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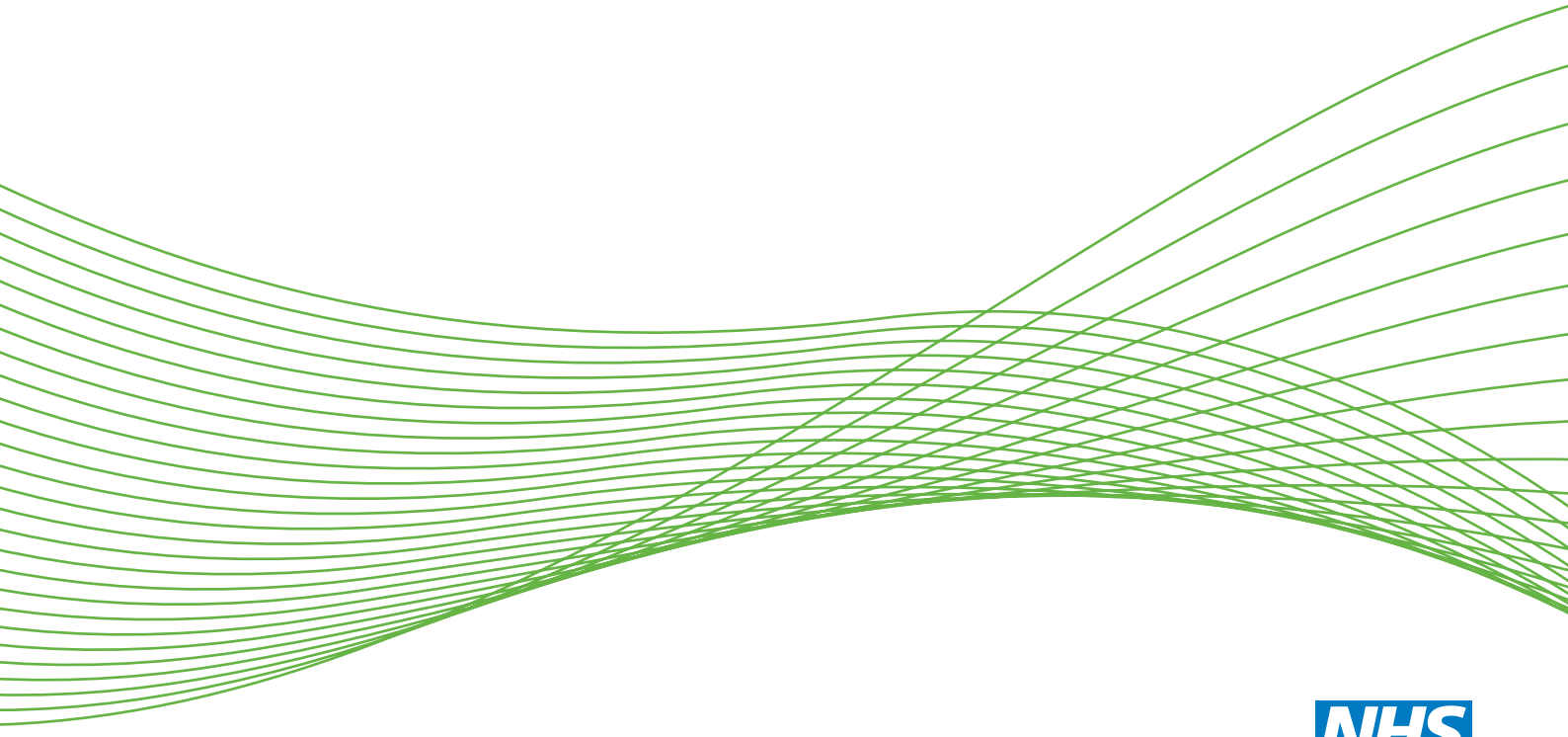

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Abstract

A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT

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Background: The therapeutic and economic benefits of continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea syndrome (OSAS) have been established in middle-aged people. In older people there is a lack of evidence.

Objective: To determine the clinical efficacy of CPAP in older people with OSAS and to establish its cost-effectiveness.

Design: A randomised, parallel, investigator-blinded multicentre trial with within-trial and model-based cost-effectiveness analysis.

Methods: Two hundred and seventy-eight patients, aged $\geq$ 65 years with newly diagnosed OSAS [defined as oxygen desaturation index at $\geq$ 4% desaturation threshold level for > 7.5 events/hour and Epworth Sleepiness Scale (ESS) score of $\geq$ 9] recruited from 14 hospital-based sleep services across the UK.

Interventions: CPAP with best supportive care (BSC) or BSC alone. Autotitrating CPAP was initiated using standard clinical practice. BSC was structured advice on minimising sleepiness.

Coprimary outcomes: Subjective sleepiness at 3 months, as measured by the ESS (ESS mean score: months 3 and 4) and cost-effectiveness over 12 months, as measured in quality-adjusted life-years (QALYs) calculated using the European Quality of Life-5 Dimensions (EQ-5D) and health-care resource use, information on which was collected monthly from patient diaries.

Secondary outcomes: Subjective sleepiness at 12 months (ESS mean score: months 10, 11 and 12) and objective sleepiness, disease-specific and generic quality of life, mood, functionality, nocturia, mobility, accidents, cognitive function, cardiovascular risk factors and events at 3 and 12 months.

Results: Two hundred and seventy-eight patients were randomised to CPAP ($n = 140$) or BSC ($n = 138$) over 27 months and 231 (83%) patients completed the trial. Baseline ESS score was similar in both groups [mean (standard deviation; SD) CPAP 11.5 (3.3), BSC 11.4 (4.2)]; groups were well balanced for other characteristics. The mean (SD) in ESS score at 3 months was –3.8 (0.4) in the CPAP group and –1.6 (0.3) in the BSC group. The adjusted treatment effect of CPAP compared with BSC was –2.1 points [95% confidence interval (CI) –3.0 to –1.3 points; $p < 0.001$]. At 12 months the effect was –2.0 points (95% CI –2.8 to –1.2 points; $p < 0.001$). The effect was greater in patients with increased CPAP use or higher baseline ESS score. The number of QALYs calculated using the EQ-5D was marginally (0.005) higher with CPAP than with BSC (95% CI –0.034 to 0.044). The average cost per patient was £1363 (95% CI £1121 to £1606) for those allocated to CPAP and £1389 (95% CI £1116 to £1662) for those allocated to BSC. On average, costs were lower in the CPAP group (mean –£35; 95% CI –£390 to £321). The probability that CPAP was cost-effective at thresholds conventionally used by the NHS (£20,000 per QALY gained) was 0.61. QALYs calculated using the Short Form questionnaire-6 Dimensions were 0.018 higher in the CPAP group (95% CI 0.003 to 0.034 QALYs) and the probability that CPAP was cost-effective was 0.96. CPAP decreased objective sleepiness ($p = 0.02$), increased mobility ($p = 0.03$) and reduced total and low-density lipoprotein cholesterol ($p = 0.05$, $p = 0.04$, respectively) at 3 months but not at 12 months. In the BSC group, there was a fall in systolic blood pressure of 3.7 mmHg at 12 months, which was not seen in the CPAP group ($p = 0.04$). Mood, functionality, nocturia, accidents, cognitive function and cardiovascular events were unchanged. There were no medically significant harms attributable to CPAP.

Conclusion: In older people with OSAS, CPAP reduces sleepiness and is marginally more cost-effective than BSC over 12 months. Further work is required in the identification of potential biomarkers of sleepiness and those patients at increased risk of cognitive impairment. Early detection of which could be used to inform the clinician when in the disease cycle treatment is needed to avert central nervous system sequelae and to assist patients decision-making regarding treatment and compliance. Treatment adherence is also a challenge in clinical trials generally, and adherence to CPAP therapy in particular is a recognised concern in both research studies and clinical practice. Suggested research priorities would include a focus on optimisation of CPAP delivery or support and embracing the technological advances currently available. Finally, the improvements in quality of life in trials do not appear to reflect the dramatic changes noted in clinical practice. There should be a greater focus on patient centred outcomes which would better capture the symptomatic improvement with CPAP treatment and translate these improvements into outcomes which could be used in health economic analysis.

Trial registration: Current Controlled Trials ISRCTN90464927.

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List of abbreviations

BMI	body mass index
BP	blood pressure
BSC	best supportive care
CHD	coronary heart disease
CI	confidence interval
CPAP	continuous positive airway pressure
CRF	case report form
DSS	Digit Symbol Substitution
EQ-5D	European Quality of Life-5 Dimensions
ESS	Epworth Sleepiness Scale
FEV_1	forced expiratory volume in 1 second
FP	fractional polynomial
FVC	forced vital capacity
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HbA_{1c}	glycated haemoglobin
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IQR	interquartile range
LDL	low-density lipoprotein
MCS	mental component summary scale
MI	myocardial infarction
MMSE	Mini Mental State Examination
MRC CTU	Medical Research Council Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ODI	oxygen desaturation index
ORTU	Oxford Respiratory Trials Unit
OSA	obstructive sleep apnoea
OSAS	obstructive sleep apnoea syndrome
OSLER	Oxford Sleep Resistance
PCS	physical component summary scale
PIS	patient information sheet
PREDICT	Positive Airway Pressure in Older People: a randomised controlled trial
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
RTA	road traffic accident
SAQLI	Sleep Apnoea Quality of Life Index
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
SF-6D	Short Form questionnaire-6 Dimensions
TDS	Townsend Disability Scale
TMG	Trial Management Group
TMT–B	Trail Making Test Part B
TSC	Trial Steering Committee
TUG	Timed Up and Go

Plain English summary

Obstructive sleep apnoea (OSA) is a condition in which the walls of the throat relax during sleep, repeatedly blocking the airway for a few seconds, which disrupts sleep and makes some people very sleepy in the daytime. OSA affects up to one in five older people, so as more people get older the best treatment needs to be found. OSA can be treated with continuous positive airway pressure (CPAP), in which the patient breathes pressurised air through a mask, keeping the throat open. CPAP is already known to help middle-aged people with OSA, but the benefit in older people is unknown.

We carried out the trial in 278 people with OSA syndrome (which means OSA plus symptoms of sleepiness) aged > 65 years in UK sleep centres. Some patients were randomly allocated to receive CPAP and some to receive their usual care without CPAP. We measured daytime sleepiness and treatment costs for 12 months. We took steps to avoid a biased result by ensuring that the researchers assessing the sleepiness were unaware of which treatment the patients received.

Our results showed that OSA syndrome patients treated with CPAP had significantly less daytime sleepiness than those who did not receive CPAP. We believe that this result is reliable because 83% of the patients who started the trial completed it. A comparison of the costs of treatment suggests that CPAP would meet the usual criteria for being funded by the NHS.

Overall, this study supports the use of CPAP in older people with OSA syndrome and shows that it would be good value for money in the NHS.

Scientific summary

Background

Obstructive sleep apnoea syndrome (OSAS) is a disorder which gives rise to breathing difficulties during sleep as a result of repetitive closure of the pharyngeal airway. The resulting sleep disruption sometimes leads to severe daytime sleepiness, high blood pressure (BP) and a possible increased risk of heart attack, stroke and neurocognitive dysfunction. OSAS is the third most common respiratory disorder, after asthma and chronic obstructive pulmonary disease. In its severe form it affects from 2–4% of middle-aged people. In older people, the prevalence is much greater, with up to 20% of older people having OSAS.

Obstructive sleep apnoea syndrome can be treated with continuous positive airway pressure (CPAP), which stops the pharyngeal airway closure, thereby normalising breathing. A recent report by the National Institute for Health and Care Excellence concluded that CPAP is clinically effective at reducing sleepiness and is a cost-effective treatment for OSAS in middle-aged people. However, these beneficial effects of CPAP are not generalised across all groups with OSAS, including older people. This is because older patients with OSAS appear to experience fewer symptoms of sleepiness and therefore may receive less benefit from treatment. In the older population there are also likely to be many other causes of sleepiness, making it more difficult to know what symptoms are a result of OSA. Prior to the publication of this report, very little information was available for clinicians and health-care professionals regarding the best way to treat OSAS in older people, and even less information was available about how CPAP treatment impacted on quality of life and about its cost-effectiveness in this population.

Objectives

Positive Airway Pressure in Older People: a randomised controlled trial (PREDICT) aimed to determine the clinical efficacy of CPAP in older people with OSAS by way of reducing subjective sleepiness and to establish its cost-effectiveness. A number of secondary outcomes, focusing on the important consequences of untreated OSAS, were also measured, including neurocognitive function, road traffic accidents (RTAs), changes in BP and metabolism. More general aspects thought to reflect successful treatment of a chronic condition, such as improvements in mobility, quality of life overall and the use of health-care resources such as visits to a general practitioner or hospital for treatment, were also measured. Adherence to CPAP treatment was the tertiary outcome measure. Patients also recorded any side effects of CPAP treatment. The specific outcomes are listed below.

Coprimary outcomes

1. Subjective sleepiness at 3 months was assessed using the Epworth Sleepiness Scale (ESS) mean score at months 3 and 4, answering the question ‘Is CPAP clinically effective at 3 months?’ The ESS is a well-established and validated scale for measuring subjective sleepiness; a reduction in ESS score reflects symptom improvement.
2. Cost-effectiveness over 12 months was assessed using the European Quality of Life-5 Dimensions (EQ-5D), and health-care resource use was measured monthly over the duration of the trial. Costs were evaluated from the NHS perspective, and health outcomes were expressed as quality-adjusted life-years (QALYs).

Secondary outcomes

1. Subjective sleepiness at 12 months: the ESS mean scores at months 10, 11 and 12 were used to answer the question 'Is CPAP cost-effective at 12 months?'

The following outcomes were measured at 3 and 12 months:

1. objective sleepiness, measured using the Oxford Sleep Resistance (OSLER) test
2. quality of life and mood, assessed using the Short Form questionnaire-36 items (SF-36), the Sleep Apnoea Quality of Life Index (SAQLI; a disease-specific sleep apnoea questionnaire which included CPAP side effects) and the Hospital Anxiety and Depression Scale
3. functionality, as measured using the Townsend Disability Scale
4. nocturia, as self-reported frequency
5. mobility according to Timed Up and Go test
6. self-reported road accidents
7. cognitive function determined by the Mini-Mental State Examination, Trail Making Test Part B, Digit Symbol Substitution test and simple and four-choice reaction time test
8. cardiovascular risk factors, such as systolic and diastolic BPs and fasting blood profile
9. new cardiovascular events, including myocardial infarction, stroke, transient ischaemic attack, angina, atrial fibrillation and peripheral vascular disease.

Tertiary outcome

Treatment compliance was measured objectively, by downloading data from the CPAP machines at 3- and 12-month assessments.

Methods

Design

This was a randomised, parallel, investigator-blinded multicentre trial over 12 months. Consecutive eligible patients were offered trial entry. Patients had to be 65 years or older with newly diagnosed OSAS at enrolment. The diagnosis of OSAS was based on a routine clinical sleep study performed in the recruiting centres. The severity of OSAS was defined as oxygen desaturation index (ODI) at $\geq 4\%$ desaturation threshold level for > 7.5 events/hour and an ESS score of ≥ 9. All enrolled patients also underwent a domiciliary overnight respiratory polygraphy (Embletta® GOLD™, Embla®, Amsterdam, the Netherlands).

Setting and team

The trial took place in NHS sleep clinics across the UK: Scotland (Edinburgh), Wales (Newport) and England (12 centres). These centres had expertise in the assessment and treatment of OSAS. The cost-effectiveness analysis was carried out by the Centre for Health Economics, York. The Medical Research Council Clinical Trials Unit (MRC CTU) allocated the randomisation codes and carried out the clinical analysis. The trial was managed by the Oxford Respiratory Trial Unit and Imperial College London and monitored by Trial Steering and Data Monitoring Committees. An industrial partner [ResMed (UK) Ltd] supported the trial by providing the CPAP machines and loaning the equipment required for the sleep studies.

Interventions

Patients were randomised (1 : 1) to CPAP with best supportive care (BSC) or BSC alone for 12 months. Patients assigned to CPAP were established on autotitrating CPAP delivered using the standard clinical protocols in the recruiting centres. BSC was defined as advice on minimising daytime sleepiness through improved sleep hygiene, using naps or caffeine as required and weight loss if appropriate, which was summarised in a booklet format. A booklet containing this information was compiled by the trial

management team and provided to all patients. This could also be supplemented with information routinely given at each centre.

Patients were randomised centrally by the MRC CTU using computer-generated randomisation. The allocation group was revealed by telephone to the person initiating the intervention once baseline data collection was complete. Structured assessments were performed at baseline, 3 and 12 months. All patients received a telephone call at 1 week, 1 month and 6 months to record symptoms and side effects and to optimise CPAP adherence. Patients also completed monthly diaries recording symptoms, side effects, health-care resource use, change in medications, functionality and quality-of-life questionnaires. Domiciliary overnight pulse oximetry was performed at 3 and 12 months.

Analysis

All analyses were pre-specified in the analysis plan. Analysis was by intention to treat with adjustment for treatment allocation, minimisation factors and the corresponding baseline variable of the outcome using standard statistical techniques and incorporating multiple imputation analysis.

