as the Trail Making Test Part A and the Trail Making Test Part B. It is a timed test and the goal is to complete the tests accurately and as quickly as possible.

The TMT Part A consists of 25 circles on a piece of paper with the numbers 1–25 written randomly in the circles. The test taker's task is to start with number one and
draw a line from that circle to the circle with the number two in it to the circle with the three in it, etc.

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: TrailMaking B,s at 4 weeks; Group 1: mean 63 (SD 33); n=34, Group 2: mean 65 (SD 27); n=34; Comments: The Trail Making Test (TMT) is an evaluation tool that has two parts that are referred to as the Trail Making Test Part A and the Trail Making Test Part B. It is a timed test and the goal is to complete the tests accurately and as quickly as possible.

The TMT Part B
consists of 24 circles on a piece of paper, but rather than all of the circles containing numbers, half of the circles have the numbers 1–12 in them and the other half (12) contain the letters A-L.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: Digit symbol (correct) at 4 weeks; Group 1: mean 59 (SD 12); n=34, Group 2: mean 57 (SD 14); n=34; Comments: The digit symbol test involves a key consisting of the numbers 1-9, each paired with a unique, easy-to-draw symbol such as a "V", "+" or ">". Below the key are a

series of the numbers 1-9 in random order and repeated several times. The test taker is then allowed 90 or 120 seconds (depending on the test version) to fill in the corresponding symbol for each number. This task requires the individual to visually scan the answer key provided at the top of the test and then write the correct symbol by each number.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: Block design score at 4 weeks; Group 1: mean 31 (SD 12); n=34, Group 2: mean 32 (SD 10); n=34; Comments: block design test is a subtest on many IQ test batteries used as part of assessment of human intelligence. It is thought to tap spatial visualization ability and motor skill. The test-taker uses hand movements to rearrange blocks that have various color patterns on different sides to match a pattern. The items in a block design test can be scored both by accuracy in matching the pattern and by speed in completing each item.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: Performance IQ score at 4 weeks; Group 1: mean 109 (SD 18); n=34, Group 2: mean 108 (SD 19); n=34; Comments: Performance IQ is a score derived from the administration of selected subtests from the Wechsler Intelligence Scales, designed to provide a measure of an individual's overall visuospatial intellectual abilities. The Performance IQ is a measure of fluid reasoning, spatial processing, attentiveness to details, and visual-motor integration
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: PASAT 2-s (correct) at 4 weeks; Group 1: mean 40 (SD 11); n=34, Group 2: mean 36 (SD 14); n=34; Comments: The PASAT is a measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability. It was developed by Gronwell in 1977 and later adapted by Rao and colleagues in 1989 for use in MS. The PASAT is presented using audio cassette tape or compact disk to ensure standardization in the rate of stimulus presentation. Single digits are presented every 3 seconds and the patient must add each new digit to the one immediately prior to it. Shorter inter-stimulus intervals, e.g., 2 seconds or less have also been used with the PASAT but tend to increase the difficulty of the task. Two alternate forms have been developed to minimize possible familiarity with the stimulus items when the PASAT is repeated over more than one occasion. The PASAT is the third and last component of the MSFC to be administered at each visit.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Adherence in hours of use at >1 month
- Actual outcome for Fixed CPAP: Adherence at 4 weeks; Reported only for CPAP group
mean(SD) - 3.2(2.4);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Patient preference at >1 month
- Actual outcome for Fixed CPAP: Preference at 4 weeks; Group 1: 14/34, Group 2: 20/34
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - High; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

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; 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	**Weaver 2012[206]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=223)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: polysomnography
Stratum	Fixed CPAP: n/a
Subgroup analysis within study	Not applicable: n/a
Inclusion criteria	Eligibility criteria included patients with newly diagnosed milder OSA (AHI 5–30 events/h) who were naive to CPAP and had an Epworth Sleepiness Scale (ESS) score greater than 10 (13). Additionally, participants had a stable medical condition in the past 3 months; greater than fifth grade reading level; and no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident, or sleepiness sensitive occupation. The study was approved by the Institutional Review Board at each participating site and informed consent was obtained from all participants
Exclusion criteria	no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident, or sleepiness sensitive occupation.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): active CPAP group - 49.5 (10.9); Sham CPAP 51.7(11.9). Gender (M:F): Active CPAP group males - 54.5%; Sham CPAP - 62.7%. Ethnicity: N/A
Further population details	1. Age: Age <65 (CPAP group - 49.5(10.9) SHAM - 51.7 (11.9). 2. BMI: BMI >/=30 (CPAP group - 33.2(6.3); SHAM - 34.2(7.8)). 3. Co-existing conditions: Not stated / Unclear 4. High risk occupation group: Not applicable
Indirectness of population	Serious indirectness: severity of the population

Interventions	(n=121) Intervention 1: CPAP - Fixed CPAP . CPAP for 8 weeks. Duration 8 weeks. Concurrent medication/care: All PSGs were scored at a centralised reading laboratory that selected the optimal setting for active treatment. An unmasked polysomnographic technologist performed the CPAP set-ups (Philips Respironics, Monroeville, PA) and distributed CPAP data cards (Philips Respironics Encore SmartCard). Participants sent these cards weekly to the clinical centre. Indirectness: No indirectness (n=118) Intervention 2: placebo. Sham CPAP - The sham CPAP looked identical to active CPAP, but delivered less than 1.0 cm H2O of pressure. Duration 8 weeks. Concurrent medication/care: All PSGs were scored at a centralised reading laboratory that selected the optimal setting for active treatment. An unmasked polysomnographic technologist performed the CPAP set-ups (Philips Respironics, Monroeville, PA) and distributed CPAP data cards (Philips Respironics Encore SmartCard). Participants sent these cards weekly to the clinical centre. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FIXED CPAP versus PLACEBO

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Fixed CPAP: FOSQ at 8 weeks; Group 1: mean 0.98 (SD 2.89); n=113, Group 2: mean -0.14 (SD 2.61); n=110
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: 8; Group 2 Number missing: 8
- Actual outcome for Fixed CPAP: SF36 - Physical at 8 weeks; Adjusted difference in mean change (active - sham)
mean change 3.85; SE - 1.17; p value - 0.001; CI (1.53; 6.17);
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: 8; Group 2 Number missing: 8
- Actual outcome for Fixed CPAP: SF36 - Mental at 8 weeks; Adjusted difference in mean change (active - sham)
mean change 0.86; SE = 1.42; p value = 0.546; CI (-1.95; 3.67);
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: 8; Group 2 Number missing: 8
- Actual outcome for Fixed CPAP: SF36 - Vitality at 8 weeks; Mean; , Comments: Adjusted difference in mean change (active - sham)
mean change 12.66; SE = 3.14; p value = 0.37; CI (0.39; 12.8);
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: 8; Group 2 Number missing: 8

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Fixed CPAP: ESS at 8 weeks; Group 1: mean -2.6 (SD 4.3); n=113, Group 2: mean -0.5 (SD 3.5); n=110

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: 8; Group 2 Number missing: 8 Protocol outcome 3: Adverse effects of treatment at >1 month - Actual outcome for Fixed CPAP: Adverse effects at 8 weeks; Group 1: 93/121, Group 2: 92/118 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: 8; Group 2 Number missing: 8 Protocol outcome 4: Adherence in hours of use at >1 month - Actual outcome for Fixed CPAP: Adherence at 8 weeks; Group 1: mean 4 (SD 2); n=113, Group 2: mean 3.1 (SD 2.1); n=110 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: 8; Group 2 Number missing: 8 Protocol outcome 5: Systolic blood pressure for hypertension at >1 month - Actual outcome for Fixed CPAP: Systolic blood pressure at 8 weeks; Adjusted difference in mean change (active - sham) mean change -1.32; SE = 1.58; p value = 0.407; CI (-4.5; 1.8); 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: 8; Group 2 Number missing: 8	
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; 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; Patient preference at >1 month; Cardiovascular events at >1 month

Study	**Wimms 2020[209]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=233)
Countries and setting	Conducted in United Kingdom; Setting: Patients were referred to NHS sleep centres for investigation of possible sleep apnoea
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: home respiratory polygraphy
Stratum	Auto CPAP: Airsence 10 autoset; or Airsence 10 Autoset for her, Resmed LTD. Oxfordshire ,UK
Subgroup analysis within study	Not applicable: N/A
Inclusion criteria	Patients (≥18 years to ≤80 years) with an AHI of at least 5 events per h to 15 or fewer events per h (by either AASM2007 or AASM 2012 scoring criteria) were eligible. The primary analysis population was patients with an AHI of at least 5 events per h to 15 or fewer events per h diagnosed using AASM 2012 scoring criteria.Patients diagnosed by the more widely used AASM 2007 scoring criteria were included in the secondary analysis.
Exclusion criteria	Exclusion criteria were as follows: inability to give fully informed consent, BMI of 40 kg/m^2 or more, unstable cardiac disease, use of supplemental oxygen, secondary sleep pathology (e.g., periodic limb movement syndrome, narcolepsy, circadian disorder, and obesity hypoventilation syndrome), previous CPAP usage, Epworth Sleepiness Scale (ESS) score of 15 or higher, concerns over driving while sleepy, or an inability to tolerate the 1 h CPAP tolerance test. The MERGE trial protocol and statistical analysis plan can be found on the MERGE.
Recruitment/selection of patients	N/A
Age, gender and ethnicity	Age - Mean (SD): CPAP group - 50.6(11.3); standard - 50.2(12.1). Gender (M:F): 162/72. Ethnicity: N/A
Further population details	1. Age <65 (CPAP - 50.6 (11.3); Standard - 50.2 (12.1). 2. BMI: BMI >/=30 (CPAP - 30.3 (4); Standard - 30.2(4.6). 3. Co-existing conditions: Not stated / Unclear 4. High risk occupation group: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=115) Intervention 1: CPAP - Auto CPAP . CPAP plus standard care (sleep hygiene counselling) and followed up for 3 months. Duration 3 months. Concurrent medication/care: N/A. Indirectness: No indirectness (n=118) Intervention 2: usual care. Standard care alone, and followed up for 3 months. Duration 3 months. Concurrent medication/care: N/A. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (ResMed Ltd for funding, donation of CPAP machines, ApneaLink Air devices, and consumables, and supportof the MERGE Trial)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AUTO CPAP versus USUAL CARE