Cost-effectiveness analysis took the perspective of the UK NHS over a time horizon of 1 year. Health outcomes were expressed as QALYs using EQ-5D and Short Form-6 dimensions (SF-6D) derived from the SF-36.

Results

From February 2010 to May 2012, 278 patients were randomised. Follow-up visits were conducted in 245 (88%) and 231 (83%) patients at 3 and 12 months, respectively. Overall, 231 (83%) patients completed the trial. Mean (standard deviation; SD) age was 70.6 years (SD 4.7 years; range 65–89 years), ODI 28.7 (SD 19.1) events/hour (range 0.4–120.4 events/hour) and ESS score of 11.6 (SD 3.7; range 4–22).

In total, 140 patients were randomised to CPAP and 138 to BSC. Baseline ESS score was similar between groups, mean (SD) 11.5 (SD 3.3) CPAP and 11.4 (SD 4.2) BSC. The demographics and clinical characteristics were broadly similar between the two groups.

Coprimary outcomes

1. Subjective sleepiness at 3 months: there was a significant reduction in ESS score at 3 months in patients allocated to CPAP was –3.8 (SD 0.4) compared with BSC –1.6 (SD 0.3), with a difference of –2.1 [95% confidence interval (CI) –3.0 to –1.3; $p < 0.001$]. The treatment effect was significantly greater in patients with higher baseline ESS score or higher CPAP use.
2. Cost-effectiveness at 12 months: the average QALYs obtained using the EQ-5D were 0.680 (95% CI 0.638 to 0.722) QALYs for CPAP and 0.666 (95% CI 0.627 to 0.705) QALYs for BSC. The relative increase in QALYs with CPAP was 0.005 (95% CI –0.034 to 0.044). The average cost per patient allocated to CPAP was £1363 (95% CI £1121 to £1606) and for BSC was £1389 (95% CI £1116 to £1662).

Overall, the CPAP group accrued on average –£35 (95% CI –£390 to £321) lower costs. The results were not sensitive to different assumptions regarding missing data, although they were sensitive to different scenarios regarding the cost of equipment. In addition, the probability of CPAP being cost-effective was more certain in patients with higher baseline ESS scores. The probability that the intervention was cost-effective at the thresholds conventionally used in the NHS (£20,000 per QALY gained) was 0.61.

Secondary outcomes

1. The improvement in the ESS score on CPAP was maintained at 12 months [treatment effect –2.0 (95% CI –2.8 to –1.2; $p < 0.001$)].
2. When cost-effectiveness was assessed using SF-6D, CPAP improved QALYs by 0.018 (95% CI 0.003 to 0.034) and the probability of CPAP being cost-effective was 0.96.
3. Objective sleepiness was significantly reduced at 3 months ($p = 0.02$) but less so at 12 months ($p = 0.06$).
4. Mobility was reduced at 3 months ($p = 0.03$) but not at 12 months ($p = 0.8$).
5. The energy/vitality domain of the SF-36 improved at 3 months ($p = 0.001$) and 12 months ($p = 0.004$); this was also the case for the disease-specific quality-of-life SAQLI (3 months $p = 0.005$; 12 months $p = 0.001$).
6. CPAP improved total and low-density lipoprotein cholesterol at 3 months [treatment effect –0.2 mmol/l (95% CI –0.3 to 0.0 mmol/l; $p = 0.05$) and –0.15 mmol/l (95% CI –0.29 to –0.01 mmol/l; $p = 0.04$), respectively], but the effect was not sustained at 12 months.
7. There was a treatment effect on systolic BP, which was 3.7 mmHg (95% CI 0.2 to 7.3 mmHg; $p = 0.04$) lower at 12 months, which was entirely attributable to a fall in systolic BP in the BSC group.
8. The incidence of new cardiovascular events did not differ between groups at 3 ($p = 0.48$) or 12 months ($p = 0.72$). Atrial fibrillation was the predominant new pathology.
9. Measures of mood, functionality, nocturia, accidents and cognitive function were unchanged at 3 and 12 months.

Tertiary outcome

Of the 140 patients randomised to CPAP, 120 (86%) at 3 months and 99 (71%) at 12 months reported they were still using CPAP. CPAP usage data were obtained in 117 patients at 3 months [median duration of use 1 hour 52 minutes/night; interquartile range (IQR) 0 hours 19 minutes to 5 hours 12 minutes/night] and in 102 patients at 12 months (median usage 2 hours 22 minutes/night; IQR 0 hours 10 minutes to 5 hours 9 minutes/night).

Serious adverse events

There were 37 serious adverse events, all of which were independently classified as unrelated to the trial: in the CPAP group there were 15 serious adverse events (including one death) in 12 patients and in the BSC group there were 22 serious adverse events (including one death) in 13 patients. CPAP was associated with several common self-reported side effects, such as dry mouth. There was no clinically important harm from CPAP use.

Conclusions

This trial found that CPAP reduced subjective sleepiness in older people with OSAS at 3 months, despite low overall CPAP usage. The beneficial effects were maintained at 12 months and the magnitude of the improvements was similar to that seen in middle-aged patients treated with CPAP.

The reduction in subjective sleepiness was corroborated by a significant improvement in objective sleepiness measured by the OSLER test at 3 months. Quality of life, assessed using the SAQLI and SF-6D, was significantly improved by CPAP.

Overall, the economic benefit of CPAP was linked to potential reduction in health-care use, offsetting the cost of the CPAP equipment, although the EQ-5D may not have been the appropriate measure to use in this disease group.

Secondary outcomes related to cognitive function did not differ between the two groups despite reductions in sleepiness in the CPAP group. In addition, mood, which may impact on cognitive function, did not change. Nor were other secondary outcomes, nocturia and RTAs, improved with CPAP, which may reflect their multifactorial aetiologies.

In terms of the cardiovascular outcomes, there was a significant reduction in total cholesterol at 3 months in the CPAP group, but this was not sustained at 12 months. CPAP produced no improvement in BP. In the BSC group, systolic BP fell, an observation previously reported and difficult to explain.

The mean CPAP usage was low at 3 and 12 months, although similar to other trials in minimally symptomatic OSAS patients. Adopting a standard clinical approach rather than an intensive trial approach may have resulted in lower CPAP use. In addition, other factors, such as reduced social support, may have contributed to lower CPAP adherence, since 50% of the patients reported sleeping alone.

Limitations and strengths

A possible limitation of this trial was that sham CPAP was not used as a comparator, although any placebo effect there might have been in the CPAP group is very likely to have disappeared by 12 months. In addition, the objective OSLER test and the dose–response relationship between the treatment effect and CPAP usage support a real effect.

One of the strengths of this trial was that patients were drawn from geographically diverse areas, with treatment in a real-life clinical setting. PREDICT has also been the longest randomised CPAP treatment trial in OSAS, assessing both clinical and economic benefits. In addition, it is one of the first trials specifically aimed at older people ($\geq$ 65 years).

Generalisability

The trial did not focus on asymptomatic older people with OSA and, although it could be argued that the patients studied had a relatively low mean ESS score at baseline, they were sufficiently symptomatic to seek treatment. At the other end of the disease spectrum, exclusion of highly symptomatic OSAS patients (20%) in whom CPAP was considered mandatory is likely to have diminished the effect size. The exploratory analyses revealed that the treatment effect was larger in patients with a higher baseline ESS score or more frequent CPAP use. Equally, the marginal improvement in cost-effectiveness was more favourable in the more symptomatic patients.

Recommendations

Based on the results of this trial, we suggest that future research:

- focus on how best to optimise CPAP delivery especially in the older patient
- aim to stratify older patients with OSAS according to comorbidities and to assess the effectiveness of CPAP treatment
- define patient-centred outcomes for treatment of OSAS in women and ethnic groups, both of whom are currently under-represented in clinical trials
- explore the hypothesis that OSA in different groups may have different causes anatomically and physiologically, with different consequences.

This last point remains to be investigated and is fundamental to the understanding of OSAS.

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Chapter 1 Introduction

Overview of sleep apnoea

Obstructive sleep apnoea (OSA) is caused by occlusion of the pharyngeal airway during sleep that results in a pause in breathing (apnoea). Each apnoea event or partial occlusion (hypopnoea) is associated with hypoxaemia, and is usually terminated by a brief arousal from sleep and an acute surge in blood pressure (BP).[1] The subsequent sleep disruption leads to symptoms of excessive daytime sleepiness in some,[2] but not all, people with OSA.[3] When OSA occurs with symptoms of excessive daytime sleepiness it is termed obstructive sleep apnoea syndrome (OSAS).

The long-term implications of severe[4] OSAS are considerable in middle-aged people. Daytime sleepiness impairs function and increases accident risk,[5,6] with OSAS patients being two to four times more likely to have road traffic accidents (RTAs) as a result of reduced alertness while driving.[7] OSAS patients are also more likely to experience mood changes[8,9] and reduced quality of life,[10,11] which is often attributed to reduced social functioning and vitality.[12] In addition, there is some evidence of reduced cognitive function,[13–16] although the extent of the neurocognitive deficits in patients with OSA is currently debated.[17]

The cardiovascular impact of OSAS has been established using epidemiological data to show that people with OSA have a threefold increased likelihood of developing hypertension over 4 years, independent of other risk factors.[18,19] In addition, treatment trials in patients with severe OSAS have produced a 2 mmHg to 3 mmHg reduction in BP.[20–22] Untreated severe OSAS may be associated with an increased risk of stroke,[23,24] cardiovascular disease[25–27] and death.[28–30] However, the close association between OSAS and obesity,[31] as well as other disorders that predispose to vascular disease, makes it difficult to determine the risk factors associated with OSAS.[32] This is especially true in older people, who are more likely to have comorbidities.

Obstructive sleep apnoea syndrome in older people

The prevalence of OSAS was reported to be approximately 4% in males and 2% in females in a US cohort of 602 employed men and women (30–60 years).[33] However, more recent estimates from the same cohort predict that up to 14% of males and 5% of females have OSAS.[34,35] This represents a substantial increase since 1990, in part because of the increasing prevalence of obesity[36] and the ageing population. Specifically, the prevalence of OSA (in the absence of daytime sleepiness) appears to increase with age, although there is some evidence to suggest that it plateaus or decreases in the population over the age of 65 years.[37] In a study that used similar criteria to define sleep apnoea in younger and older people, prevalence was eight times higher in community-dwelling older men (65–100 years) compared with 3% in a younger population (20–44 years).[38] *Table 1* reviews in detail the prevalence of OSA and OSAS in older people. The wide variation in estimates is likely to reflect the definitions used to quantify the OSA or OSAS and the different health status of the older populations studied, for example relatively healthy community-dwelling individuals or nursing home residents with comorbidity.

TABLE 1 Prevalence of sleep apnoea in older people

Reference	*n*	Female (%)	Age (years)	Population	Prevalence of OSA (%)	
					AHI (events/hour) ≥ 5	AHI (events/hour) ≥ 10/≥ 15
Carskadon *et al.*, 1981[39]	40	55	62–86	Community	36	–
Coleman *et al.*, 1981[40]	83	28	66 ± 5	Sleep clinic	39	–
McGinty *et al.*, 1982[41]	26	0	64.4 ± 4.4	Community	–	62
Roehrs *et al.*, 1983[42]	97	0	61–81	Sleep clinic	27	–
Smallwood *et al.*, 1983[43]	30	20	50–80	Community	37	–
Yesavage *et al.*, 1985[44]	41	0	69.5 ± 6.5	Both	73	–
Hoch *et al.*, 1986[45]	56	52	69.3 ± 5.4	Community	5	4
Knight *et al.*, 1987[46]	27	NG	75.8 ± 5.9	Primary care	37	–
Mosko *et al.*, 1988[47]	46	65	68.7 ± 6.7	Community	28	16
Ancoli-Israel *et al.*, 1989[48]	233	65	65–101	Nursing home	70	–
Hoch and Reynolds 1990[49]	105	53	60–91	Community	26	13
Philips *et al.*, 1992[50]	92	52	64.2 ± 8.6	Community	15	–
Ancoli-Israel *et al.*, 1995[51]	346	53	72.8 ± 6.1	Community	–	30
	54	57	70.8 ± 6.2	Community	–	32
Bixler *et al.*, 1998[52]	75	0	65–100	Community	31	24
Young *et al.*, 2002[53]	3448	NG	60–99	Community	54	20
Endeshaw *et al.*, 2004[54]	58	76	77.7 ± 6.7	Community	56	19
Haas *et al.*, 2005[55]	3643	52	70.2 ± 6.9	Community	46	20
Hader *et al.*, 2005[56]	80	50	74.1 ± 6.3	General clinic	43	19

–, data is mutually exclusive; AHI, Apnoea–Hypopnoea Index; NG, not given.
Table adapted from Glasser *et al.* Sleep apnoea in older people. *Breathe* 2011;**7**:248–56 (reproduced with permission).

Aetiology of obstructive sleep apnoea syndrome in older people

The high prevalence of OSA in older people has led to debate regarding its causes and the consequences of the disease in this population.[57–59] In middle-aged people, pharyngeal occlusion occurs as a result of a reduction of pharyngeal dilator muscle tone during sleep[60] coupled with excessive extraluminal pressure around the airway, produced by excessive adipose tissue.[61,62] In susceptible individuals these factors lead to airway collapse during sleep. Therefore, it is perhaps not surprising that neck circumference is a significant risk factor for OSA.[63,64] However, in older people, additional factors, such as an age-related reduction in pharyngeal muscle function[65,66] and structural changes to the upper airway, increase the vulnerability to collapse.[67] Specifically, a decrease in the size of the upper airway lumen in older people,[68] associated with an age-related lengthening of the pharyngeal airway in women[69] and a descent of the hyoid bone,[70] creates a predisposition to airway collapse.

Symptoms of obstructive sleep apnoea in older people

Older people report different levels of sleepiness and, compared with younger populations, rate their health differently for the same level of OSA severity.[71] This may be because older people have become habituated to the reduction in sleep quality that occurs as part of the normal ageing process.[72–74] Hence, older people may not suffer symptoms of daytime sleepiness as a result of the further sleep disruption caused by OSA. Alternatively, increased daytime sleepiness may be less debilitating in older people, who have different family and work demands and may have more time for daytime naps. In addition, older populations are more likely to have comorbidities which may cause sleep disruption[75] and polypharmacy contributing to excessive daytime sleepiness.[76] Specifically, nocturia may disturb sleep, and there is some suggestion that OSA exacerbates nocturia.[77,78] Taken together, these factors could modify daytime sleepiness and obscure the symptoms of OSA. Therefore, although excessive sleepiness (regardless of its cause) is associated with increased all-cause mortality in older people,[79] the proportion of sleepiness that is a result of OSA in older people, and hence could be modified by treatment, is unknown.

Both the ageing process[80] and OSA[14,15,81] are associated with a reduction in cognitive function. However, few studies have investigated the impact of OSA on cognitive function in older people. In those studies that have measured cognitive function in older people, cognitive impairment appears to be independently related to both OSA severity and increasing age, but the coexistence of these factors does not further increase dysfunction.[57,82,83] One explanation for the preservation of cognitive function in OSA patients is that neural compensation can overcome the cognitive deficits that are associated with the effects of intermittent hypoxia and/or sleep deprivation on the brain.[84] Whether or not the capacity for neural compensation is decreased in older people, who have less neural reserve, is unknown.[57] Recent data have shown that poorer sleep quality is associated with factors that may accelerate cognitive decline in older people and this finding requires further investigation.[85]

With respect to the cardiovascular impact of OSA in older people, there are limited studies on the long-term consequences. Prospective observational data over 8 years[86] showed that severe OSA in older people is associated with cardiovascular mortality, as it is in middle-aged people. Specifically, the cardiovascular risk in older people with untreated OSAS resulted from increased stroke and heart failure deaths.[23,25,86] However, a potential survival bias in people who have survived into older age means that they may be different in some way from younger people with OSAS. Alternatively, studies in older people with OSA may be selecting those who have developed OSA later in life.

Treatment of obstructive sleep apnoea syndrome

The evidence-based treatment of choice for moderate to severe OSAS in middle-aged patients is continuous positive airway pressure (CPAP) therapy, which modifies the cardinal symptom of excessive daytime sleepiness[20] and is cost-effective.[20,87]

A literature search of the PubMed and The Cochrane Library databases to September 2013 (discussed in more detail in *Chapter 4*, *Reviews for external evidence*), without language restrictions, for full articles reporting randomised controlled trials (RCTs) assessing the efficacy of CPAP treatment in OSAS, in a population with an average age of 60 years or older and the capacity to give informed consent, identified only three studies which included patients with cardiovascular conditions and compared CPAP with sham CPAP[88] or no CPAP.[89,90] None of the studies was conducted in the UK or in a secondary care setting. Furthermore, they did not collect generic measures of health utility. These studies were not generalisable to the overall patient population; consequently, these studies were not used to inform the cost-effectiveness estimates in the health economic model, and which were derived solely from the results of Positive Airway Pressure in Older People: a randomised controlled trial (PREDICT).

Multiple systematic reviews and meta-analyses have assessed the efficacy of CPAP therapy; the most recent and relevant to date being the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) systematic review and economic analysis of CPAP devices for the treatment of OSAS.[20] This review concluded that CPAP is a clinically effective and cost-efficient treatment for moderate to severe OSA in well-defined middle-aged populations. It found that the majority of studies investigating the effect of CPAP treatment had enrolled patients between 44 and 58 years of age. However, it highlighted evidence gaps, with a need for trials in other patient groups, one such group being older people. It concluded that 'clinical trials to define treatment effects at the extremes of age particularly in the elderly where cardiovascular comorbidity complicates assessment would be beneficial'.[20] Therefore, despite the high prevalence of OSA in older people, there is a paucity of evidence on the relative benefits or risks of CPAP treatment in older people. In addition, it cannot be assumed the benefits of CPAP treatment in younger populations will be replicated in older people.

Establishing the efficacy and cost-effectiveness of treatments for all common disease in older populations is a priority for health-care planners. PREDICT was an investigator-initiated project, funded by the HTA programme of the UK NIHR to address the evidence gap and enable the formulation of good-quality guidance on care for older people with OSAS.

Chapter 2 Methods

Trial design

Positive Airway Pressure in Older People: a randomised controlled trial (ISRCTN90464927) was a pragmatic, single-blinded (investigator-blinded), parallel-group, multicentre RCT of 12 months' duration (*Figure 1*).

All patients were randomised to receive CPAP plus best supportive care (BSC) or BSC only. The coprimary outcomes were the clinical effectiveness of CPAP in improving subjective sleepiness at 3 months and the cost-effectiveness of CPAP over the 12-month period.

Recruiting centres

Recruitment took place at secondary and tertiary care referral centres in England, Scotland and Wales, serving a variety of ethnic and social groups, and including both urban and rural areas.

At the start of the trial, patients were recruited through six secondary/tertiary care referral centres: Churchill Hospital (Oxford), Musgrove Park Hospital (Taunton), Royal Brompton Hospital (London), Royal Infirmary Edinburgh (Edinburgh), St James's University Hospital (Leeds) and St Woolos Hospital (Newport). As the trial progressed, a further 18 centres requested to join via NIHR portfolio database; these centres were sent a feasibility questionnaire and subsequently nine further centres were opened, one of which was later closed because of recruitment difficulties. This left eight additional secondary care referral centres:

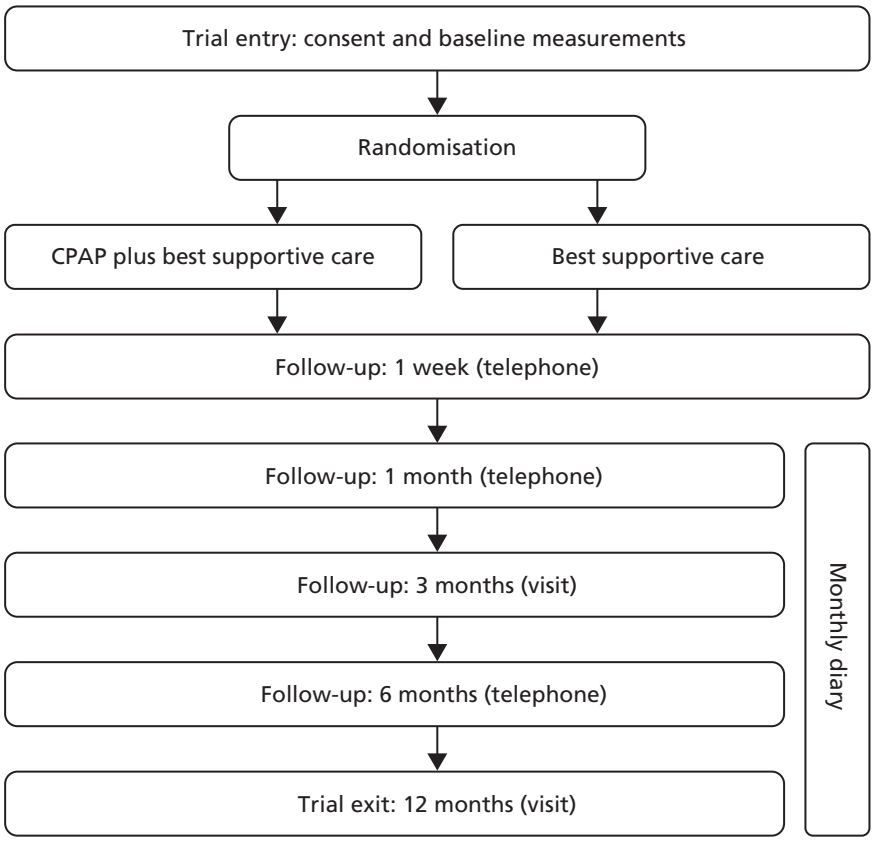

FIGURE 1 Trial design.

Aintree Hospital (Liverpool), Blackpool Victoria Hospital (Blackpool), City General Hospital (Stoke-on-Trent), Freeman Hospital (Newcastle upon Tyne), Great Western Hospital (Swindon), Heartlands Hospital (Birmingham), New Cross Hospital (Wolverhampton) and Royal Berkshire Hospital (Reading). All centres had established sleep services where patients with OSAS are diagnosed and treated with CPAP therapy.

Ethical consideration

The trial was approved via the Integrated Research Application System (National Research Ethics Service/NHS/Health and Social Care Committees) (reference number 09/H0708/33). The trial was also approved by the local NHS Research and Development Office at each site.

Patients

Eligibility criteria

Patients were invited to participate if they were aged ≥ 65 years at the enrolment visit and had newly diagnosed OSAS. OSAS was defined as a oxygen desaturation index (ODI) at ≥ 4% desaturation threshold level for > 7.5 events/hour and an Epworth Sleepiness Scale (ESS) score of ≥ 9. Patients were not admitted to the trial if any of the following criteria applied:

- previous exposure to CPAP therapy
- arterial awake oxygen saturation < 90% on room air
- forced expiratory volume in 1 second (FEV_1)//forced vital capacity (FVC) ratio < 60%
- substantial problems with sleepiness while driving (in those who are still driving)
- currently using heavy goods vehicle or professional service vehicle driving licence
- shift work
- any very severe complication of OSAS such that CPAP therapy was mandatory
- inability to give informed consent or comply with the protocol.

Screening

All patients potentially eligible to participate in the trial were identified from sleep and respiratory clinics predominantly by the principal investigator or nominated research staff member attending outpatient clinics and were initially assessed either by review of case notes or in person.

Once the diagnosis of OSAS was confirmed, based on the normal clinical practice in that centre, they were contacted by the principal investigator or nominated member of staff. Consecutively eligible patients were offered trial entry. Screening logs were kept documenting the number of patients assessed for eligibility and, if applicable, the reasons for non-inclusion.

Informed consent

Patients provided written informed consent at the enrolment visit.

Interventions

Patients were randomised to receive CPAP plus BSC or BSC alone.

Continuous positive airway pressure

Continuous positive airway pressure is the mainstay of medical treatment in middle-aged people with OSAS. CPAP machines are small electric pumps that deliver pressurised air to the upper airway via a hose and tightly fitting plastic mask that is worn over the nose and/or mouth during sleep. The air pressure acts as a pneumatic splint, opening up the airway, particularly at the pharyngeal level, thus preventing the soft

tissue from collapsing. The pressure can be delivered as a fixed optimal pressure, which is usually manually set based on observation or titration during sleep. Alternatively, the pressure can be automatically adjusted, which is known as autotitrating CPAP. The autotitrating CPAP machines automatically increase and decrease the air pressure needed to maintain airway patency through the night, and hence they optimise OSA control. As the pressure delivered is adjusted by autotitrating machines, the mean pressure is often lower than that set on the fixed CPAP machines and therefore they are thought to reduce both the pressure required and associated side effects. However, it is important to note that no clinically important changes in adherence or other outcomes have been found using autotitrating CPAP versus fixed-level CPAP.[91] It has been proposed that autotitrating CPAP may benefit certain subgroups, although these have not yet been identified.[92] Serious side effects from CPAP are thought to be very rare.

There are many variations and adaptations to the delivery of CPAP therapy, such as humidification, which has been shown to prevent upper airway dryness associated with CPAP use,[93] and various delivery interfaces (i.e. the type of mask). A recent systematic review[94] highlighted the lack of research on the impact of different masks on adherence to treatment. Similarly, there is no evidence of increased adherence with humidified CPAP.[20]

The recruitment centres were provided with identical autotitrating CPAP machines and humidification [AutoSet™, ResMed (UK) Ltd, Abingdon, Oxfordshire, UK] and a range of interfaces routinely used in clinical practice. They were asked to initiate CPAP treatment in keeping with their normal clinical practice by staff who were not involved in the trial outcome assessments or data analysis. Humidification and the choice of interface were made according to individual patient preference. At each follow-up visit, data on the hours of CPAP use, delivered pressure and any leaks were downloaded from the CPAP machine. All recruiting centres had established clinical expertise in the diagnosis and treatment of OSAS. The cost of the CPAP equipment will be discussed in *Chapter 4*.

Best supportive care

Best supportive care was defined as the provision of advice on minimising daytime sleepiness through sleep hygiene, using a nap/caffeine sleepiness management strategy and weight loss if appropriate. A booklet containing this information was compiled by the trial management team in conjunction with the Edinburgh and Oxford sleep centres and provided to all patients. This could also be supplemented with information routinely given at each centre.

Evidence for lifestyle modification as an efficacious treatment for OSAS is weak at present; however, lifestyle management is often recommended.[95,96] BSC was used as a comparator in the National Institute for Health and Care Excellence (NICE) HTA systematic review and economic analysis of CPAP machines for the treatment of OSAS.[20] This report showed that trials using BSC as a comparator produced results essentially identical to those from trials using subtherapeutic or sham CPAP as a comparator. Sham devices (CPAP machines that have been modified to deliver subtherapeutic pressure) have been validated as a placebo for CPAP; however, there is no consensus on the ideal comparator in sleep apnoea trials. Alternative comparators such as placebo pills or nasal dilator strips have been used, since it is argued that subtherapeutic CPAP may have an adverse impact on sleep quality. Two of our lead centres had substantial experience and expertise in using sham CPAP (Oxford and Edinburgh); however, these skills were not present across all recruiting centres and would have been difficult to establish widely. In addition, in a recent 6-month RCT, trial retention was lower in those allocated to sham CPAP.[15] BSC was, therefore, chosen as the trial comparator as it improved the simplicity of the trial delivery and was more appropriate for a multicentre design. The greater simplicity of BSC was also thought to be more suitable for a trial with a 12-month follow-up. Additionally, all patients were asked to continue with their normal medication and usual medical care for the duration of the trial.

Assessment

Both groups had identical visit schedules. Structured clinical assessments were performed at baseline and at 3 months and 12 months. Assessment visits were carried out at each local centre. Occasionally, research nurses agreed to see a patient in the patient's own home if he/she was unable to attend the hospital. All patients received a telephone call from their centres at 1 week, 1 month and 6 months to record symptoms and side effects and to optimise CPAP adherence. Additionally, all patients completed monthly diaries recording their ESS score, functionality, quality of life, health-care usage, change in medication, caffeine and alcohol intake, frequency of exercise and any side effects.

All patients enrolled in the trial underwent a domiciliary overnight respiratory polygraphy (Embletta® GOLD™, Embla®, Amsterdam, the Netherlands) prior to treatment allocation, which was scored centrally. Domiciliary overnight pulse oximetry (Pulsox®–300i, Konica-Minolta Inc., Osaka, Japan) was performed at 3 and 12 months. *Table 2* summarises the assessments completed at each time point.

Outcome measures

Coprimary outcomes

The first coprimary outcome was the change in subjective sleepiness from baseline to 3 months, which was measured by the mean ESS score at 3 and 4 months. The ESS is the most widely used subjective severity scale in clinical and research practice. It is a self-administered short questionnaire with eight questions that requires the patient to rate his or her tendency to fall asleep in eight everyday situations using a scale of 0–3 to represent the chance of dozing, where 0 is 'none', 1 is 'slight', 2 is 'moderate' or 3 is 'high'. The score is the sum of the eight questions and can range from 0 to 24; a reduction in the score represents an improvement.[97] Patients completed the ESS themselves, without input from family of friends. A standard operating procedure was provided for the administration of the questionnaire. In addition, the ESS score was measured monthly throughout the trial.

The other coprimary outcome was the cost-effectiveness and estimated health outcomes of providing CPAP plus BSC compared with BSC alone over 12 months. Health outcomes were expressed as quality-adjusted life-years (QALYs) using the European Quality of Life–5 Dimensions (EQ-5D)[98] and Short Form questionnaire-6 Dimensions (SF-6D) derived from the Short Form questionnaire-36 items (SF-36)[99] as an alternative scenario. Patients reported health-related quality of life (HRQoL) by filling in the EQ-5D questionnaire every month and the SF-36 at baseline, 3 and 12 months. The EQ-5D scores were valued using standard UK tariffs. Health-care resource use was recorded in the monthly diaries completed by the patients. Costs were evaluated in pounds sterling at 2012 prices from the UK NHS perspective.[100] The health economics analysis and results will be discussed in *Chapter 4*.

Secondary outcomes

Secondary outcomes included subjective sleepiness at 12 months, measured by the mean ESS score at months 10, 11 and 12, plus the following outcomes recorded at the 3- and 12-month assessments:

- Objective sleepiness. This was measured by the Oxford Sleep Resistance (OSLER) test. The test measures the patient's ability to resist sleep for up to 40 minutes.[101]
- Generic quality of life. This was assessed by the SF-36 questionnaires, which consist of 36 quality of life-related questions. Answers to questions are condensed into eight summary scores, which are further condensed into a mental component summary scale (MCS) score and a physical component summary scale (PCS) score.[102]
- Disease-specific quality of life. This was assessed using the Sleep Apnoea Quality of Life Index (SAQLI), a sleep apnoea questionnaire which included CPAP side effects.[103]
- Mood. This was assessed using the Hospital Anxiety and Depression Scale (HADS), a questionnaire with 14 questions, seven on each aspect.[104]

TABLE 2 Summary of assessments by time point

Assessment and measurement	Screening	Baseline	Week	Month											
			1	1	2	3	4	5	6	7	8	9	10	11	12
Eligibility and exclusions	✗														
Informed consent and enrolment		✗													
Respiratory polygraphy		✗													
Overnight pulse oximetry						✗									✗
Clinical assessment visit		✗				✗									✗
Telephone call			✗	✗					✗						
Patient diary returned via post				✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Demographics		✗													
Subjective sleepiness (ESS score)		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Objective sleepiness (OSLER) test		✗				✗									✗
Quality of life (EQ-5D)		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Generic quality of life (SF-36)		✗				✗									✗
Disease-specific quality of life (SAQLI)		✗				✗									✗
Mood (HADS)		✗				✗									✗
Functionality (TDS)		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Nocturia		✗		✗		✗			✗						✗
Mobility (TUG test)		✗				✗									✗
Accidents		✗		✗		✗			✗						✗
Cognitive function (MMSE, TMT–B, DSS test, RT)		✗				✗									✗
Anthropometry		✗				✗									✗
BP and resting pulse		✗				✗									✗
Fasting bloods		✗				✗									✗
Vascular events		✗				✗									✗
Health-care usage		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Change in medication		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Caffeine and alcohol intake		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Exercise		✗		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
CPAP compliance			✗			✗									✗
CPAP side effects			✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Adverse events			✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

DSS, Digit Symbol Substitution; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental State Examination; OSLER, Oxford Sleep Resistance; RT, reaction time (simple and four-choice reaction time); SAQLI, Sleep Apnoea Quality of Life Index; SF-36, Short Form questionnaire-36; TDS, Townsend Disability Scale; TMT–B, Trail Making Test Part B; TUG, Timed Up and Go.

- Functionality. This was assessed by the Townsend Disability Scale (TDS), a nine-item questionnaire scored on a scale from 0 to 2 for each question (total 18).[105]
- Nocturia. The patients were asked if they had to pass urine and how many times per night on average.
- Mobility. This was measured using the Timed Up and Go (TUG) test. This is the time taken in seconds to stand up from an armchair, walk 3 metres, turn, walk back to the chair and sit down.[106]
- Domestic accidents and RTAs. Domestic accidents were recorded in the case report forms (CRFs) and driving accidents were self-reported confidentially at each assessment.
- Cognitive function was assessed using the following four tests:

    - Mini Mental State Examination (MMSE): a widely used screening tool that provides a measure of orientation, registration (immediate memory), short-term memory (but not long-term memory) and language functioning. It is scored out of 30; scores of 25–30 are considered normal.[107]
    - Trail Making Test Part B (TMT–B): this gives information on visual search, scanning, speed of processing, mental flexibility and executive functions. It requires individuals to draw a line sequentially connecting 25 encircled numbers and letters on a piece of paper alternating between numbers and letters (e.g. 1, A, 2, B, 3, C, etc.). The score represents the amount of time required to complete the task, and performance decreases with increasing age and lower levels of education.[108]
    - Digit Symbol Substitution (DSS) test: a coding exercise. At the top of a piece of paper is a code; each symbol in the code corresponds to a single-digit number. The individual is required to copy the code under rows of random numbers and complete as many as possible in 90 seconds. The score is the total number of correct answers completed in this time.[108]
    - Simple and four-choice reaction time: a two-part test. The first part measures the time to react to a symbol appearing in a white box on a computer screen by pressing any button on a computer keyboard. The second part requires the individual to respond to the symbol appearing in any one of four white boxes at random. They have to respond using the allocated key on the keyboard, and the numbers of correct responses and errors are recorded.