Protocol outcome 1: Quality of life at >1 month
- Actual outcome for Fixed CPAP: SF 36 vitality at 3 months; Group 1: mean 7.5 (SD 8.2); n=115, Group 2: mean 0 (SD 8.2275); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: SF 36 Physical component at 3 months; Group 1: mean 1 (SD 5.9547); n=115, Group 2: mean -0.6 (SD 6.582); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: SF 36 Mental component at 3 months; Group 1: mean 4.2 (SD 7.5787); n=115, Group 2: mean -0.7 (SD 7.679); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: FOSQ at 3 months; Group 1: mean 1.4 (SD 1.6424); n=115, Group 2: mean 0.1 (SD 1.6455); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: EQ5D index at 3 months; Group 1: mean 0.03 (SD 0.1624); n=115, Group 2: mean 0 (SD 0.1646); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: EQ5D (VAS) at 3 months; Group 1: mean 3.1 (SD 15.1574); n=115, Group 2: mean -0.9 (SD 15.358); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: FSS - fatigue severity score at 3 months; Group 1: mean -7.2 (SD 9.2027); n=115, Group 2: mean 1.4 (SD 9.3245); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: HADS(hospital anxiety and depression score) - Anxiety at 3 months; Group 1: mean -0.5 (SD 2.7067); n=115, Group 2: mean 0.3 (SD 2.7425); n=118
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: 0; Group 2 Number missing: 0
- Actual outcome for Fixed CPAP: HADS(hospital anxiety and depression score) - Depression at 3 months; Group 1: mean -1.2 (SD 2.7067); n=115, Group 2: mean 0.4 (SD 2.7425); n=118
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: 0; Group 2 Number missing: 0

Protocol outcome 2: Sleepiness score at >1 month
- Actual outcome for Fixed CPAP: ESS at 3 months; Group 1: mean -3 (SD 3.248); n=115, Group 2: mean 0 (SD 3.291); n=118
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: 0; Group 2 Number missing: 0

Protocol outcome 3: Adherence in hours of use at >1 month
- Actual outcome for Fixed CPAP: Adherence at 3 months; adherence only reported only in CPAP groupMedian IQR - 4 (1h 36 min - 5 h 44 min);
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: 0; Group 2 Number missing: 0

- Actual outcome for Fixed CPAP: Preference at 3 months; Preference only reported in CPAP group81 of 100 wished to continue CPAP; 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: 0; Group 2 Number missing: 0	
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; Patient preference at >1 month; Cardiovascular events at >1 month; HbA1c for diabetes at >1 month; Patient preference at >1 month; Systolic blood pressure for hypertension at >1 month

Appendix E: Forest plots

E.1 CPAP compared to Placebo/standard care Mild population (AHI 5 – 15)

Figure 4: SF 36 Physical change score, 0-100 (Better indicated by higher score)

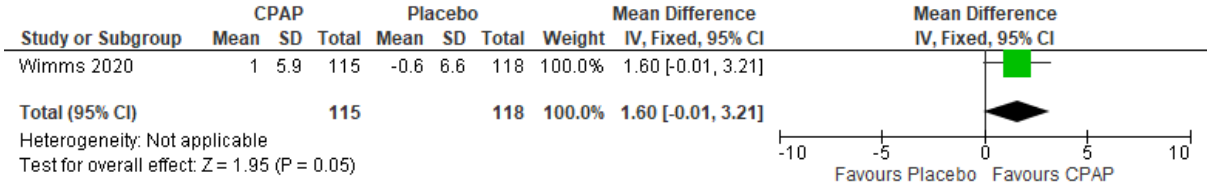


Figure 5: SF 36 Mental change score, 0-100 (Better indicated by higher score)

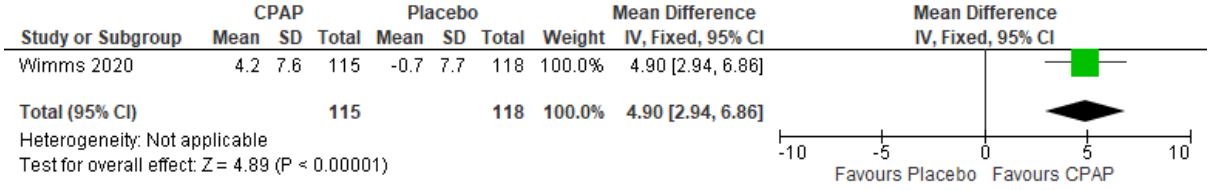


Figure 6: SF 36 Vitality, 0-100 (Better indicated by higher score)

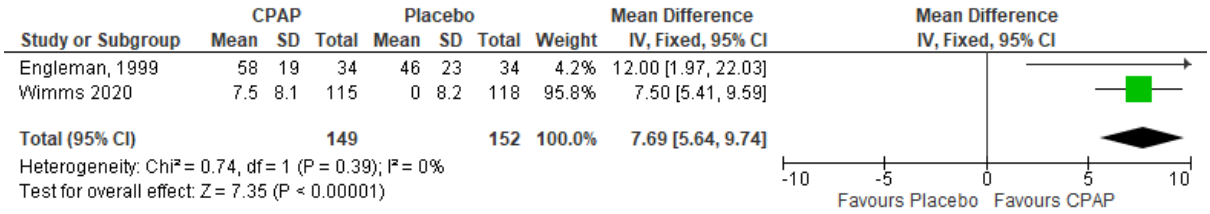


Figure 7: EQ5D change score, 0.59-1 (Better indicated by higher score)

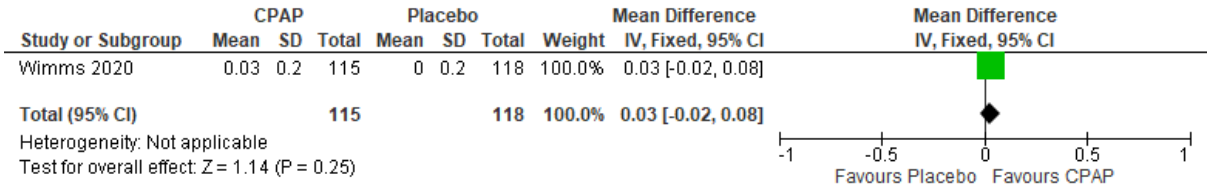


Figure 8: EQ5D (VAS), 0-100 change score (Better indicated by higher score)

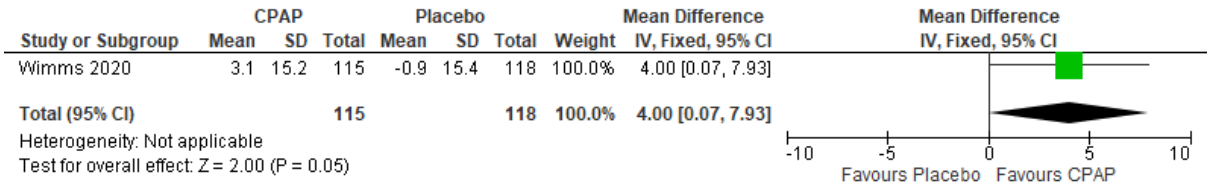


Figure 9: FOSQ change score, 5-20 (Better indicated by higher score)

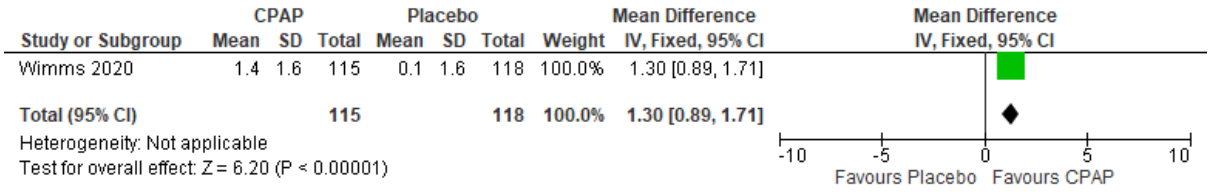


Figure 10: FSS Fatigue severity score – change score, 1-7 (Better indicated by lower score)

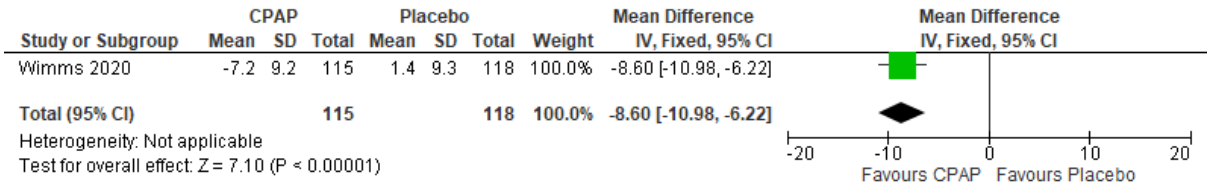


Figure 11:HADS – anxiety, 0-7 normal, 8-10 borderline abnormal (borderline case), 11-21 abnormal (case) (Better indicated by lower score)