- Cardiovascular risk factors. These included systolic and diastolic office BP, fasting glucose, lipids and glycated haemoglobin (HbA_{1c}).
- New cardiovascular events. These included angina, newly diagnosed hypertension, atrial fibrillation, myocardial infarction (MI), heart failure, diabetes, stroke, transient ischaemic attack and peripheral vascular disease.

Tertiary outcomes

Treatment compliance was measured objectively by downloading data from a smart card located in the CPAP machine at the 3- and 12-month visits. The output was in a standardised, commercially available, format provided by the manufacturers of the CPAP machines. It contained data on hours and days used, pressure provided and estimated leaks. CPAP usage was recorded as the total hours used, divided by the numbers of days between the initiation of CPAP and the date of the 3- or 12-months visit. Non-users were defined as those who admitted to stopping CPAP therapy, had returned their machines or had no recorded usage data at their visits or who did not use CPAP at all in the month prior to their scheduled follow-up. Hours of usage was set to 0 hours per night in those with missing data and those who had subsequently stopped treatment.

Data collection and monitoring

Data generated by all centres were collected on CRFs, which were posted to the Oxford Respiratory Trials Unit (ORTU), the trial data co-ordinating centre, where they were entered on to a database that was created and maintained by the Medical Research Council Clinical Trials Unit (MRC CTU). The staff entering the data into the database had no part in the data collection, analysis or interpretation. All patients' trial consent forms were reviewed and a 100% automated check was conducted for the ESS inclusion criteria. Automated data checks for consistency and date were completed for all CRFs. Data were also checked for

inconsistencies in range and missing data. Missing or ambiguous data were queried with individual research nurses and resolved whenever possible. Quality control of CRF data entry was completed on a regular basis throughout the duration of the trial. Site initiation visits were organised for all sites prior to commencing recruitment and were conducted by the chief investigator, trial manager and clinical research fellow. Interim monitoring visits were completed for five centres and source data verification was completed during those visits. Eleven close-out visits were completed remotely and four centres were visited. All adverse events were reviewed by the Independent Data Monitoring Committee (IDMC).

Randomisation

Patients were randomised using a telephone computerised service provided by the MRC CTU. Allocation was physically carried out during working hours from Monday to Friday. The allocation group was indicated to the unblinded research nurse once the baseline data collection was completed.

The randomisation programme was created by the MRC CTU in accordance with its standard operating procedure and held on a secure server, access to which was confined to the CTU data manager. Allocation was on a 1 : 1 basis with a random element of 80% and stratified by disease severity (enrolment ESS score of >13 vs. ≤ 13), functionality using the TDS score of >1 versus ≤ 1 and recruitment centre. In the analysis, baseline ESS scores and TDS scores were entered into models as fixed-effects continuous variables. Recruiting centre was adjusted for using random effects in order to avoid dropping centres that may recruit only a single patient.

Blinding

As this was a physical device trial, the treatment allocation for the individual patients could not be concealed, although the treatment allocation could be concealed from a member of the research team completing follow-up assessments. Each centre was asked to identify a member of the research team who could be the blinded researcher and remain blinded to the treatment allocation throughout the trial. The CRFs were designed to collect blinded and unblinded data separately. Patients were discouraged from discussing their treatment allocation with the blinded research staff and the importance of maintaining blinding was highlighted in the patient information sheets (PISs). It was not possible to blind all trial staff, although the assessments were done blind wherever possible.

The trial manager and trial support staff at the co-ordinating centres in Oxford and London did not have contact with the patients. The trial statisticians analysed the results based on a treatment code, using an analysis plan that had been finalised prior to locking the database and prior to the blinded data analysis. Patients continued to see other health-care professionals unrelated to the trial for their usual medical care.

Sample size

The primary analysis was the difference between the two treatment groups in the mean change of ESS score from baseline to 3 months. The ESS is a scale from 0 to 24 and a 1-point change on the ESS is indicative of a shift in the symptom state in one domain which was considered to be the minimally clinically important difference. In the recent NICE/HTA appraisal of CPAP for OSAS in middle-aged patients,[20] the effect of CPAP treatment on the difference in ESS score in middle-aged patients with mild OSA was –1.07 [standard deviation (SD) 2.4]. The inclusion criterion for this trial was in the range of moderate OSAS severity, but, since sleepiness may be less pronounced in older people, the power calculations were performed assuming a treatment response similar to that seen in mild OSAS in middle-aged patients. To detect a 1-point change in ESS score (SD of change 2.4) required 244 patients randomised in a 1 : 1 ratio with a 90% power at the two-sided 5% significance level. In shorter (less than 6 months' duration) randomised trials with a similar design, the loss to follow-up rate was approximately 5%. Since PREDICT was of longer duration and undertaken in older people with comorbidity, it was conceivable that the loss to

follow-up rate could be up to 10%. Therefore, the sample size for the trial was 270 patients (135 in each group).

Statistical methods

The statistical analysis plan was finalised and approved by the Trial Management Group (TMG). Statistical significance was tested at the 5% level for all analyses. All analyses were adjusted for the minimisation factors (enrolment ESS score of >13 vs. ≤ 13, functionality using the TDS of >1 vs. ≤ 1 and recruitment centre) to optimise power and reduce bias. In addition to the minimisation factors, age, sex, ODI and body mass index (BMI) were also adjusted for in an additional analysis of the primary outcome. All analyses were by intention to treat, incorporating all randomised patients who had complete data on the outcome of interest (complete-case analysis). No adjustments for multiple testing were made, but the statistical significance of the secondary outcomes was interpreted cautiously because of the large number of secondary analyses performed.

A secondary sensitivity analysis of the primary outcome was performed in order to establish proof of principle whereby patients who swapped from the BSC group to CPAP were excluded from the analysis. The effect of baseline ESS score, age, ODI and BMI and the effect of CPAP use on the primary outcome were also investigated.

All analyses and modelling were undertaken in Stata version 12.0 (StataCorp LP, College Station, TX, USA).

Descriptive statistics

All baseline data were summarised by treatment groups. Only descriptive statistics were utilised; no formal statistical comparisons were undertaken, since any differences should be the result of chance rather than bias. Categorical variables were summarised by number (*n*) and percentage (%) and continuous variables were summarised by mean, SD or median, 25th and 75th percentiles as appropriate.

Coprimary outcomes analysis

Subjective sleepiness

Subjective sleepiness was assessed using the ESS. The mean of the 3- and 4-month ESS score was calculated for each patient and compared with baseline. The ESS score is the sum of its eight components and, therefore, if one of the components was missing, the ESS score was set to missing. If any non-integer values were given these were included in the sum and the final ESS score rounded up or down to the next integer. Any scores obtained outside the pre-specified window of 2 to 5 months after randomisation were excluded. If either the 3- or the 4-month score was missing, the single observed score was used. If both scores were missing or outside the required time frame, the patient was excluded from the primary analysis. The difference between the randomisation ESS score and follow-up ESS score was calculated for each patient and compared between groups using a multivariable linear regression model. The analysis was adjusted for the minimisation factors as outlined previously.

Cost-effectiveness

The cost-effectiveness analysis took the perspective of the UK NHS over a time horizon of 12 months. Health outcomes were expressed in QALYs using EQ-5D and SF-6D. The analysis incorporated health-care utilisation, including inpatient and outpatient hospital visits and general practitioner (GP) visits during the trial. The cost-effectiveness analysis will be discussed in more detail in *Chapter 4*.

Secondary outcome analyses

Subjective sleepiness at 12 months: the mean ESS score at 10, 11 and 12 months was calculated for each patient and was taken to be the 12 month score. The same principles described for primary analysis were used for calculating the mean ESS score at 12 months. The difference between the two groups in the

change in subjective sleepiness at 12 months compared with baseline was analysed using a multivariable linear regression model adjusting for the minimisation factors as outlined previously.

In addition, the changes from baseline were compared at 3 and 12 months for the following outcomes between treatment groups.

Objective sleepiness
Objective sleepiness was measured by the OSLER test. Two tests were conducted at each visit (baseline, 3 months and 12 months) and the average time taken to fall asleep at each visit was used for the analysis. Kaplan–Meier plots were used to summarise the mean time taken to fall asleep (the event of interest) at baseline, 3 months and 12 months with log-rank tests used to compare survival curves. The change from baseline in the mean time taken to fall asleep at each follow-up visit was compared between treatment groups.

Generic quality of life
Generic quality of life was assessed by the SF-36. The MCS and PCS scores were calculated. If any of the 36 questions were not answered, the MCS and PCS were set to missing along with any of the eight summary scores dependent on the missing answers.

Disease-specific quality of life
Disease-specific quality of life was assessed by the SAQLI. The score is the average of 14 sleep-related questions and, if applicable, adjusted for side effects attributable to CPAP. If any of the answers were missing, the SAQLI was also set to missing.

Mood
Mood was assessed by the HADS. The anxiety and depression summary components of the score were reported. If any of the answers were missing the relevant summary component was also set to missing.

Functionality
Functionality was assessed by the TDS. Each of the nine items of the TDS is scored 0 (yes, with no difficulty), 1 (yes, with some difficulty) or 2 (no, need help). Items are then summed to give a total score out of 18.[109] If at least one of the components was missing, the TDI was also set to missing.

Nocturia
Nocturia was assessed by the self-reported average number of times that patients get up to pass urine at night.

Mobility
Mobility was assessed by the TUG test and was measured in seconds. There is no upper time limit and the time in seconds is rounded up or down to a whole second.

The number of road and domestic accidents
The proportion of patients experiencing any accidents was analysed adjusting accident history at baseline (whether or not they had an accident at home in the month before enrolment or while driving in the 3 months before enrolment).

Cognitive function
Cogitative function was assessed using the MMSE, TMT–B, the DSS test and the simple and four-choice reaction time test. The change in the score for each of the four tests was analysed.

Cardiovascular risk factors
Cardiovascular risk factors were assessed using systolic and diastolic BPs, fasting glucose, fasting lipids and HbA_{1c}.

New adverse cardiovascular events

These were assessed as the proportion of patients reporting any new adverse cardiovascular event at the 3- and 12-month assessment. The analysis was adjusted for the proportion of patients with any cardiovascular event at baseline.

The continuous outcomes (SF-36, SAQLI, HADS, TDS, cognitive function tests, cardiovascular risk factors, mobility test and frequency of nocturia) were analysed using multivariable regression models and adjusted for their corresponding baseline score/measurement and the minimisation factors. Non-normal (skewed) data were not an issue and could be analysed using this method because of the implications of the central limit theorem that for a large sample size the mean will be approximately normally distributed.

For binary outcomes (accident and adverse cardiovascular events) the odds of experiencing the outcome were compared between treatment groups using logistic regression. All analyses were adjusted for the minimisation factors.

Tertiary outcomes analyses

Continuous positive airway pressure usage was taken to be the mean number of hours that CPAP was used per night during follow-up (total number of hours used divided by total number of days' follow-up). CPAP use was summarised using the median and 25th and 75th percentiles. Patients who had stopped CPAP during follow-up and were missing adherence data were assumed to have 0 hours/night usage. The number of patients stopping CPAP or swapping to CPAP from BSC was summarised along with reasons at the 3- and 12-month time points.

Sensitivity analyses

Patients who were randomised to BSC alone and who subsequently started CPAP therapy during the follow-up potentially dilute the results of the ESS score comparisons. Sensitivity analyses of the primary and secondary ESS score outcomes were performed in which BSC patients who swapped to CPAP were excluded from the analysis if CPAP therapy had been started before the visit at which the observation was recorded.

Multiple imputation analyses

Multiple imputation using chained equations was used to impute missing ESS scores over follow-up and produce an unbiased analysis under a missing at random assumption. Missing at random assumes that the probability of missing data depends only on the values of the observed data and not on the values of the missing data. The plausibility of the missing at random assumption was explored by comparing observed data in those patients with and without the outcome of interest.

All 12 ESS follow-up scores were entered into an imputation model along with the minimisation variables and the previously listed covariates (age, sex, ODI and BMI). Imputations were performed separately within treatment groups. CPAP compliance at the 3- and 12-month visits were also included in the imputation model for the CPAP group. For each treatment group, 50 imputation models were created using the 'ice' command in Stata. In analyses secondary to those described previously, the primary and secondary ESS score outcomes were reanalysed on the imputed data sets and the results combined using Rubin's rules.

The missing at random assumption is untestable and may be inappropriate; therefore, the probability that 'missing data could depend on values of the missing data' (missing not at random) was considered. The ESS score outcomes were reanalysed on all randomised individuals under a range of 'missing not at random' scenarios. The aim of this technique was to determine how sensitive the observed results were to different assumptions on the unobserved outcomes in the two groups.

Exploratory analyses

Effect of continuous positive airway pressure adherence on the Epworth Sleepiness Scale score

Patients who were randomised to the CPAP group were split into tertiles by their average CPAP use in the last month of follow-up prior to the 3-month visit. Each group was compared with the BSC group in a single model on the change in the primary ESS score outcome. The minimisation variables were adjusted and a global test was used to determine whether or not the treatment effect in each of the three CPAP groups differed. A similar analysis was conducted on the secondary ESS score outcome at 12 months, splitting patients into tertiles by their average CPAP use in the last 3 months of follow-up before the 12-month visit. The effect of CPAP usage on ESS score at each time point was also modelled using multivariable fractional polynomial (FP) models[110] adjusting for the minimisation variables. Since the BSC group had no compliance data, the mean change in ESS score in this group was displayed on a FP plot.

Interaction analyses

The variation of the effect of CPAP therapy compared with BSC on the primary ESS score outcome was investigated over age, BMI, ODI and ESS score at baseline. FPs were used to model the interaction between the treatment effect and each covariate, using either one or two FP transformations of the covariate of interest, whichever had the lower Akaike information criterion.[110] The minimisation variables were also adjusted for in each model with continuous variables centred about their mean. A continuous plot of the treatment effect over the original, untransformed baseline covariate was then produced with 95% confidence interval (CI). To check the plausibility of the interaction curve, the covariate was categorised at its quartiles and the treatment effect in each subgroup was estimated. These treatment effects were then plotted against the subgroup means over the continuous plot. Consistency between the results of the two analyses increases the plausibility and evidence of any treatment interaction. Disagreement between the two models may be an indicator of an erroneous FP model or a type I error of the FP approach, in which case the results of the subgroup analysis were interpreted with caution.

Analysis of monthly diaries

A longitudinal analysis of the effect of CPAP compared with BSC over the whole follow-up period was performed using the ESS scores from the monthly diaries. A multilevel model for repeated measures was used with ESS score as the response variable and patient- and month-specific random effects. A treatment-by-month interaction was added to the model to test whether or not the effect of CPAP varied over the course of follow-up. This model makes the assumption that all trial visits and monthly diaries are completed on the expected dates. An unstructured covariance matrix was used. Month was treated as a categorical variable. From the model a plot of the treatment effect and its 95% CI at each month was constructed.

Summary of changes to the protocol

The changes to the trial documents following National Research Ethics Committee (REC) approval in October 2009 are summarised below; a copy of the Statistical and health economic analysis plans is given in *Appendix 1*.

1. Substantial amendment SA01 (approved by the REC on 4 November 2009). Changed the version number of the PIS mentioned in the consent form to match the PIS version 2.0 already approved.
2. Substantial amendment SA02 (approved by the REC on 2 December 2009). Changed contact details, updated staff details, minor editing and formatting of the sleep diaries and added information regarding data transfer in the PIS. Clarified which ESS score measurements would be used in the analysis, quantified what was meant by a clinical diagnosis of OSAS, corrected a mistake in one of the exclusion criteria, added sections explaining the blinding in more detail and the delivery of CPAP/service provision and clarified the procedure for returning the driving questionnaire.

3. Substantial amendment SA03 (approved by the REC on 10 May 2010). Updated staff/committee details, minor editing and administrative changes. Further information added to the PIS. Standard letters inviting patients to attend their 3- and 12-month visits were introduced at the request of the participating centres. The sleep diaries were updated and information regarding Sibutramine was removed from the BSC booklet. Clarifications were required for the blinding procedure, one of the exclusion criterion, the minimisation criteria, the trial treatment, loss to follow-up and the procedure for assessing safety, quality control and adverse events section.
4. Non-substantial amendment NA04 (acknowledged by the REC on 14 May 2010). One of the minimisation criterion had been changed in error and was corrected.
5. Substantial amendment SA05 (approved by the REC on 24 February 2011). Updated staff/committee membership and contact details. Clarified that the results of the Embletta test done prior to trial enrolment were acceptable as long as they were done not more than 3 months before randomisation. Amended the coenrolment guidelines and listed the blood tests. Updated the monitoring, amendments and safety-reporting section so that it referred to a device trial rather than an investigational medicinal product trial.
6. Substantial amendment SA06 (approved by the REC on 20 June 2011). Clarified the primary and secondary outcomes, selection of centres and patients and treatment data collection. Updated the follow-up section. Corrected the sample size calculation and added information regarding the role of the IDMC and TMG.
7. Substantial amendment SA07 (approved by the REC on 8 June 2012). Clarification of how the cardiovascular risk is measured, the ESS score calculations and the analysis plan. Corrections of the statistical calculations, update of the trial manager's details and administrative corrections.

All amendments were implemented prior to breaking of the treatment allocation code and prior to finalising the analysis plan.

Trial conduct

Trial organisation

The trial was managed and co-ordinated from the National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, London, UK (Professor Mary Morrell and Dr Alison McMillan) and the ORTU (Magda Laskawiec-Szkonter). The ORTU was also responsible for data collection and management. Statistical analysis was overseen by Professor Andrew Nunn and Daniel Bratton and conducted at the MRC CTU in London.

The Trial Steering Committee (TSC) carried overall responsibility for the safe delivery of the trial. It initially met every 6 months until it was satisfied that trial recruitment was achievable, and thereafter it met annually to provide overall supervision of the trial. The TMG was responsible for the management of the trial and met frequently. An IDMC was also appointed. Memberships of the TMG, TSC and IDMC are listed at the end of the report. A full list of the PREDICT investigators is included in *Appendix 2*.

Patient involvement

Two patient representatives participated in the PREDICT management; in particular, Mr Frank Govan from Oxford acted as the patient representative. He attended the TSC meetings and his feedback was very helpful in progressing the trial. For example, he raised awareness of the study to the Sleep Apnoea Trust Association, which in turn, publicised the study with their members. The protocol was discussed with Sleep Apnoea Trust Association members at their annual meeting in 2012, and we were invited to present the results at their 2014 meeting (www.sleep-apnoea-trust.org/user/image/sm52.pdf).

Members of the Welsh Sleep Apnoea Society have also supported the PREDICT study by providing publicity for the trial. In 2011, Professor Morrell was made an honorary member of the society in recognition of the research that the team was carrying out (www.welshsas.org).

Mr Govan and other patients regularly discussed the rigours of participating in research studies with the TMG. These comments have been taken into account in designing subsequent trails. Mr Govern also voted at TSC meetings, and his independent views were sought when discussing topics such as opening new trial sites, through to trial authorship.

The patients who participated in PREDICT from the London centre were invited to an annual patient and public involvement event at the Royal Brompton Hospital (once their direct involvement in the trial was over) to provide feedback on their experiences. This feedback was collated and has been used to improve the study facilities at the site, as well as trial logistics, for example increased time for travel between sites.

Trial finances

Positive Airway Pressure in Older People: a randomised controlled trial was funded by the UK NIHR HTA (project number 08/56/02). Subcontracts were established between Imperial College London, ORTU, York University or Edinburgh University and each of the recruitment centres. Trial patients' travel expenses were paid.

Trial insurance and indemnity

The usual NHS indemnity arrangements for negligent harm were applied to the trial. Imperial College London acted as sponsor for the trial and had third-party liability insurance in accordance with all local legal requirements. The CPAP machines in the trial were covered by product warranty.

Working with industry

Continuous positive airway pressure is delivered by a specialised but widely used medical device otherwise known as a CPAP machine. For a detailed description of the type of CPAP machine used see *Continuous positive airway pressure*. The CPAP machine and associated equipment (masks, tubing, filters and humidification units) were supplied by ResMed (UK) Ltd, which also provided on loan the sleep diagnostic equipment (Embletta GOLD). The consumables were purchased. At the start of the trial, ResMed (UK) Ltd provided information regarding the logistics of ordering and delivering equipment to multiple centres but it had no involvement in the trial design, data collection, analysis or interpretation. At the end of the trial, ResMed (UK) provided a small financial contribution to a second joint research study day (and a trial investigators meeting), which helped cover the cost of venue hire.

At the end of the trial, any unused CPAP machines or loaned equipment were purchased or returned to ResMed (UK) Ltd. Any patients established on the autotitrating CPAP who wished to continue using it were allowed to keep the machine as a goodwill gesture from ResMed (UK) Ltd.

Positive Airway Pressure in Older People: a randomised controlled trial offers numerous examples of good practice in the industry, in which the needs of the trial are put foremost. During the first 6 months of the trial, the number of failed home respiratory polygraphy sleep studies (performed on the Embletta GOLD equipment) was higher than expected. This issue was addressed with the help of the industry and in collaborative meetings with staff at the co-ordinating centres. It became apparent there had been a technical problem in the equipment that was supplied for use in the trial. This was identified quickly and addressed by ResMed (UK) Ltd, which provided its expertise, operational and delivery infrastructure for free.

The estimated cost saving for the trial by the provision of CPAP machines and associated equipment was £122,896.00. The loan of Embletta GOLD equipment and software was approximately £103,485.00, generating a total cost saving of £226,381.00.

Chapter 3 Results

Recruitment

Recruitment took place between February 2010 and May 2012. The overall recruitment rate is shown in *Figure 2*. All the 12-month visits and trial exit were completed by May 2013. Although the trial was powered for 270 patients, 278 were recruited. This occurred because when approaching the target number a randomisation stop date was announced to coincidence with the end of a calendar month. Eight additional patients had completed their enrolment visit and randomisation prior to the official stop date. The TMG agreed the additional patients should be included.

The Consolidated Standards of Reporting Trials diagram shows the flow of patients through the trial (*Figure 3*). 'Withdrew consent' implies the patients withdrew from the treatment and trial, and 'discontinued treatment' implies the patient stopped their allocated treatment but remained in the trial. In total, 1614 individuals were screened as potential patients: of these 541 (34%) were eligible and subsequently 278 (51%) were randomised. 245 (88%) completed their 3-month follow-up and 231 (83%) completed their 12-month follow-up and the trial.

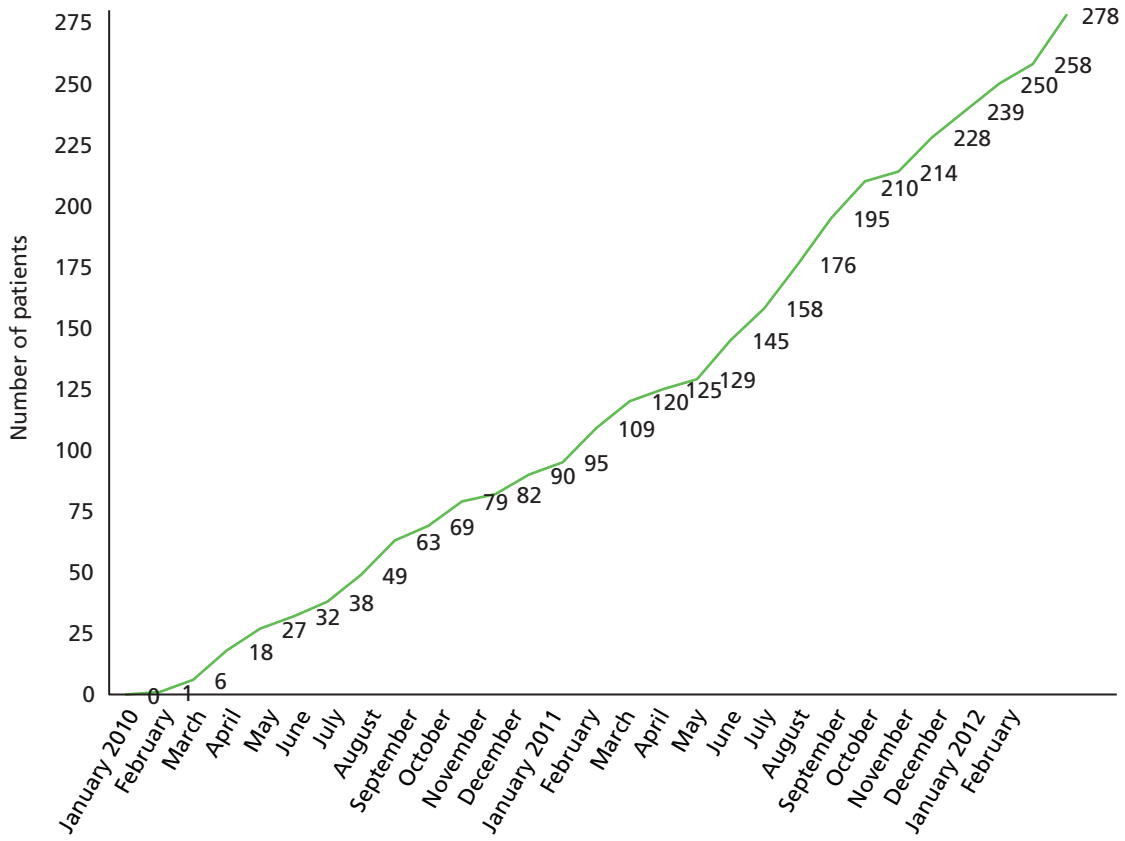

FIGURE 2 Cumulative recruitment.

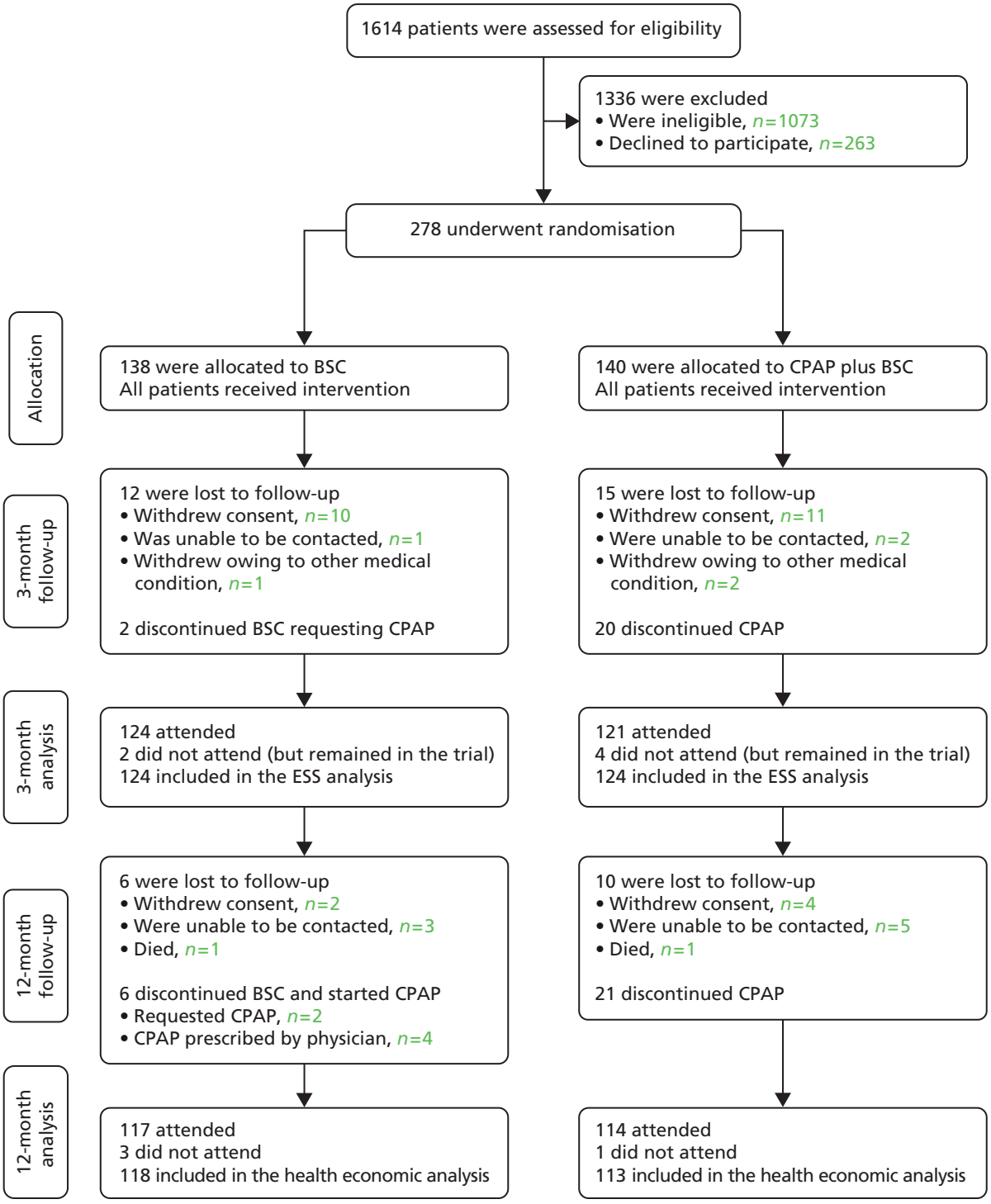

FIGURE 3 Trial screening, enrolment, randomisation and follow-up.

Data collected on the screening logs enabled the 1073 ineligible patients to be grouped into the following categories:

- not meeting inclusion ODI or ESS criteria, $n = 442$ (41%)
- previous exposure to CPAP, $n = 79$ (7%)
- awake oxygen saturations < 90% on air or $FEV_1/FVC < 60\%$, $n = 171$ (16%)
- being a professional driver, reporting sleepiness while driving, shift work or any severe symptom of OSAS for which the referring physician felt CPAP was mandatory, $n = 216$ (20%)
- no information or incomplete data, $n = 165$ (15%).

Baseline data

In total, 278 patients were randomised; 140 to the CPAP with BSC and 138 to BSC alone. All 278 patients completed the baseline enrolment visit. The majority of patients were male (82%), with a mean age of 70 years, ranging from 65 to 89 years, and had on average moderate OSAS: ESS mean score (SD) of 11.6 (SD 3.7) and ODI 28.7 (SD 19.1) events/hour. The majority of patients were white (96%) and obese and had on average 11 years of education and normal MMSE. A total of 228 (82%) were current drivers, and 146 (53%) slept alone. Baselines demographic are shown in *Table 3*, clinical characteristics in *Table 4*, sleep characteristics in *Table 5* and sleep measurements in *Table 6*. None of the baseline data between groups were considered different to any important degree.

TABLE 3 Baseline demographics

Characteristic or descriptor		BSC	CPAP
n		138	140
Age (years), median (25th–75th percentiles)		70.3 (68.0–73.8)	69.5 (67.1–74.1)
Male sex, *n* (%)		109 (79)	120 (86)
Education (years), median (25th–75th percentiles)		11 (10–14)	11 (10–15)
MMSE, median (25th–75th percentiles)		29 (28–30)	29 (27–30)
Current drivers, *n* (%)		111 (80)	117 (84)
Ethnicity, *n* (%)	White	134 (97)	133 (95)
	Asian	3 (2)	5 (4)
	Other	1 (1)	2 (1)
BMI (kg/m^2), mean (SD)		33.6 (6.4)	33.9 (5.7)
Neck circumference (cm), mean (SD)		42.6 (4.0)	44.0 (4.4)
Waist size (cm), mean (SD)		114.1 (15.5)	115.3 (13.6)
Hip size (cm), mean (SD)		115.7 (12.8)	116.6 (12.1)
Waist-to-hip ratio, mean (SD)		1.0 (0.1)	1.0 (0.1)
Smoking status, *n* (%)	Never	45 (33)	42 (30)
	Ex	86 (62)	92 (66)
	Current	7 (5)	6 (4)
Caffeinated drinks/day, mean (SD)		5.1 (2.7)	5.2 (2.6)
Alcoholic drinks/week, median (25th–75th percentiles)	Beer (pints)	0 (0–2)	0 (0–2.3)
	Wine (glasses)	0 (0–2)	0 (0–2)
	Spirits (measure)	0 (0–1)	0 (0–1)
Exercise frequency (defined as lasting over 10 minutes), *n* (%)	5–7 times/week	67 (49)	69 (49)
	2–4 times/week	37 (27)	37 (26)
	Once/week	9 (7)	10 (7)
	< once/week	5 (4)	8 (6)
	None	19 (14)	16 (11)

TABLE 4 Clinical characteristics

Characteristic	BSC	CPAP
n	138	140
Asthma/chronic obstructive pulmonary disease, *n* (%)	34 (25)	31 (22)
Other chronic lung diseases, *n* (%)	13 (9)	9 (6)
Ischaemic heart disease, *n* (%)	49 (36)	42 (30)
Hypertension, *n* (%)	104 (75)	98 (70)
Diabetes, *n* (%)	43 (31)	40 (29)
Peripheral vascular disease, *n* (%)	32 (23)	26 (19)
Atrial fibrillation, *n* (%)	41 (30)	28 (20)
Heart failure, *n* (%)	11 (8)	7 (5)
Cerebral vascular disease, *n* (%)	19 (14)	16 (11)
Systolic BP (mmHg), mean (SD)	140.4 (20.0)	137.7 (17.7)
Diastolic BP (mmHg), mean (SD)	77.6 (12.4)	77.7 (10.2)
FEV_1, % predicted, mean (SD)	84.5 (19.9)	86.5 (19.4)
FVC, % predicted, mean (SD)	5.1 (2.7)	5.2 (2.6)
FEV_1/FVC, mean (SD)	83.6 (13.4)	82.4 (12.8)
Nocturia (no. of times/night), mean (SD)	2.1 (1.3)	1.9 (1.3)
Incontinent overnight, *n* (%)	8 (6)	10 (7)
TDS, median (25th–75th percentiles)	2.5 (1–7)	2.5 (1–5)