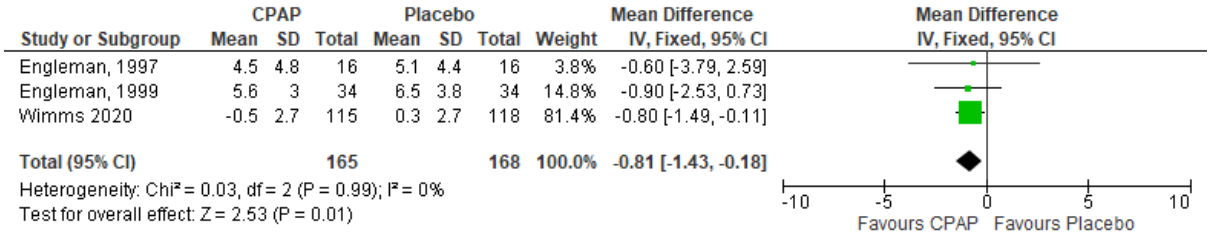


Figure 12: HADS depression, 0-7 normal, 8-10 borderline abnormal (borderline case), 11-21 abnormal (case) (Better indicated by lower score)

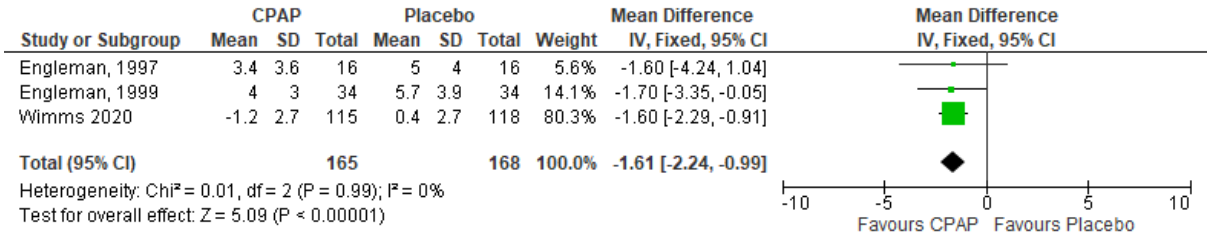


Figure 13: ESS, 0-24 (Better indicated by lower score)

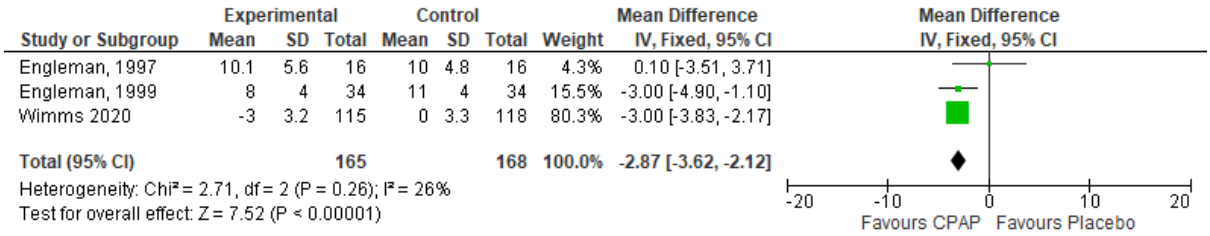


Figure 14: Preference, (Better indicated by higher)

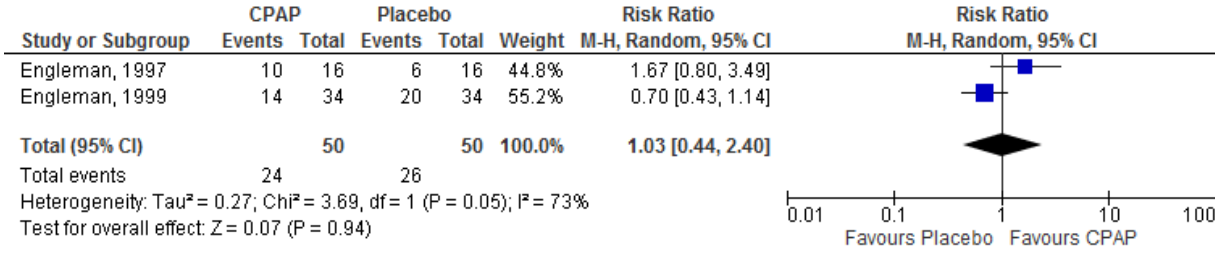


Figure 15: Adverse events (Better indicated by lower)

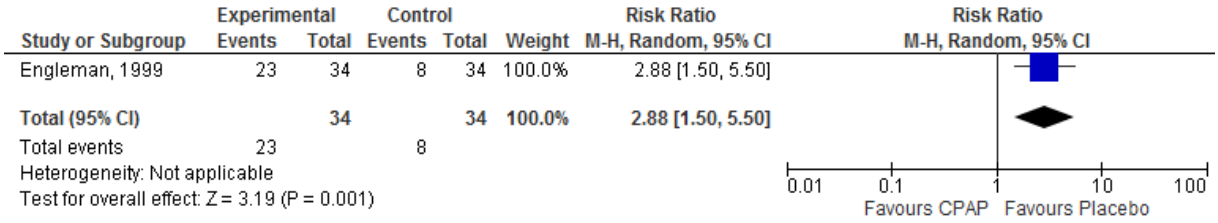


Figure 16: Driving outcomes – SteerClear (Number of obstacles hit)– 30 minute test (Better indicated by lower score)

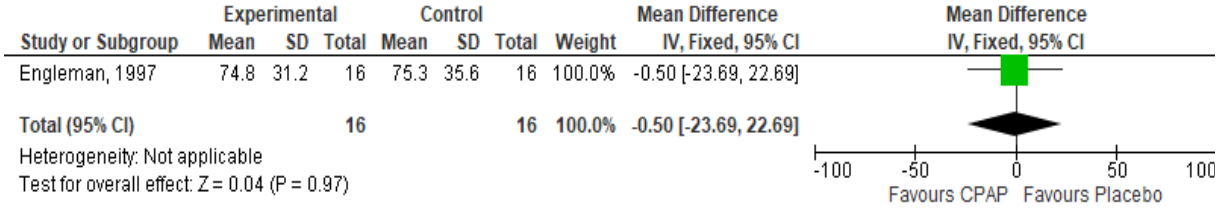


Figure 17: Driving outcomes – SteerClear (number of obstacles hit) 60 minute test (Better indicated by lower score)

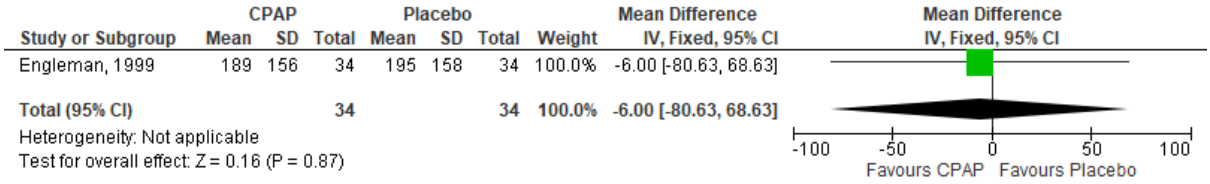


Figure 18: Neurocognitive outcomes – Block design score (Better indicated by lower score)

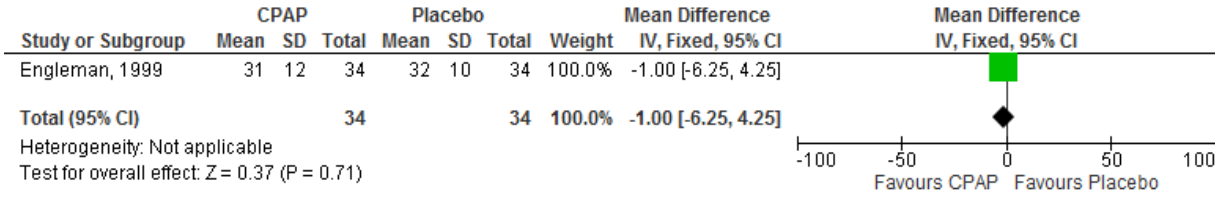


Figure 19: Neurocognitive outcomes – Trailmaking A(sec)(Better indicated by lower score)

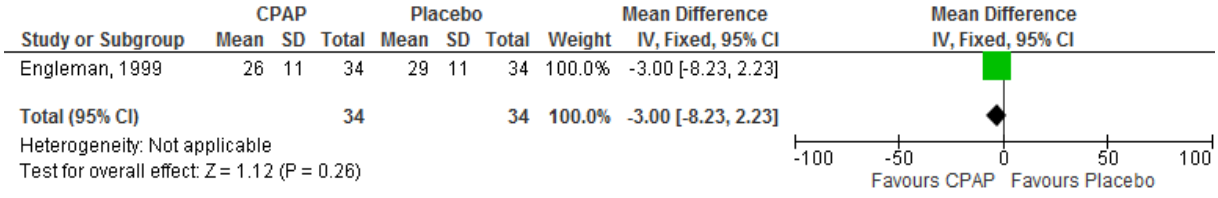


Figure 20: Neurocognitive outcomes – Trailmaking B (sec) (Better indicated by lower score)