TABLE 5 Sleep characteristics

Characteristic		BSC	CPAP
n		138	140
ESS score, mean (SD)		11.6 (3.9)	11.6 (3.4)
OSLER (minutes), median (25th–75th percentiles)		20.3 (9.4–37.5)	22.4 (13.3–40.0)
SAQLI, mean (SD)		4.7 (1.2)	4.8 (1.2)
Self-reported sleep duration (hours), mean (SD)		8.7 (1.4)	8.5 (1.4)
Sleep alone, *n* (%)		71 (51)	75 (54)
Daytime nap, *n* (%)		104 (75)	107 (76)
Number of naps/week, median (25th–75th percentiles)		7 (3–7)	7 (3–7)
Duration of each nap (minutes), median (25th–75th percentiles)		38 (25–60)	30 (15–60)
Snoring, *n* (%)	Yes	127 (92)	127 (91)
	No	7 (5)	8 (6)
	Unknown	4 (3)	5 (4)
Nocturnal choking, *n* (%)	Yes	67 (49)	68 (49)
	No	62 (45)	55 (39)
	Unknown	9 (7)	17 (12)
Witnessed apnoea, *n* (%)	Yes	97 (70)	105 (75)
	No	25 (18)	19 (14)
	Unknown	16 (12)	16 (11)

TABLE 6 Sleep measurements

Measurements	BSC	CPAP
n	138	140
Time in bed (hours), mean (SD)	8.7 (1.4)	8.5 (1.4)
Apnoea Index (events/hour in bed), median (25th–75th percentiles)	7.4 (2.7–17.3)	7.1 (1.7–17.4)
Obstructive, median (25th–75th percentiles)	6.5 (1.9–15.7)	6.0 (1.4–15.5)
Central, median (25th–75th percentiles)	0 (0–0.1)	0 (0–0)
Mixed, median (25th–75th percentiles)	0 (0–0.5)	0 (0–0.2)
Hypopnea index (per hour in bed), median (25th–75th percentiles)	18.6 (12.4–25.7)	17.8 (11.6–28.4)
Total (per hour in bed), median (25th–75th percentiles)	29.4 (18.9–46.0)	28.1 (16.3–47.7)
Mean overnight O_2 saturation (%), median (25th–75th percentiles)	92.6 (90.9–93.7)	92.6 (91.0–93.7)
Lowest O_2 saturation (%), median (25th–75th percentiles)	79 (73–83)	79 (73–83)
Average desaturation (%), median (25th–75th percentiles)	6.3 (5.3–7.5)	6.3 (5.4–7.8)
Saturation < 90% (% of total sleep time), median (25th–75th percentiles)	8.8 (3.3–26.3)	8.6 (2.8–26.7)
ODI (> 4% events/hour), median (25th–75th percentiles)	24.4 (15.2–39.2)	28.1 (13.3–46.0)

Coprimary outcomes

Subjective sleepiness

The primary outcome, the change in subjective sleepiness between groups at 3 months, is shown in *Table 7*. CPAP resulted in a mean change [standard error (SE)] of –3.8 (0.4) from an average (SD) of 11.5 (3.3) at baseline to 7.7 (4.0) at 3 months. BSC showed a mean change (SE) of –1.6 (0.3) from a baseline average (SD) of 11.4 (4.2) to 9.8 (4.3) at 3 months. The adjusted treatment effect at 3 months was –2.1 (95% CI –3.0 to –1.3) in favour of CPAP, which is statistically significant ($p < 0.001$). An additional analysis adjusting for age, sex, BMI and baseline ODI did not alter this result.

Sensitivity analysis

Sensitivity analyses were performed (1) excluding two patients who swapped from BSC to CPAP prior to the 3-month assessment and (2) including all randomised patients by replacing missing values using multiple imputation. Excluding the two patients who swapped from BSC to CPAP prior to the 3-month visit resulted in a treatment effect of –2.1 (95% CI –3.0 to –1.3), $p < 0.001$, in favour of CPAP, identical to the primary analysis.

TABLE 7 Change in ESS score at 3 months

Time assessed	BSC	CPAP
n randomised	138	140
n analysed	124	124
Baseline (at randomisation), mean (SD)	11.4 (4.2)	11.5 (3.3)
Month 3, mean (SD)	9.8 (4.7)	7.7 (4.1)
Month 4, mean (SD)	9.7 (4.2)	7.7 (4.3)
Mean of months 3 and 4 (SD)	9.8 (4.3)	7.7 (4.0)
Mean change from baseline (SE)	–1.6 (0.3)	–3.8 (0.4)
Treatment effect (95% CI), *p*-value	–2.1 (–3.0 to –1.3), $p < 0.001$	

SE, standard error.

Results from the imputation analyses, calculating the effect of the incomplete ESS score data reported by 14 patients, estimated a change of –2.0 (95% CI –2.8 to –1.2) in favour of CPAP ($p < 0.001$). Once again this showed the primary result to be robust. The imputation analysis assumes missing outcomes are similar to the observed outcomes in patients with similar characteristics, but this may not be true, as missing outcomes may be better or worse than those observed. The assumption can be varied to see how sensitive the observed results are to the missing data. *Figure 4* shows that observed results are not sensitive and that extreme assumptions about the missing data are needed to make any significant change to the primary analysis (i.e. a 5-point difference between missing and observed values) so any sensible assumptions about the missing data do not change the results.

Planned exploratory analysis

Exploratory analysis were planned to investigate the effect of CPAP use and age, BMI, ESS score and ODI at baseline on the primary ESS score outcome. Patients were split into tertiles by their average CPAP use in the last month of follow-up prior to their 3-month visit. The analysis by CPAP use is shown in *Table 8*. The change in ESS score between baseline and 3 months in those who used CPAP the most (third tertile) was 11.4 at baseline and 6.1 at 3 months. This resulted in a treatment effect of –3.7 (95% CI –4.8 to –2.6), $p < 0.001$, compared with BSC.

The effect of CPAP therapy compared with BSC on the primary ESS score outcome was also assessed separately over age, BMI, ESS score and ODI at baseline using FPs and is shown in *Figure 5*. The treatment effect was larger in patients with higher ESS score at baseline ($p < 0.001$).

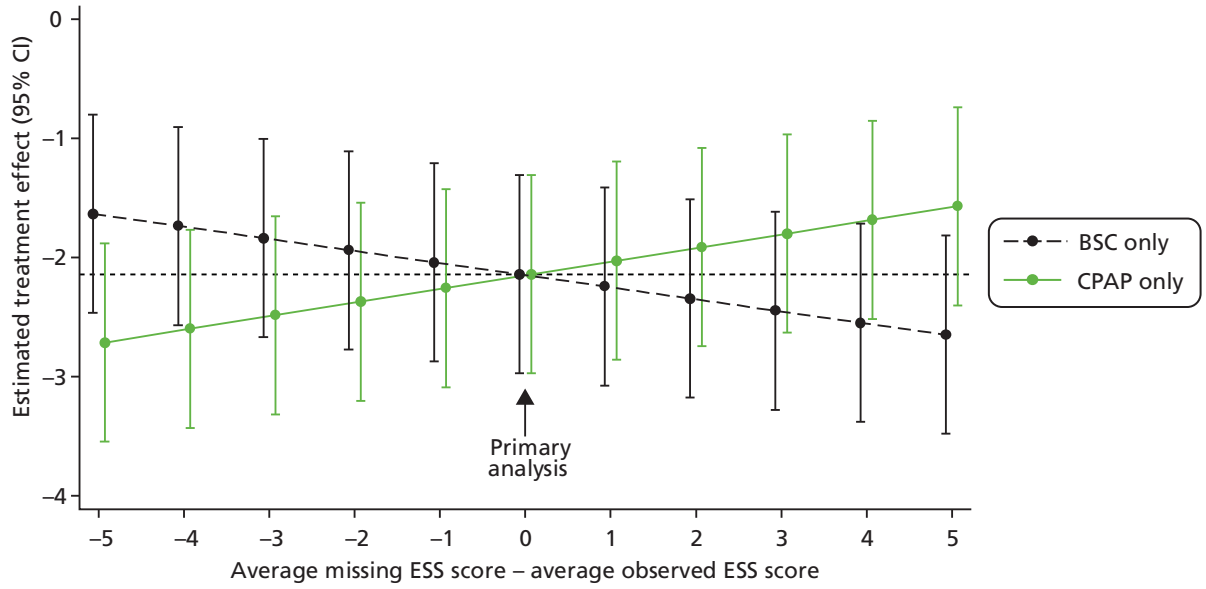

FIGURE 4 Sensitivity analysis of the primary outcome to missing data. Missing outcomes are imputed under the assumption that the average of the missing outcomes differ to the mean of the observed outcomes by an amount corresponding to each point of the *x*-axis. Imputation is performed for each treatment group separately.

TABLE 8 The effect of the CPAP use on the ESS score over the month prior to 3-month assessment

		CPAP		
Time assessed	BSC	First tertile	Second tertile	Third tertile
n	124	38	37	41
Mean usage (hours/night), (minimum–maximum)	–	0 (0–0)	1.9 (0.001–4.6)	6.4 (4.6–8.6)
Baseline ESS score, mean (SD)	11.4 (4.2)	10.6 (3.0)	12.0 (3.9)	11.4 (2.7)
ESS score month 3, mean (SD)	9.8 (4.3)	8.0 (3.9)	9.0 (4.5)	6.1 (2.7)
Change, mean (SD)	–1.6 (2.9)	–2.6 (3.9)	–3.1 (4.3)	–5.3 (3.4)
Treatment effect (95% CI)	–	–1.3 (–2.4 to 0.1)	–1.3 (–2.4 to –0.1)	–3.7 (–4.8 to –2.6)
p-value	–	0.032	0.034	< 0.001

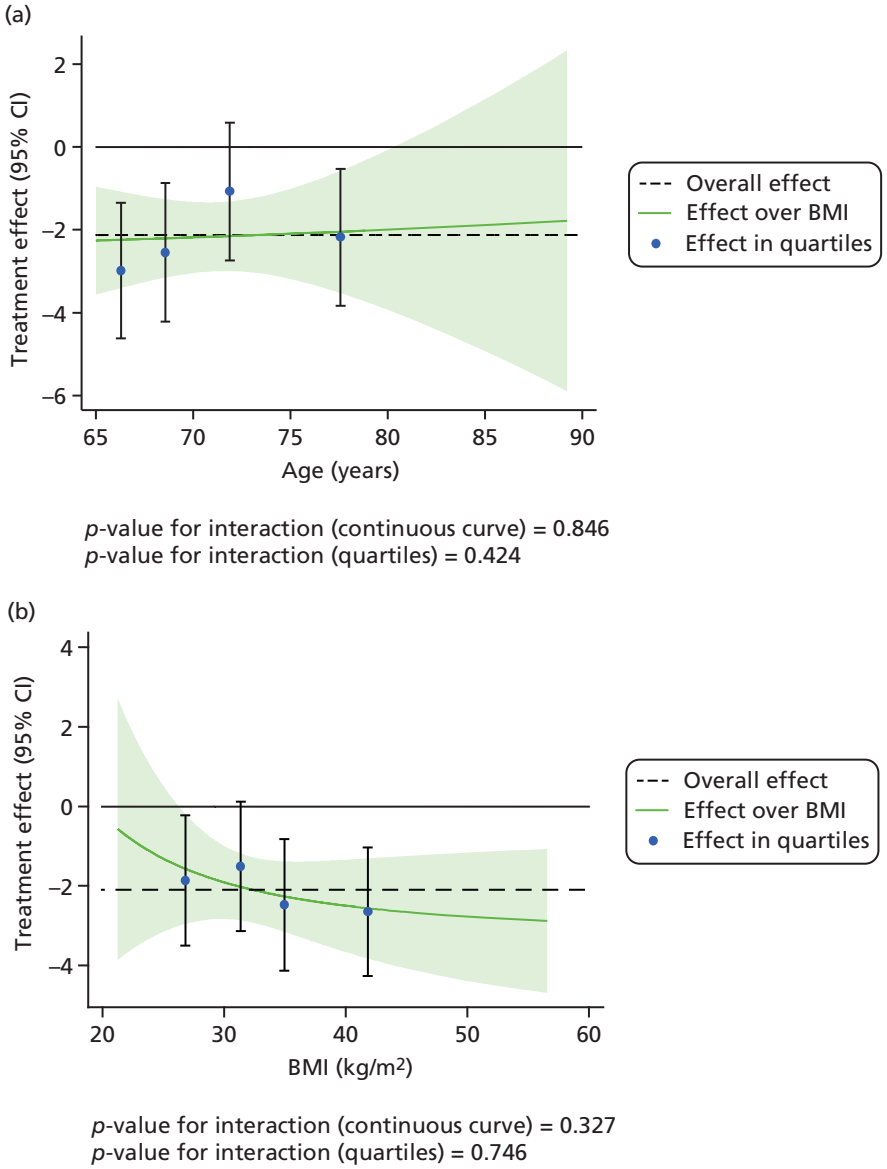

FIGURE 5 Interactions between primary treatment effect on ESS score and age, BMI, baseline ESS score and ODI. (a) Treatment effect over age; (b) treatment effect over BMI; (c) treatment effect over baseline ESS score; and (d) treatment effect over ODI. (*continued*)

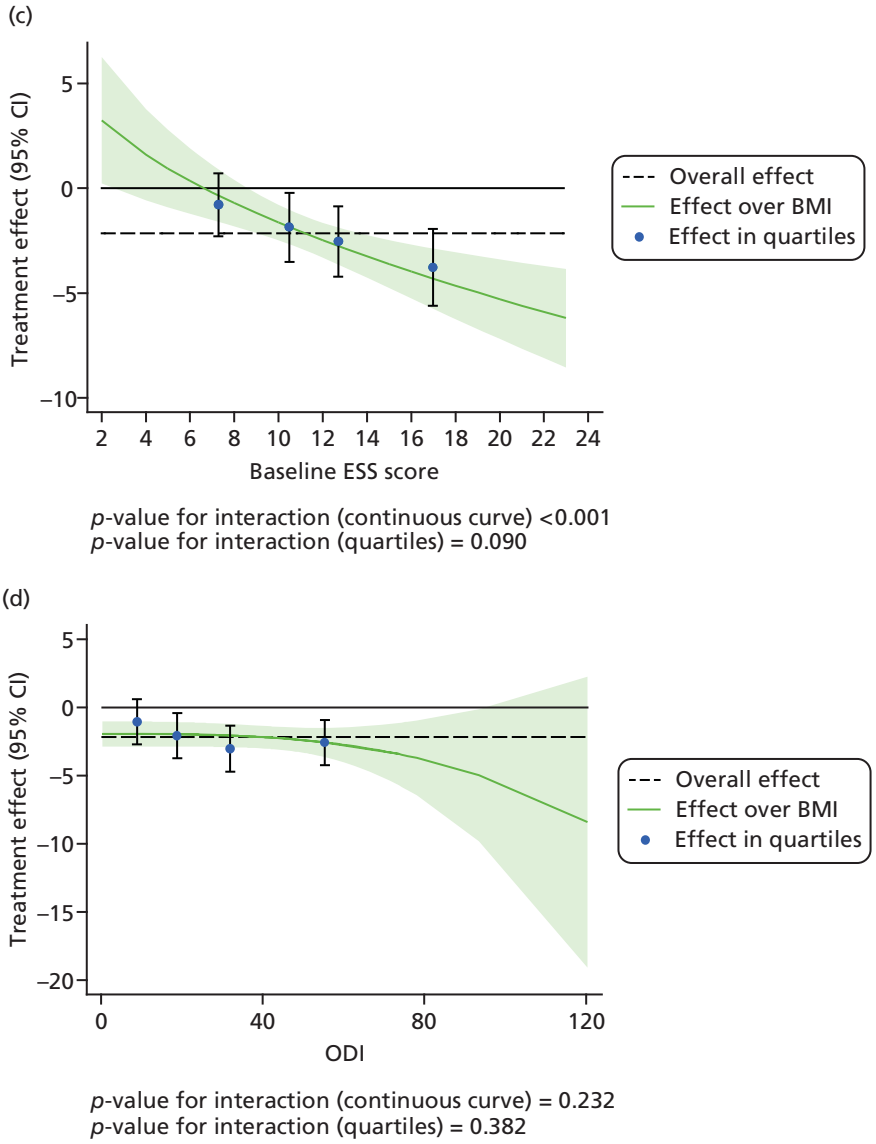

FIGURE 5 Interactions between primary treatment effect on ESS score and age, BMI, baseline ESS score and ODI. (a) Treatment effect over age; (b) treatment effect over BMI; (c) treatment effect over baseline ESS score; and (d) treatment effect over ODI.