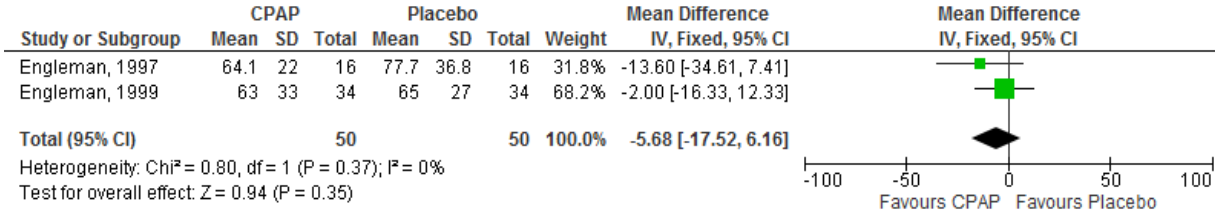


Figure 21: Neurocognitive outcomes – Performance IQ score (Better indicated by higher score)

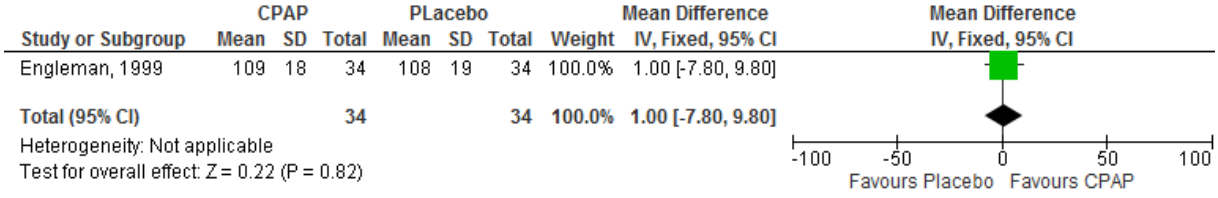


Figure 22: Neurocognitive outcomes – IQ decrement score (Better indicated by lower score)

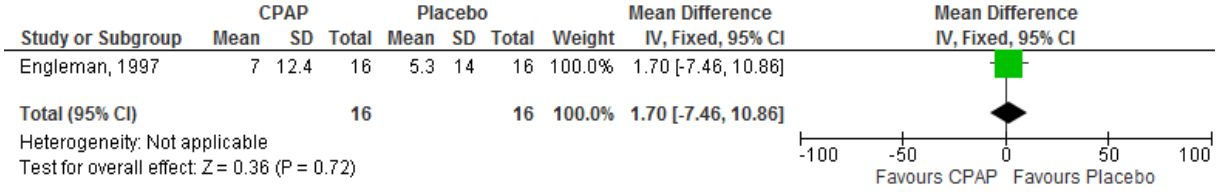


Figure 23: Neurocognitive outcomes – PASAT 2 (sec) (Better indicated by higher score)

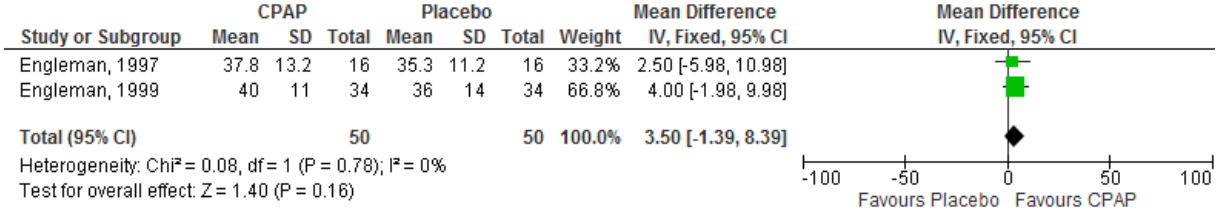


Figure 24: Neurocognitive outcomes – RVIPT (correct) (Better indicated by higher score)

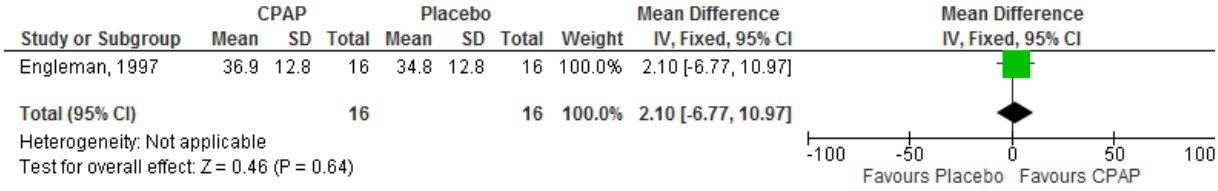


Figure 25: Neurocognitive outcomes – Median eight choice reaction time (ms) (Better indicated by lower score)

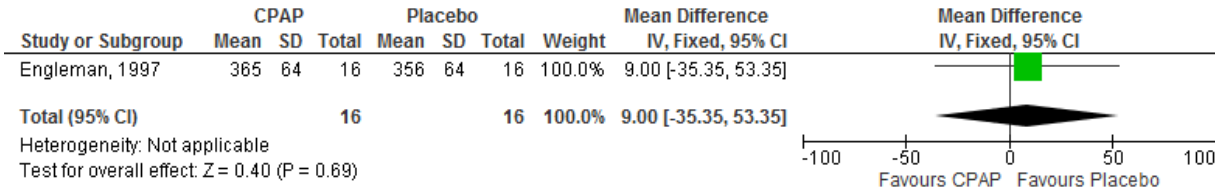


Figure 26: Neurocognitive outcomes – Verbal fluency (total words) (Better indicated by higher score)

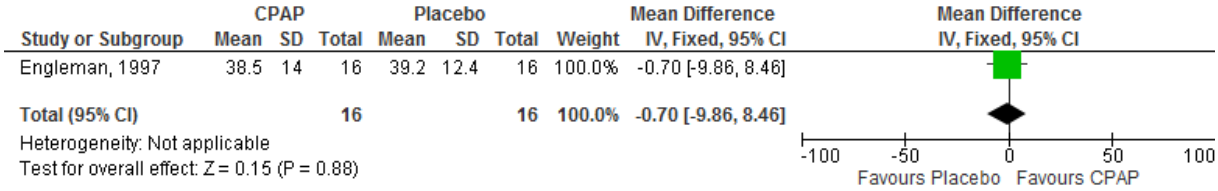
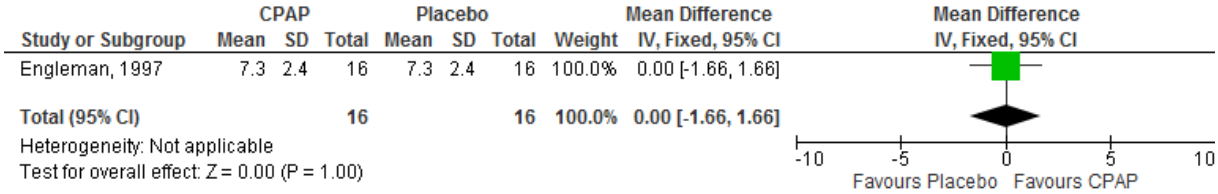


Figure 27: Neurocognitive outcomes – BVRT (correct) (Better indicated by higher score)



E.2 CPAP compared to placebo/standard care Mixed severity population (mean AHI 5 – 15)

Figure 28: SF 36 Mental component, 0-100 (Better indicated by higher score)

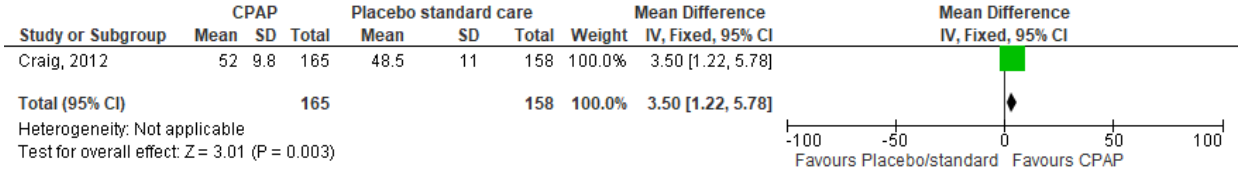


Figure 29: SF36 Vitality, 0-100 (Better indicated by higher score)

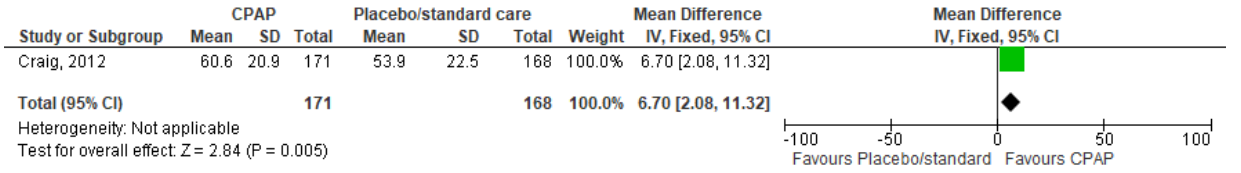


Figure 30: EQ5D, 0.59-1 (Better indicated by higher score)

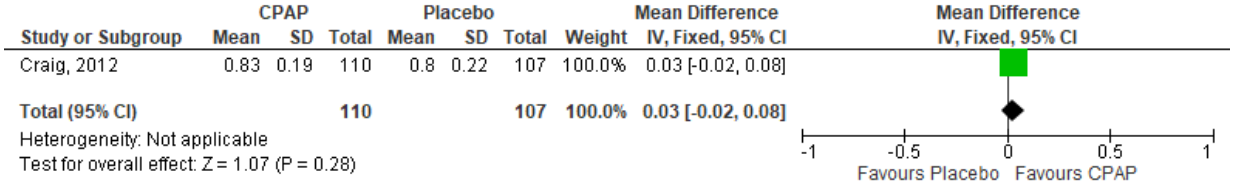


Figure 31: EQ5D (VAS score), 0-100 (Better indicated by higher score)

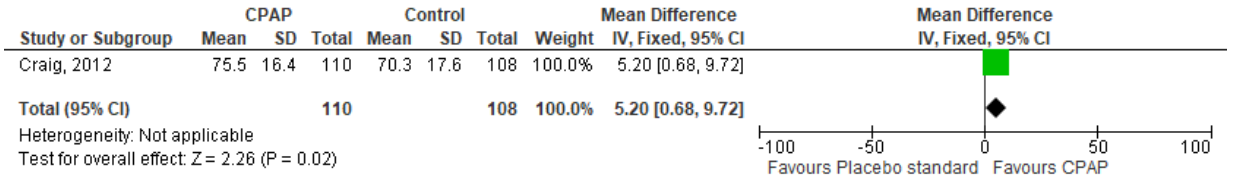


Figure 32SAQLI, 1-7 (Better indicated by higher score)

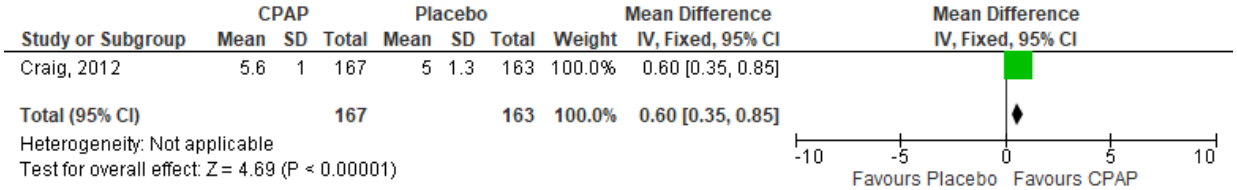


Figure 33: FOSQ, 5-20 (Better indicated by higher score)

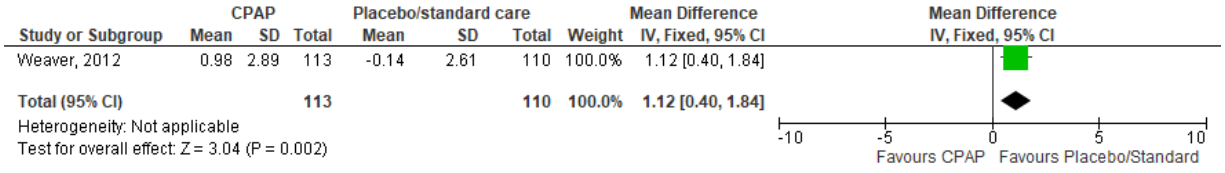


Figure 34: ESS, 0-24 (Better indicated by lower score)

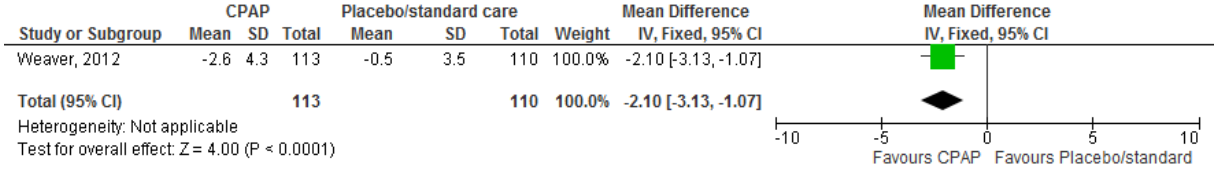


Figure 35: ODI (Better indicated by lower score)

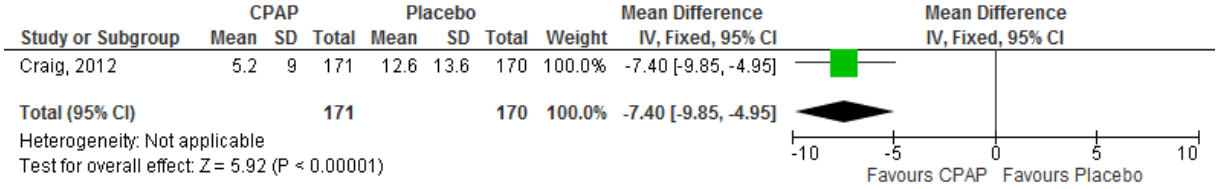


Figure 36: Adherence (Better indicated by higher score)

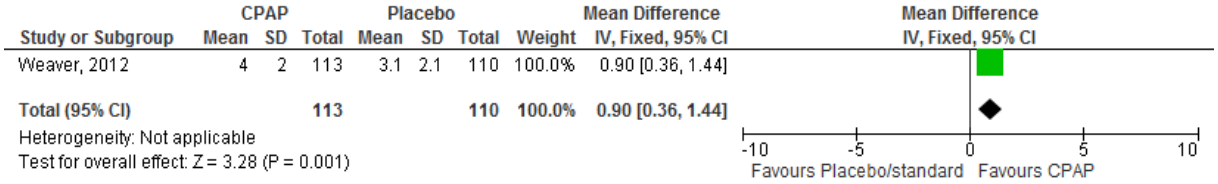


Figure 37: Adverse events (Better indicated by lower score)

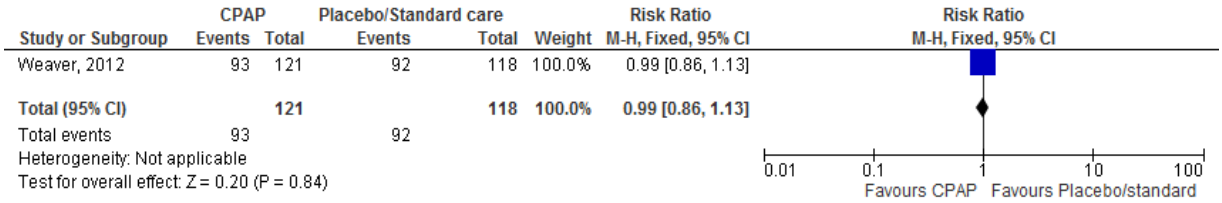


Figure 38: Systolic blood pressure (Better indicated by lower score)

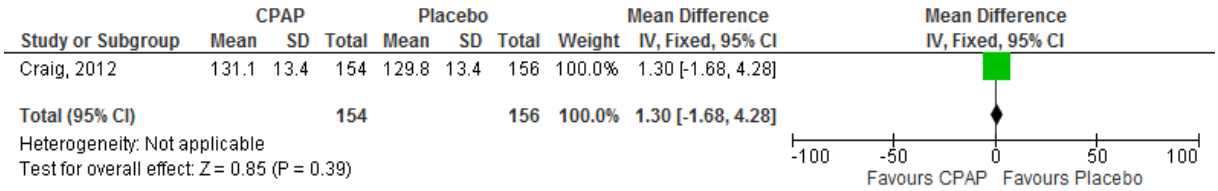


Figure 39: 24 hour Systolic blood pressure (change value) (Better indicated by lower score)

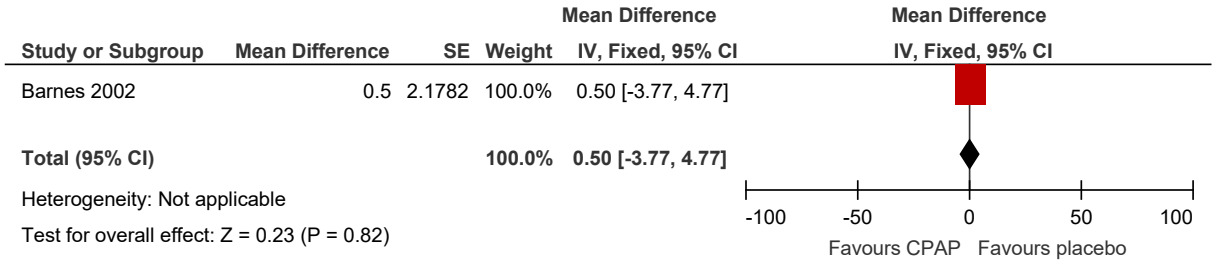


Figure 40: 24 hour diastolic blood pressure (change value) (Better indicated by lower score)