Cost-effectiveness

The primary outcome of cost-effectiveness is shown in *Table 9*. There was small difference between those treated with CPAP and those treated with BSC. The average cost per patient was £1363 (95% CI £1121 to £1606) for those allocated to CPAP and £1389 (95% CI £1116 to £1662) for those receiving BSC. Overall, the cost accrued by the CPAP group was, on average, £35 (95% CI –£390 to £321) lower than in the BSC group, a difference which was not statistically significant. The results were not sensitive to different assumptions regarding the missing data. However, the results were sensitive to the assumptions used to cost CPAP treatment. This is discussed in *Chapter 4*.

During the trial follow-up, the BSC group gained 0.666 (95% CI 0.627 to 0.705) QALYs using EQ-5D and 0.658 (95% CI 0.643 to 0.673) QALYs using SF-6D; the CPAP group gained 0.680 (95% CI 0.638 to 0.722) QALYs using EQ-5D and 0.678 (95% CI 0.664 to 0.691) QALYs using SF-6D. The QALY difference between the CPAP and the BSC groups was 0.005 (95% CI –0.034 to 0.044) QALYs using the EQ-5D and 0.018 (95% CI 0.003 to 0.034) QALYs using the SF-6D.

Overall, the probability that the intervention was cost-effective at the threshold conventionally used in the NHS of £20,000 per QALY gained was 0.61 using EQ-5D QALYs and 0.96 using SF-6D QALYs.

TABLE 9 Cost-effectiveness of CPAP compared with BSC over 12 months

Cost-effectiveness	BSC	CPAP
Costs of CPAP treatment	0	£201
Costs of health-care resource use, mean (SE)	£1389 (£139)	£1363 (£123)
EQ-5D QALYs, mean (SE)	0.666 (0.020)	0.680 (0.021)
SF-6D QALYs, mean (SE)	0.658 (0.008)	0.678 (0.007)
CPAP versus BSC		
Difference in costs, mean (SE, 95% CI)	–£35 (£180, –£390 to £321)	
Difference in EQ-5D QALYs, mean (SE, 95% CI)	0.005 (0.020, –0.034 to 0.044)	
Difference in SF-6D QALYs, mean (SE, 95% CI)	0.018 (0.008, 0.003 to 0.034)	

Secondary outcomes

Subjective sleepiness

The change in subjective sleepiness, as measured by the mean ESS score of months 10, 11 and 12, is shown in *Table 10*. CPAP resulted in a mean change (SD) of –4.2 (SD 4.1) in ESS score, from an average of 11.4 (SD 3.4) at baseline to 7.2 (SD 3.6) at 12 months. BSC showed a change of –2.1 (SD 3.6), from a baseline of 11.3 (SD 4.0) to 9.2 (SD 4.0) at 12 months. The difference between the two groups at 12 months was –2.0 (95% CI –2.8 to –1.2) in favour of CPAP, which was statistically significant ($p < 0.001$). A sensitivity analysis excluding eight patients who swapped from BSC to CPAP was performed but this did not alter the conclusion; the difference between the two groups was –2.1 (95% CI –3.0 to –1.3; $p < 0.001$), in favour of CPAP.

Continuous positive airway pressure reduced subjective sleepiness at 3 months; the effect was maintained at 12 months and was statistically significant ($p < 0.001$). This is shown graphically in *Figure 6*. Similarly, the effect was larger in patients with greater CPAP use. The analysis by CPAP use is given in *Table 11*.

TABLE 10 Change in ESS score at 12 months

Timed assessed	BSC	CPAP
n randomised	138	140
n analysed	122	116
ESS score baseline (at randomisation), mean (SD)	11.3 (4.0)	11.4 (3.4)
ESS score month 10, mean (SD)	9.3 (4.3)	7.3 (4.1)
ESS score month 11, mean (SD)	9.6 (4.4)	7.2 (4.1)
ESS score month 12, mean (SD)	9.0 (4.1)	7.0 (3.8)
Mean of months 10, 11 and 12, mean (SD)	9.2 (4.0)	7.2 (3.6)
Mean change from baseline (SD)	–2.1 (3.6)	–4.2 (4.1)
Treatment effect (95% CI), *p*-value	–2.0 (–2.8 to –1.2), $p < 0.001$	

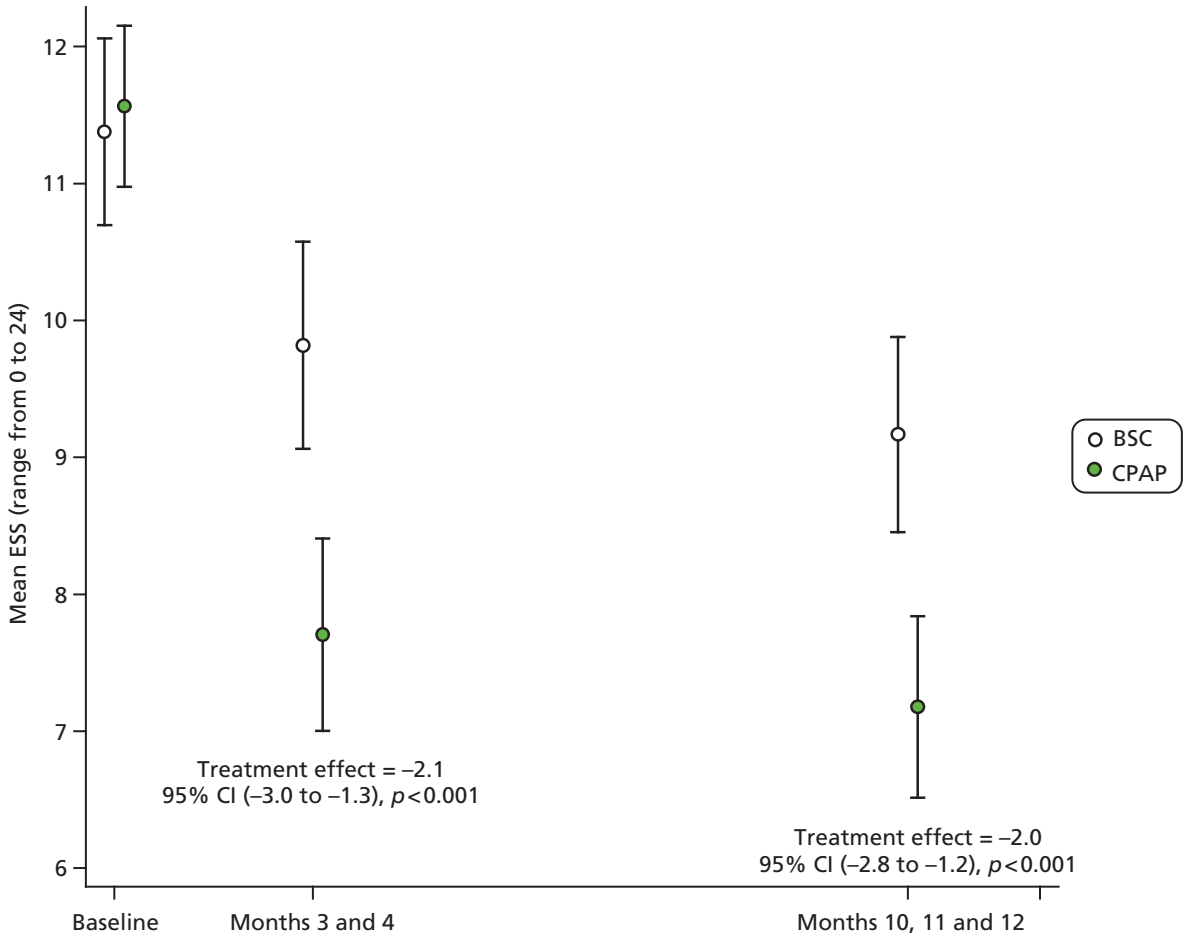

FIGURE 6 The treatment effect of CPAP compared with BSC care on subjective sleepiness. Adjusted treatment effects of CPAP and BSC and their 95% CI on the mean ESS score of months 3 and 4 (coprimary outcome) and of months 10, 11 and 12 (secondary outcome). Lower scores indicate an improvement.

TABLE 11 The effect of the CPAP use on the ESS score over the 3 months prior to 12-month assessment

		CPAP		
Descriptor	BSC	First tertile	Second tertile	Third tertile
n	122	52	30	30
Mean usage (hours/night) (minimum–maximum)	–	0 (0–0)	2.3 (0.002–4.4)	6.3 (4.5–8.9)
Baseline ESS score, mean (SD)	11.3 (4.0)	11.2 (3.5)	11.4 (4.0)	11.8 (2.6)
ESS score months 10,11 and 12, mean (SD)	9.2 (4.0)	8.1 (3.9)	7.3 (3.5)	5.6 (2.6)
Change, mean (SD)	–2.1 (3.6)	–3.0 (4.4)	–4.2 (3.4)	–6.2 (3.3)
Treatment effect (95% CI)	–	–1.0 (–2.0 to 0.1)	–2.0 (–3.2 to –0.7)	–3.6 (–4.9 to –2.4)
p-value	–	0.063	0.002	< 0.001

Objective sleepiness

Sleepiness was also measured objectively using the OSLER test at 3 and 12 months. The mean time to fall asleep is shown in *Tables 12* and *13* (3 and 12 months, respectively). The difference between groups was statistically significant at 3 months ($p = 0.024$) in favour of CPAP but less so at 12 months ($p = 0.058$). The mean time for patients to fall asleep is also shown in Kaplan–Meier plots in *Figure 7*.

TABLE 12 Oxford Sleep Resistance test at 3 months

Time assessed	BSC	CPAP	Treatment effect (minutes), (95% CI)	*p*-value
n	121	116	2.8 (0.4 to 5.2)	0.024
Baseline, mean time to sleep (minutes) (SD)	21.5 (13.4)	23.6 (12.7)		
Month 3, mean time to sleep (minutes) (SD)	22.8 (13.9)	27.3 (12.4)		
Mean change from baseline 3 months (SD)	1.3 (10.8)	3.6 (10.6)		

TABLE 13 Oxford Sleep Resistance test at 12 months

Time assessed	BSC	CPAP	Treatment effect (minutes), (95% CI)	*p*-value
n	115	110	2.6 (–0.1 to 5.3)	0.058
Baseline, mean time to sleep (minutes) (SD)	21.4 (13.3)	24.5 (12.7)		
Month 12, mean time to sleep (minutes) (SD)	23.8 (13.4)	27.8 (11.6)		
Mean change from baseline at 12 months (SD)	2.4 (11.9)	3.3 (13.2)		

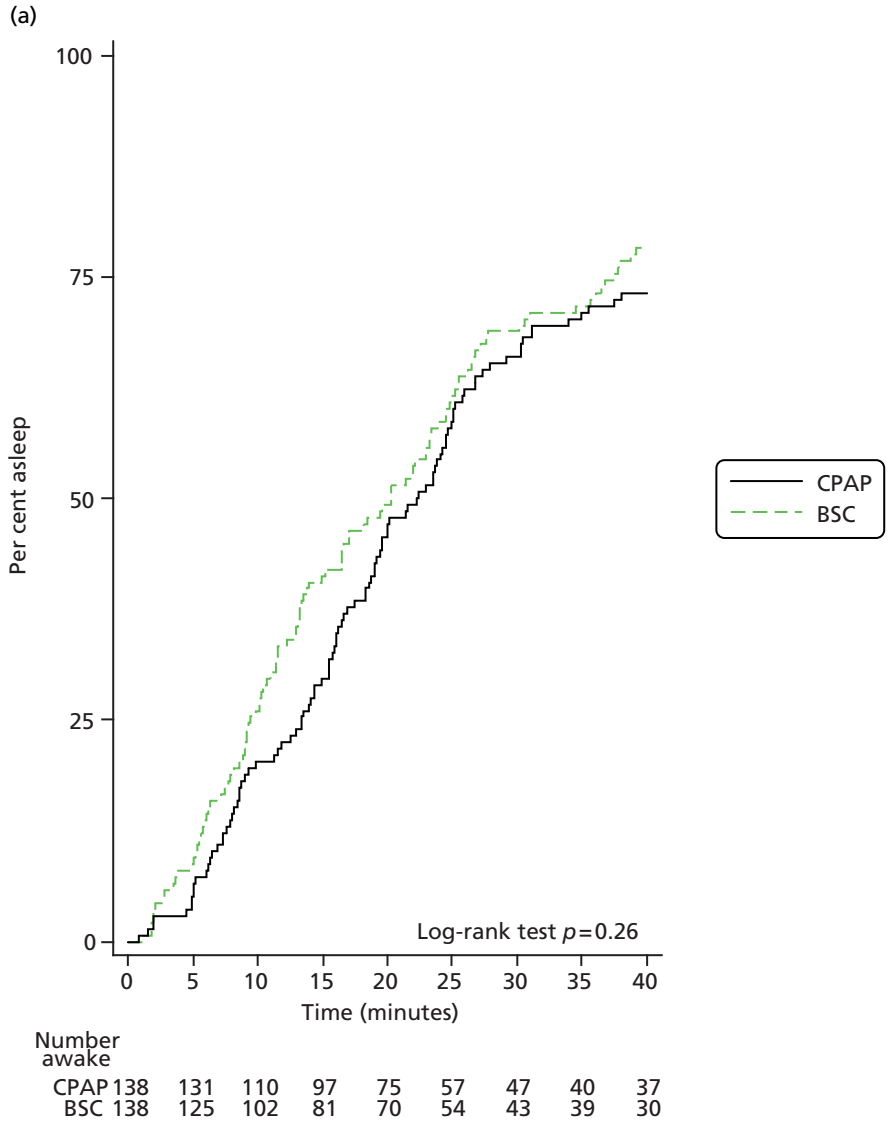

FIGURE 7 Kaplan–Meier plot of average time taken to fall asleep for each patient at baseline, 3 months and 12 months. (a) Baseline; (b) 3-month visit; and (c) 12-month visit. (*continued*)

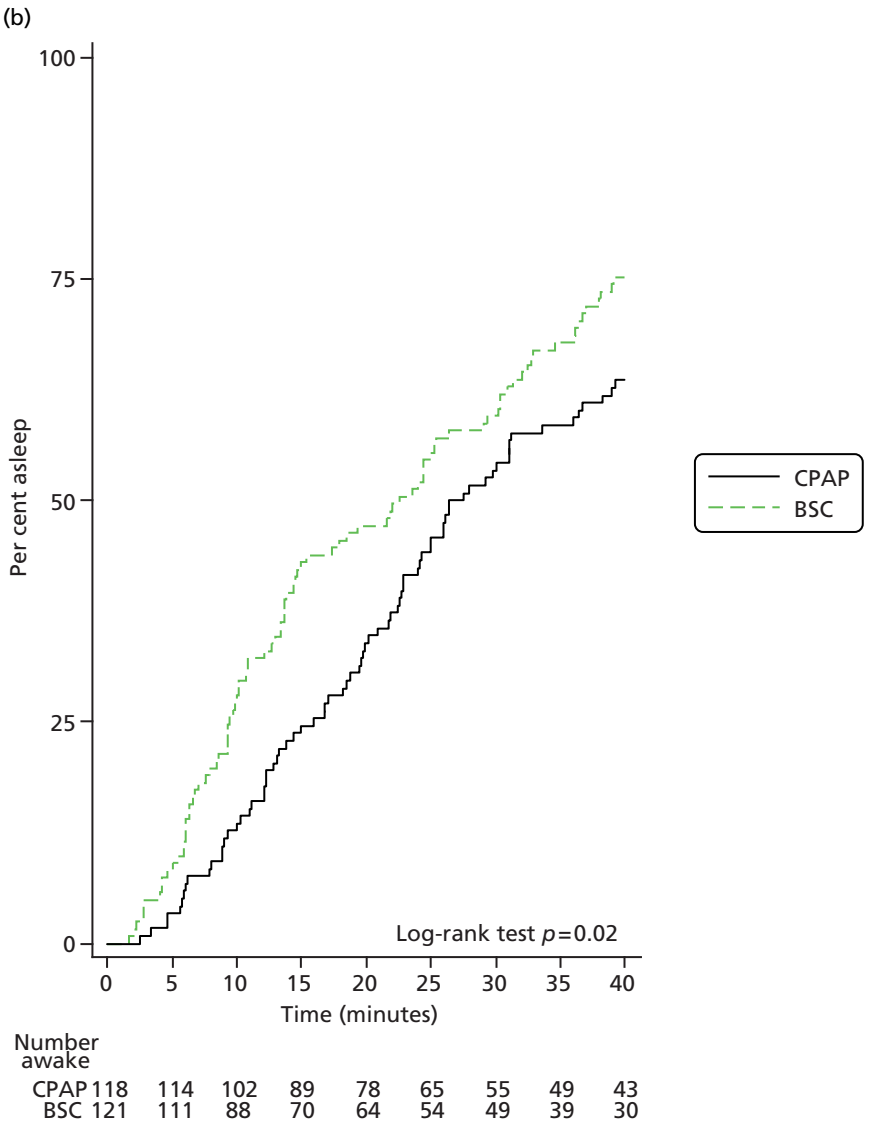

FIGURE 7 Kaplan–Meier plot of average time taken to fall asleep for each patient at baseline, 3 months and 12 months. (a) Baseline; (b) 3-month visit; and (c) 12-month visit. (*continued*)