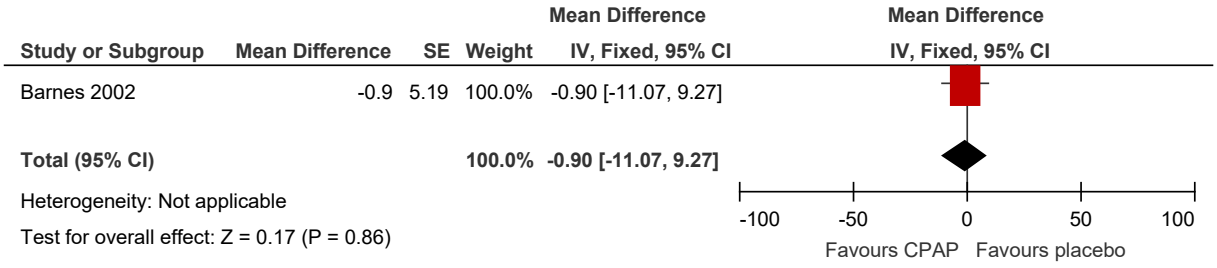
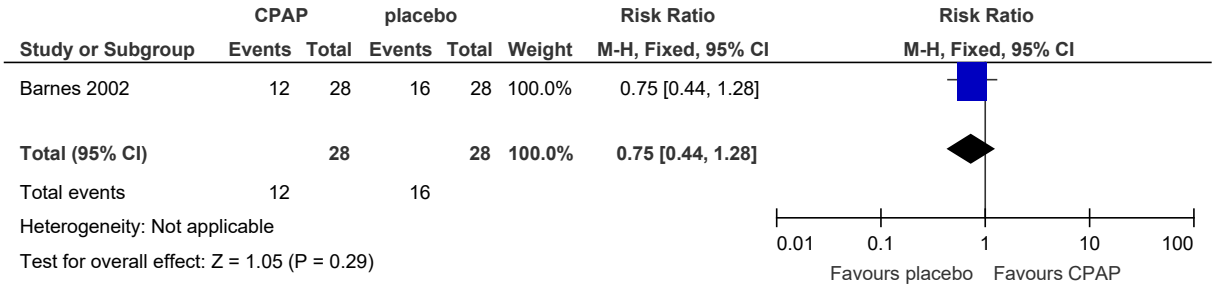


Figure 41: Patient preference



Appendix F: GRADE tables

Table 16: Clinical evidence profile: CPAP compared to Placebo/Standard care mild severity population (AHI 5 – 15)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Placebo	Relative (95% CI)	Absolute		
SF36 Physical pure mild (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	115	118	-	MD 1.6 higher (0.01 lower to 3.21 higher)	⊕OOO VERY LOW	CRITICAL
SF 36 Mental pure mild (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	115	118	-	MD 4.9 higher (2.94 to 6.86 higher)	⊕OOO VERY LOW	CRITICAL
SF 36 Energy/vitality pure mild (follow-up mean 1-3 months; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	149	152	-	MD 7.69 higher (5.63 to 9.74 higher)	⊕⊕OO LOW	CRITICAL
EQ5D (Change score) pure mild population (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	115	118	-	MD 0.03 higher (0.01 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
EQ5D (VAS change score) ESS >9 pure mild population (follow-up mean 3 months; Better indicated by higher values)												

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1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	115	118	-	MD 4 higher (0.08 to 7.92 higher)	⊕OOO VERY LOW	CRITICAL
FOSQ pure mild (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	115	118	-	MD 1.3 higher (0.88 to 1.72 higher)	⊕⊕OO LOW	CRITICAL
FSS (fatigue severity score) pure mild (follow-up mean 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	115	118	-	MD 8.6 lower (10.98 to 6.22 lower)	⊕⊕OO LOW	IMPORTANT
HADS (hospital anxiety and depression) - anxiety pure mild (follow-up mean 1-3 months; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	165	168	-	MD 0.81 lower (1.44 to 0.18 lower)	⊕⊕OO LOW	IMPORTANT
HADS (hospital anxiety and depression) - depression pure mild (follow-up mean 1-3 months; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	165	168	-	MD 1.61 lower (2.24 to 0.99 lower)	⊕OOO VERY LOW	IMPORTANT
ESS pure mild (follow-up mean 1-3 months; Better indicated by lower values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	165	168	-	MD 2.87 lower (3.62 to 2.11 lower)	⊕OOO VERY LOW	IMPORTANT
Preference pure mild (follow-up mean 1 months)												
2	randomised trials	very serious[1]	serious[3]	no serious indirectness	serious[2]	None	24/50 (48%)	26/50 (52%)	RR 1.03 (0.44 to 2.4)	16 more per 1000 (from 291 fewer to 728 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events pure mild (follow-up mean 1 months)												

ISBN: 978-1-4731-4220-9

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	23/34 (67.6%)	8/34 (23.5%)	RR 2.88 (1.5 to 5.5)	442 more per 1000 (from 118 more to 1000 more)	⊕⊕OO LOW	IMPORTANT
Driving outcomes - SteerClear (obstacles hit) 30 minute test pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 0.5 lower (23.69 lower to 22.69 higher)	⊕OOO VERY LOW	IMPORTANT
Driving outcomes - SteerClear (obstacles hit) 60 minute test pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	16	16	-	MD 0.5 lower (23.69 lower to 22.69 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Block design score pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	34	34	-	MD 1 lower (6.25 lower to 4.25 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Trailmaking A(sec) pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	34	34	-	MD 3 lower (8.23 lower to 2.23 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Trailmaking B(sec) pure mild (follow-up mean 1 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	50	50	-	MD 5.68 lower (17.52 lower to 6.16 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Performance IQ score pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	34	34	-	MD 1 higher (7.8 lower to 9.8 higher)	⊕OOO VERY LOW	IMPORTANT

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Neurocognitive outcomes - IQ decrement score pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 1.7 higher (7.46 lower to 10.86 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - PASAT 2-(sec) (Correct) pure mild (follow-up mean 1 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	50	50	-	MD 3.5 higher (1.39 lower to 8.39 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitve outcomes RVIPT (correct) pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 2.1 higher (6.77 lower to 10.97 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Median eight choice reaction time (ms) pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 9 higher (35.35 lower to 53.35 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - Verbal fluency (total words) pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 0.7 lower (9.86 lower to 8.46 higher)	⊕OOO VERY LOW	IMPORTANT
Neurocognitive outcomes - BVRT (correct) pure mild (follow-up mean 1 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	16	16	-	MD 0 higher (1.66 lower to 1.66 higher)	⊕OOO VERY LOW	IMPORTANT

[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 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; FOSQ- 2; ESS -2.5; SAQLI – 2. GRADE default MIDs (0.5XSD) used for all other continuous outcomes.
[3] Downgraded by 1 or 2 increments for heterogeneity, unexplained by sub-group analysis. Random effect analysis used.

Table 17: Clinical evidence profile: CPAP compared to Placebo/Standard care mixed severity population (mean AHI 5 -15)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Placebo/Standard care	Relative (95% CI)	Absolute		
SF 36 mental mixed population (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	165	158	-	MD 3.5 higher (1.22 to 5.78 higher)	⊕OOO VERY LOW	CRITICAL
SF 36 Energy/Vitality Mixed population (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	171	168	-	MD 6.7 higher (2.08 to 11.32 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D ESS <9 Mixed severity population (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	110	107	-	MD 0.03 higher (0.02 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
EQ5D (VAS score) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	110	108	-	MD 5.2 higher (0.68 to 9.72 higher)	⊕OOO VERY LOW	IMPORTANT
SAQLI Mixed severity population (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	167	163	-	MD 0.6 higher (0.35 to 0.85 higher)	⊕OOO VERY LOW	IMPORTANT
FOSQ Mixed severity (follow-up mean 2 months; Better indicated by higher values)												

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1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	None	113	110	-	MD 1.12 higher (0.4 to 1.84 higher)	⊕⊕⊕O MODERATE	CRITICAL
ESS mixed population (follow-up mean 2 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	113	110	-	MD 2.1 lower (3.13 to 1.07 lower)	⊕⊕OO LOW	IMPORTANT
ODI mixed population (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	171	170	-	MD 7.4 lower (9.85 to 4.95 lower)	⊕OOO VERY LOW	IMPORTANT
Adherence Mixed severity (follow-up mean 2 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	113	110	-	MD 0.9 higher (0.36 to 1.44 higher)	⊕⊕OO LOW	IMPORTANT
Adverse events Mixed severity (follow-up mean 2 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	None	93/121 (76.9%)	92/118 (78%)	RR 0.99 (0.86 to 1.13)	8 fewer per 1000 (from 109 fewer to 101 more)	⊕⊕OO LOW	IMPORTANT
Systolic blood pressure (24 hour) mixed severity population (follow-up mean 2 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	None	154	156	-	MD 1.3 higher (1.68 lower to 4.28 higher)	⊕OOO VERY LOW	IMPORTANT
24 hour systolic blood pressure (change value) (follow-up 8 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	28	28	-	MD 0.5 higher (3.77 lower to 4.77 higher)	⊕OOO VERY LOW	IMPORTANT
24 hour diastolic blood pressure (change value) (follow-up 8 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28	28	-	MD 0.9 lower (11.07 lower to 9.27 higher)	⊕OOO VERY LOW	IMPORTANT

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Patient preference (follow-up 8 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12/28 (42.9%)	57.1%	RR 0.75 (0.44 to 1.28)	143 fewer per 1000 (from 320 fewer to 160 more)	⊕OOO VERY LOW	IMPORTANT

[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; FOSQ- 2 ; ESS -2.5; SAQLI – 2. GRADE default MIDs (0.5XSD) used for all other continuous outcomes.

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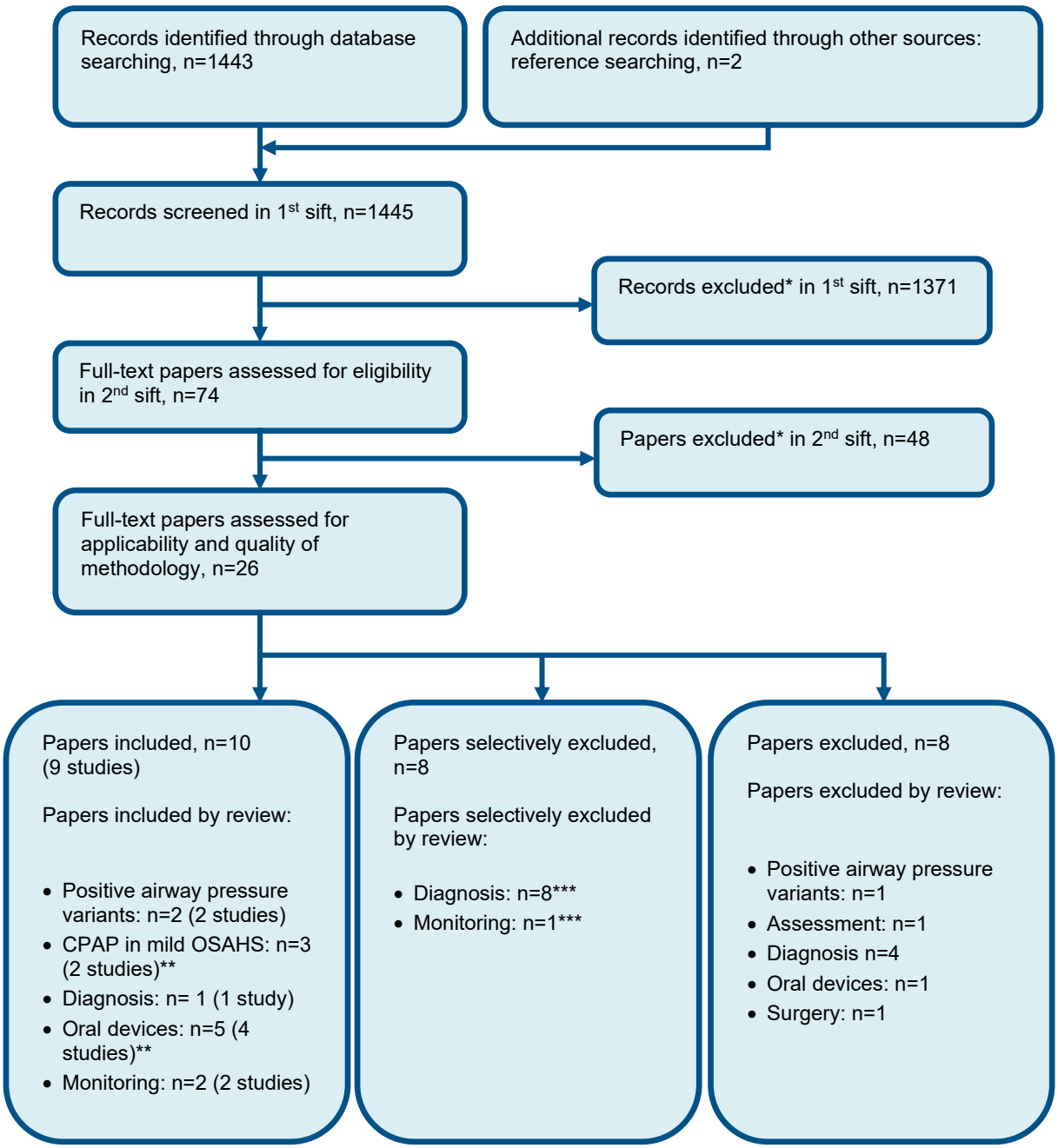
Appendix G: Health economic evidence selection

Figure 42: 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

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Appendix H: Health economic evidence tables

Study	Sharples 2014[178]			
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 (3−1): £2,191 (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 (3−1): 0.304 (95% CI: NR; p=NR) Incremental (3−2): 0.019 (95% CI: NR; p=NR)	**ICER (Intervention 3 versus Intervention 1):** £7,207 per QALY gained 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **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) =

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	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.				

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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 populations 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 would is not an accurate representation of real life. There is uncertainty around the calculations for the costs of CPAP, as the unit costs section indicates that the acute costs (year 1) are lower than the ongoing costs (per year thereafter). Given that in the acute phases patients may require device titration, education and setup of device and a review appointment, the acute costs would be expected to be higher. Therefore it appears the costs for CPAP may have been underestimated.
Overall applicability: Directly Applicable[c] **Overall quality:** Very 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 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

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Study	Weatherly 2009[205] and full report in McDaid 2009[135]			
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 mild sleep apnoea[(b)] **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:** 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.	**Total costs (mean per patient):** Intervention 1: £21 Intervention 2: £2,726 Incremental (2−1): £2705 (95% CI: NR; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** CPAP machine, staff time for CPAP/dental device setup and ongoing intervention management	**QALYs (mean per patient):** Intervention 1: 14.56 Intervention 2: 14.69 Incremental (2−1): 0.13 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £20,585 per QALY gained 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 43%/68%
Data sources				
Health outcomes: The authors conducted a systematic review to identify the clinical effectiveness of 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:** Mild OSAHS was defined using the 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. There is uncertainty around the calculations for the costs of CPAP, as the unit costs section indicates that the acute costs (year 1) are lower than the ongoing costs (per year thereafter). Given that in the acute phases patients may require device titration, education and setup of device and a review appointment, the acute costs would be expected to be higher. Therefore it appears the costs for CPAP may have been underestimated.
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 assumptions 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

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Reference	Reason for exclusion
Aarab 2005[3]	Inappropriate intervention/inappropriate comparison
Aarab 2011[1]	Wrong population – Not mild OSAHS
Aarab 2011[2]	Wrong population – Not mild OSAHS
Aarab 2017[4]	Wrong population – Not mild OSAHS
Aaronson 2016[5]	Wrong population – Not mild OSAHS
Abuzaid 2017[6]	Systematic review - references checked
Aggarwal 2014[7]	Systematic review - references checked
Aloia 2003[8]	Wrong population – Not mild OSAHS
Alshaer 2018[9]	Wrong population – Not mild OSAHS
Ancoli-Israel 2008[10]	Wrong population – Not mild OSAHS
Anonymous 2014[11]	Abstract
Anonymous 2015[12]	Abstract
Antic 2015[13]	Wrong population – Not mild OSAHS
Antonopoulos 2011[14]	Systematic review - references checked
Aslan 2018[15]	Systematic review - references checked
Baessler 2013[16]	Systematic review - references checked
Barbe 2010[17]	Wrong population – Not mild OSAHS
Barbe 2012[18]	Wrong population – Not mild OSAHS
Bardwell 2001[19]	Wrong population – Not mild OSAHS
Bardwell 2007[20]	Wrong population – Not mild OSAHS
Barnes 2004[22]	Wrong population – Not mild OSAHS
Bazzano 2007[23]	Systematic review - references checked
Becker 2003[24]	Wrong population – Not mild OSAHS
Berry 2011[25]	Inappropriate intervention
Bradley 2001[26]	Wrong population – Not mild OSAHS
Bratton, 2014[28]	Systematic review - references checked
Bratton 2015[27]	Systematic review - references checked
Bravata 2010[29]	Wrong population – Not mild OSAHS
Bravata 2011[30]	Wrong population – Not mild OSAHS
Brill 2018[31]	Systematic review - references checked
Brown 2013[32]	Inappropriate comparison/wrong population
Brown 2020[33]	inappropriate study design/ no relevant outcomes - rationale and methods of the trial
Cammaroto 2017[34]	Systematic review - references checked
Campos-Rodriguez 2006[35]	Wrong population – Not mild OSAHS
Chen 2014[43]	Systematic review - references checked
Chen 2014[37]	Systematic review - references checked

Reference	Reason for exclusion
Chen 2015[41]	Systematic review - references checked
Chen 2015[38]	Systematic review - references checked
Chen 2015[42]	Systematic review - references checked
Chen 2017[36]	Systematic review - references checked
Chen 2017[39]	Systematic review - references checked
Chen 2018[40]	Systematic review - references checked
Chirakalwasan 2018[44]	No relevant outcomes- main outcome was glucose metabolism, pregnancy outcomes were collected
Christou 2009[45]	Wrong population – Not mild OSAHS
Colrain 2013[46]	Wrong population – Not mild OSAHS
Comondore 2009[47]	Wrong population – Not mild OSAHS
Coughlin 2007[48]	Wrong population – Not mild OSAHS
Craig 2015[49]	No relevant outcomes
Crawford 2012[51]	Systematic review - references checked
Davies 1993[52]	Wrong population – Not mild OSAHS
de Araujo 2013[53]	Wrong population – Not mild OSAHS
de Vries 2018[54]	Systematic review - references checked
Deng 2018[55]	Systematic review - references checked
Dimsdale 2000[56]	Wrong population – Not mild OSAHS
Drager 2007[57]	Wrong population – Not mild OSAHS
Duran-Cantolla 2010[58]	Wrong population – Not mild OSAHS
Egea 2008[59]	Wrong population – Not mild OSAHS
El-Solh 2017[60]	Wrong population – Not mild OSAHS
Engleman 1994[62]	Wrong population – Not mild OSAHS
Engleman 1998[64]	Wrong population – Not mild OSAHS
Engleman 2002[65]	Wrong population – Not mild OSAHS
Esilva 2014[66]	Abstract
Esquinas 2013[67]	Wrong population – Not mild OSAHS
Faccenda 2001[68]	Wrong population – Not mild OSAHS
Feng 2015[69]	Systematic review - references checked
Ferguson 1996[71]	Wrong population – Not mild OSAHS
Ferguson 1997[70]	Wrong population – Not mild OSAHS
Ferrier 2008[72]	Wrong population – Not mild OSAHS
Friedman 2012[73]	Systematic review - references checked
Gallegos 2014[74]	Incorrect study design
Glantz 2017[75]	Wrong population – Not mild OSAHS
Granton 1996[76]	Wrong population – Not mild OSAHS
Guilleminault 2004[77]	Wrong population – Not mild OSAHS
Guo 2016[78]	Systematic review - references checked
Hack 2001[79]	Inappropriate intervention/inappropriate comparison
Haensel 2007[80]	Wrong population – Not mild OSAHS
Health Quality 2009[81]	Systematic review references checked
Henke 2001[82]	Wrong population – Not mild OSAHS
Hermida 2004[83]	Wrong population – Not mild OSAHS

Reference	Reason for exclusion
Horstmann 2000[84]	Wrong population – Not mild OSAHS
Hoyos 2013[85]	Post script
Hsu 2006[86]	Wrong population – Not mild OSAHS
Hu 2015[87]	Systematic review - references checked
Huang 2015[88]	Wrong population – Not mild OSAHS
Hui 2006[89]	Wrong population – Not mild OSAHS
Iftikhar 2012[91]	Systematic review - references checked
Iftikhar 2013[93]	Systematic review - references checked
Iftikhar 2015[92]	Systematic review - references checked
Iftikhar 2017[90]	Systematic review - references checked
Imran 2016[94]	Systematic review - references checked
Ip 2007[95]	Wrong population – Not mild OSAHS
Jenkinson 1999[96]	Wrong population – Not mild OSAHS
Jing 2008[97]	Systematic review - references checked
Jokic 1999[98]	Wrong population – Not mild OSAHS
Jones 2013[99]	Wrong population – Not mild OSAHS
Joyeux-Faure 2016[101]	Wrong population – Not mild OSAHS
Joyeux-Faure 2018[100]	Wrong population – Not mild OSAHS
Kaneko 2003[102]	Wrong population – Not mild OSAHS
Khayat 2020[103]	wrong population - not mild, ahi in treatment group at baseline 41(21.4) ahi in control group at baseline 37.7(16.8)
Khot 2016[104]	Inappropriate study design/wrong population
Khot 2016[104]	Incorrect study design/wrong population
Kim 2016[105]	Systematic review - references checked
Kohler 2013[106]	Substudy of Mosaic trial
Krogager 2020[107]	Wrong population - not mild, patients with ahi>15
Kuhn 2017[108]	Systematic review - references checked
Kushida 2006[110]	Inappropriate study design
Kushida 2012[109]	Wrong population – Not mild OSAHS
Kylstra 2013[111]	Systematic review - references checked
Labarca 2020[112]	systematic review - references checked (all 4 RCT's included non mild populations)
Lee 2011[114]	Wrong population – Not mild OSAHS
Lee 2012[113]	Wrong population – Not mild OSAHS
Lei 2017[115]	Systematic review - references checked
Lewis 2017[116]	Wrong population – Not mild OSAHS
Li 2013[118]	Systematic review - references checked
Li 2020[117]	systematic review - references checked
Lim 2007[119]	Wrong population – Not mild OSAHS
Lin 2017[120]	Systematic review - references checked
Liu 2016[121]	Systematic review - references checked
Liu 2017[122]	Systematic review - references checked
Loffler 2020[123]	Wrong population - not mild severity, all included patients moderate-severe
Lojander 2008[124]	Wrong population – Not mild OSAHS

Reference	Reason for exclusion
Loredo 1999[125]	Wrong population – Not mild OSAHS
Loredo 2006[126]	Wrong population – Not mild OSAHS
Lozano 2010[127]	Wrong population – Not mild OSAHS
Mansfield 2004[128]	Wrong population – Not mild OSAHS
Marshall 2005[130]	Wrong population – Not mild OSAHS
Marshall 2006[129]	Systematic review - references checked
Martinez-Ceron 2016[131]	Wrong population – Not mild OSAHS
Martinez-Garcia 2013[132]	Wrong population – Not mild OSAHS
Mason 2012[133]	Wrong population – Not mild OSAHS
McArdle 2001[134]	Wrong population – Not mild OSAHS
McMillan 2014[136]	Wrong population – Not mild OSAHS
McMillan 2015[137]	Wrong population – Not mild OSAHS
Meurice 2013[138]	Wrong population – Not mild OSAHS
Minnerup 2012[139]	Wrong population – Not mild OSAHS
Miyauchi 2015[140]	Wrong population – Not mild OSAHS
Monasterio 2001[141]	Wrong population – Not mild OSAHS
Montserrat 2001[142]	Wrong population – Not mild OSAHS
Mostafavi 2017[143]	Inappropriate comparison/wrong population/ no relevant outcomes
Myhill 2012[144]	Wrong population – Not mild OSAHS
Nagappa 2015[145]	Systematic review - references checked
Neikrug 2014[147]	Wrong population – Not mild OSAHS
Ng 2017[148]	Wrong population – Not mild OSAHS
Nikolopoulou 2017[151]	Wrong population – Not mild OSAHS
Nikolopoulou 2020[150]	Wrong population - not mild, AHI in MAD group - 21.4(11), AHI in CPAP 20.1(9), AHI in control group - 19.5(8.4)
O'Gorman 2013[152]	Wrong population – Not mild OSAHS
Oliveira 2009[153]	Wrong population – Not mild OSAHS
Oliveira 2012[154]	Wrong population – Not mild OSAHS
Olson 2008[155]	Not available
Panoutsopoulos 2012[156]	Inappropriate comparison no ASA patients compared to moderate osa patients
Peker 2016[157]	Wrong population – Not mild OSAHS
Peker 2017[158]	Wrong population – Not mild OSAHS
Pepperell 2002[160]	Wrong population – Not mild OSAHS
Pepperell 2003[159]	Wrong population – Not mild OSAHS
Phillips 2008[162]	Wrong population – Not mild OSAHS
Phillips 2011[163]	Wrong population – Not mild OSAHS
Phillips 2013[161]	Wrong population – Not mild OSAHS
Profant 2003[164]	Wrong population – Not mild OSAHS
Quan 2013[165]	Wrong population – Not mild OSAHS
Qureshi 2015[166]	systematic review references checked
Randerath 2002[167]	Wrong population – Not mild OSAHS
Rao 2010[168]	Systematic review - references checked
Redline 1998[169]	Wrong population – Not mild OSAHS

Reference	Reason for exclusion
Robinson 2006[170]	Wrong population – Not mild OSAHS
Rodway 2010[171]	Inappropriate comparison no ASA patients compared to moderate osa patients
Ruttanaumpawan 2009[172]	Wrong population – Not mild OSAHS
Ruzicka 2020[173]	Wrong population - not mild, baseline ahi 38.75 (24.63; 56.75)
Ryan 2011[174]	Wrong population – Not mild OSAHS
Sanchez-de-la-Torre 2015[175]	Wrong population – Not mild OSAHS
Sanchez-de-la-Torre 2020[176]	Wrong population - not mild, baseline ahi in CPAP group 36.4(18.6), baseline ahi in the usual care group - 35.5(18.3)
Schein 2014[177]	Systematic review - references checked
Sharples 2016[179]	Systematic review - references checked
Shechter 2015[181]	Wrong population – Not mild OSAHS
Shechter 2016[180]	Wrong population – Not mild OSAHS
Sin 2000[182]	Wrong population – Not mild OSAHS
Skinner 2004[183]	Wrong population – Not mild OSAHS
Skinner 2004[184]	Wrong population – Not mild OSAHS
Smith 2006[185]	Wrong population – Not mild OSAHS
Smith 2007[186]	Wrong population – Not mild OSAHS
Sun 2013[187]	Systematic review - references checked
Sun 2016[188]	Systematic review - references checked
Sundar 2020[189]	Wrong population - not mild severity, CPAP group AHI - 35.4(37.4), sham CPAP AHI - 30.3 (36.7)
Takaesu 2012[190]	Wrong population – Not mild OSAHS
Tan 1998[191]	Not available
Tan 1998[192]	Not available
Tan 2002[193]	Wrong population – Not mild OSAHS
Teramoto 2008[194]	Wrong population – Not mild OSAHS
Thunstrom 2017[195]	Wrong population – Not mild OSAHS
Tkacova 1997[196]	Wrong population – Not mild OSAHS
Tomfohr 2011[197]	Wrong population – Not mild OSAHS
Tregear 2010[198]	Systematic review references checked
Trzepizur 2009[199]	Wrong population – Not mild OSAHS
Vlachantoni 2013[200]	Systematic review - references checked
von Kanel 2006[201]	Wrong population – Not mild OSAHS
Wang 2015[202]	Systematic review - references checked
Wang 2015[203]	Systematic review - references checked
Wang 2018[204]	Systematic review - references checked
West 2007[208]	Wrong population – Not mild OSAHS
West 2009[207]	Wrong population – Not mild OSAHS
Xie 2013[210]	Systematic review - references checked
Xu 2014[211]	Systematic review - references checked
Yosunkaya 2015[212]	Wrong population – Not mild OSAHS
Zhang 2015[214]	Systematic review - references checked
Zhang 2016[213]	Systematic review - references checked

Reference	Reason for exclusion
Zhao 2006[215]	Wrong population – Not mild OSAHS
Zhu 2018[216]	Systematic review - references checked

I.2 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:

None.