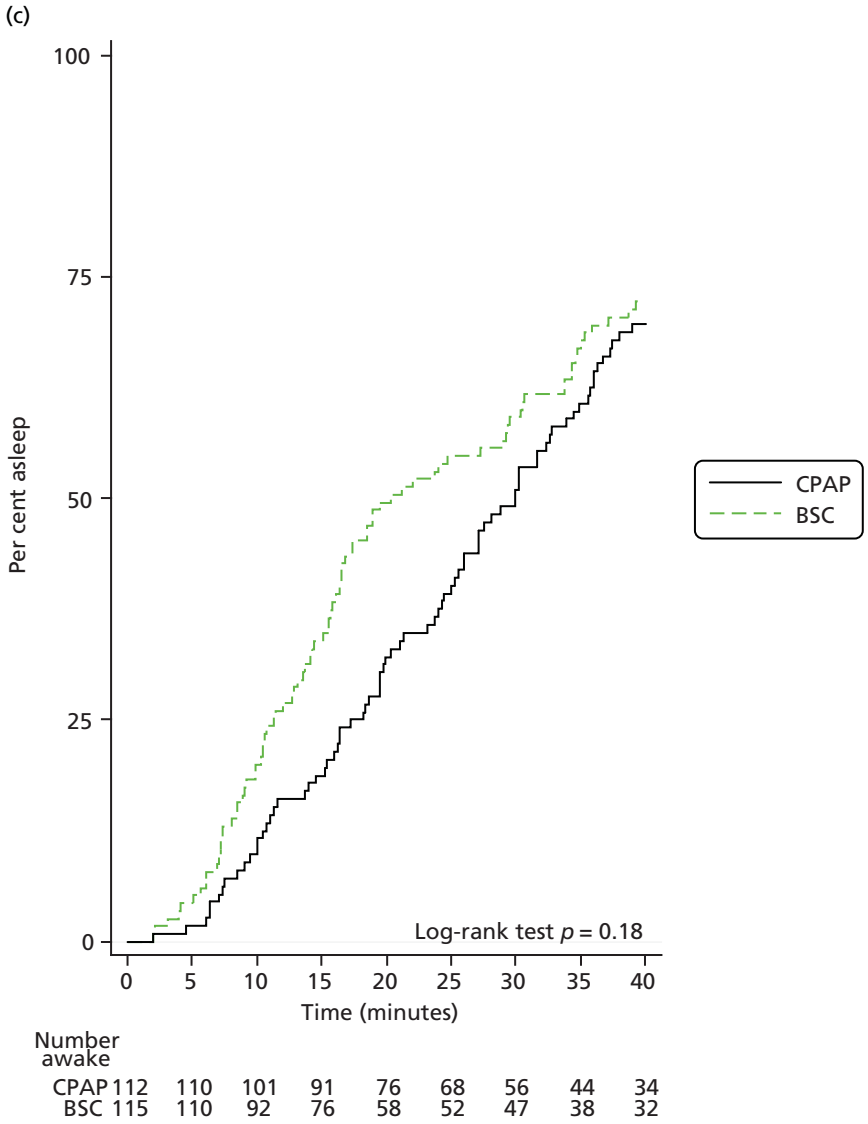

FIGURE 7 Kaplan–Meier plot of average time taken to fall asleep for each patient at baseline, 3 months and 12 months. (a) Baseline; (b) 3-month visit; and (c) 12-month visit.

Quality of life and mood

Generic quality of life was assessed using the SF-36 (version 1) at 3 and 12 months. Raw scores were analysed with factor loadings obtained from Jenkinson *et al.*[102] The difference between groups in the energy/vitality domain was statistically significant at 3 months ($p = 0.001$) and 12 months ($p = 0.004$) in favour of CPAP. The MCS score was also statistically significant at 3 months ($p = 0.046$) but not at 12 months ($p = 0.22$). The physical functioning score was also statistically significant at 12 months ($p = 0.033$) in favour of CPAP but not at 3 months ($p = 0.16$). The difference between the two groups on each summary score at the 3- and 12-month visits is shown in *Figure 8*.

Disease-specific quality of life was measured using the SAQLI, a sleep apnoea-specific questionnaire which also incorporates side effects associated with CPAP. Both groups showed an improvement but the effect was greater in the CPAP group at 3 months ($p = 0.005$) and 12 months ($p = 0.001$).

Mood was assessed using the HADS, which was summarised into an anxiety score and a depression score. Both groups showed a reduction in their score at 3 and 12 months but the difference between groups at either time point was not statistically significant.

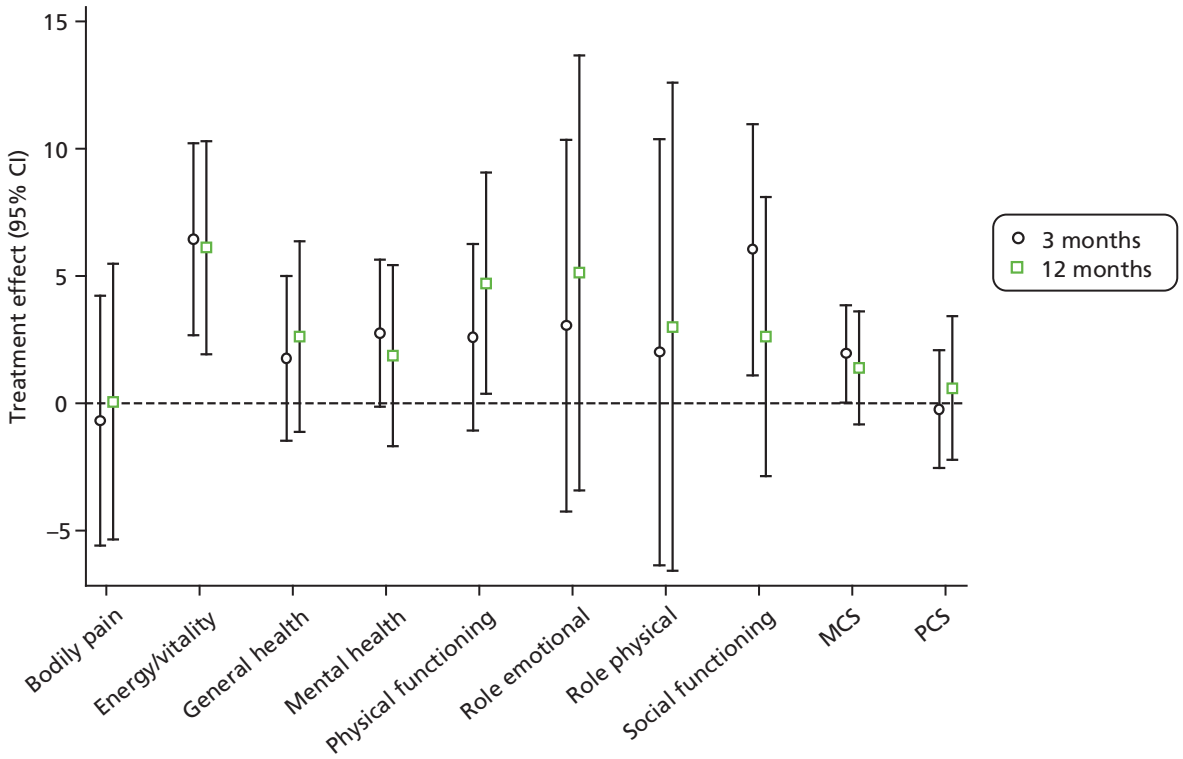

FIGURE 8 Short Form questionnaire-36 items treatment effects at 3 and 12 months. Adjusted treatment effects and their 95% CI, CPAP versus BSC, on the MCS, the PCS and the eight individual components at 3 and 12 months. Higher score indicate an improvement.

The SF-36, SAQLI and HADS scores are shown in *Tables 14* and *15* (3 and 12 months, respectively).

Functionality

The average TDS was higher at 3 and 12 months than at baseline in both groups. The difference between the groups at 3 months ($p = 0.21$) and 12 months ($p = 0.89$) was not statistically significant.

Nocturia

The frequency of nocturia appeared to decrease in both groups. The difference between the groups at 3 months ($p = 0.64$) and 12 months ($p = 0.74$) was not statistically significant.

Mobility

There was no change in the average TUG test time in the CPAP group, while there was a slight increase in the BSC group at 3 months. The difference was –0.8 seconds (95% CI –1.4 to –0.1 seconds); this difference of just under 1 second was statistically significant ($p = 0.029$) in favour of CPAP at 3 months. By 12 months the difference between the groups had reduced to –0.1 seconds (95% CI –0.9 to 0.7 seconds) in favour of CPAP, but this was not statistically significant ($p = 0.80$).

Accidents

More self-reported domestic accidents were reported at each follow-up assessment than at baseline in both groups. The difference between the groups was not statistically significant ($p = 0.28$) at 3 months or 12 months ($p = 0.11$). Very few RTAs were reported in both treatment groups at each visit. The difference in the overall number of accidents between groups was not statistically significant at 3 months ($p = 0.36$) or at 12 months ($p = 0.20$).

The results for functionality, nocturia, mobility and accidents are shown in *Tables 16* and *17*.

TABLE 14 Quality of life and mood questionnaires at 3 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 3, mean (SD)	Treatment effect (95% CI)	*p*-value
SF-36								
Bodily pain	125	59.9 (26.8)	60.5 (26.4)	123	61.9 (28.4)	61.4 (26.9)	–0.7 (–5.6 to 4.2)	0.78
Energy/vitality	123	45.8 (22.0)	47.0 (22.5)	121	49.9 (20.5)	56.6 (20.9)	6.4 (2.7 to 10.2)	0.001
General health	124	55.9 (21.8)	55.3 (22.1)	123	56.5 (23.4)	57.7 (22.1)	1.8 (–1.5 to 5.0)	0.29
Mental health	125	76.7 (14.7)	77.7 (16.8)	123	76.2 (17.2)	80.4 (15.4)	2.8 (–0.1 to 5.6)	0.062
Physical functioning	124	54.9 (29.0)	55.0 (29.5)	121	58.2 (26.3)	60.6 (27.5)	2.6 (–1.1 to 6.3)	0.16
Role emotional	125	72.3 (39.2)	72.8 (37.0)	122	76.8 (38.3)	78.7 (34.8)	3.0 (–4.3 to 10.3)	0.41
Role physical	122	40.4 (42.2)	44.5 (40.8)	122	53.1 (40.9)	53.5 (41.8)	2.0 (–6.4 to 10.4)	0.64
Social functioning	125	73.7 (27.8)	72.0 (29.0)	123	76.5 (25.8)	80.1 (25.1)	6.0 (1.1 to 11.0)	0.017
MCS	118	51.2 (9.9)	51.5 (10.0)	119	51.9 (10.1)	54.1 (8.9)	1.9 (0.0 to 3.8)	0.046
PCS	118	31.0 (13.6)	31.7 (15.1)	119	34.2 (13.8)	34.2 (14.3)	–0.2 (–2.5 to 2.1)	0.84
SAQLI								
–	119	4.7 (1.2)	5.0 (1.1)	121	4.8 (1.2)	5.3 (1.1)	0.3 (0.1 to 0.5)	0.005
HADS								
Anxiety	125	5.5 (3.7)	4.9 (3.5)	123	5.3 (4.0)	4.2 (3.4)	–0.5 (–1.1 to 0)	0.064
Depression	124	4.4 (3.0)	4.3 (2.9)	123	4.5 (2.8)	4.0 (2.9)	–0.4 (–0.9 to 0.1)	0.17

TABLE 15 Quality of life and mood questionnaires at 12 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 12, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)	Treatment effect (95% CI)	*p*-value
SF-36								
Bodily pain	117	60.2 (26.3)	59.2 (27.2)	114	61.2 (28.4)	60.5 (26.9)	0.1 (–5.4 to 5.5)	0.98
Energy/vitality	116	46.6 (21.8)	48.4 (22.6)	112	49.4 (20.4)	56.7 (21.4)	6.1 (1.9 to 10.3)	0.004
General health	116	56.0 (21.4)	54.8 (22.0)	114	55.9 (23.6)	57.8 (21.8)	2.6 (–1.1 to 6.4)	0.17
Mental health	117	76.7 (14.5)	78.0 (18.0)	113	76.3 (17.9)	79.7 (17.2)	1.9 (–1.7 to 5.4)	0.30
Physical functioning	117	55.5 (28.5)	54.3 (29.1)	113	57.2 (26.3)	60.7 (29.1)	4.7 (0.4 to 9.1)	0.033
Role emotional	117	72.6 (38.8)	72.9 (38.9)	113	76.4 (38.8)	79.6 (33.5)	5.1 (–3.4 to 13.7)	0.24
Role physical	116	41.8 (41.7)	42.2 (42.0)	112	52.5 (41.2)	50.4 (42.8)	3.0 (–6.6 to 12.6)	0.54
Social functioning	117	73.1 (26.9)	74.3 (29.2)	114	76.2 (26.2)	78.9 (25.3)	2.6 (–2.9 to 8.1)	0.35
MCS	114	51.1 (9.8)	52.0 (10.4)	108	52.1 (10.2)	53.9 (9.4)	1.4 (–0.8 to 3.6)	0.22
PCS	114	31.3 (13.2)	30.9 (15.3)	108	33.8 (13.9)	33.7 (14.9)	0.6 (–2.2 to 3.4)	0.68
SAQLI								
–	114	4.7 (1.2)	5.1 (1.1)	113	4.8 (1.2)	5.5 (1.1)	0.4 (0.2 to 0.6)	0.001
HADS								
Anxiety	117	5.5 (3.6)	4.5 (3.5)	114	5.2 (3.9)	4.1 (3.5)	–0.2 (–0.9 to 0.5)	0.58
Depression	116	4.4 (3.0)	4.2 (3.2)	114	4.6 (2.9)	3.9 (3.1)	–0.4 (–1.0 to 0.3)	0.23

TABLE 16 Functionality (TDS); nocturia, mobility (TUG test); and accidents at 3 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 3, mean (SD)	Treatment effect (95% CI)	*p*-value
TDS	118	4.0 (4.5)	4.7 (4.8)	120	3.6 (4.0)	3.9 (4.1)	–0.4 (–1.0 to 0.2)	0.21
Nocturia (times/night)	123	2.1 (1.3)	1.8 (1.2)	121	1.9 (1.3)	1.7 (1.2)	0.1 (–0.2 to 0.3)	0.64
TUG test (seconds)	117	12.0 (4.5)	12.5 (5.3)	117	11.4 (4.6)	11.3 (3.9)	–0.8 (–1.4 to –0.1)	0.029
Domestic accidents *n* of patients with event(s), *n* (%)	124	12 (9.7)	14 (11.2)	121	6 (5.0)	18 (14.9)	1.53 (0.71 to 3.31)	0.28
Driving accidents *n* of patients with event(s), *n* (%)	88	2 (2.3)	1 (1.1)	81	1 (1.2)	0	–	–
All accidents *n* patients with event(s), *n* (%)	124	13 (10.5)	15 (12.1)	121	7 (5.8)	18 (14.9)	1.42 (0.67 to 3.03)	0.36

TABLE 17 Functionality (TDS); nocturia, mobility (TUG test); and accidents at 12 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)	Treatment effect (95% CI)	*p*-value
TDS	115	4.0 (4.3)	4.8 (5.2)	115	3.7 (4.1)	4.2 (4.5)	–0.1 (–0.9 to 0.8)	0.89
Nocturia (times/night)	116	2.1 (1.3)	1.8 (1.1)	113	1.9 (1.3)	1.6 (1.4)	0 (–0.2 to 0.3)	0.74
TUG test (seconds)	107	11.7 (4.2)	12.0 (4.6)	108	11.5 (4.7)	11.8 (4.5)	–0.1 (–0.9 to 0.7)	0.80
Domestic accidents, *n* of patients with event(s) (%)	117	12 (10)	18 (15)	113	6 (5)	9 (8)	0.49 (0.21 to 1.18)	0.11
Driving accidents, *n* of patients with event(s) (%)	77	2 (3)	1 (1)	73	1 (1)	2 (3)	–	–
All accidents, *n* of patients with event(s) (%)	117	13 (11)	19 (16)	113	6 (5)	11 (10)	0.59 (0.26 to 1.32)	0.20

Cognitive function

Cognitive function was assessed at 3 and 12 months with the following tests: MMSE, TMT–B, the DSS test and simple and four-choice reaction time test. The results are shown in *Tables 18* and *19*. The difference between the groups was not statistically significant for any of the four tests at 3 or 12 months.

Cardiovascular risk factors

The cardiovascular risk factors at 3 and 12 months are shown in *Tables 20* and *21*, respectively. CPAP reduced total cholesterol at 3 months compared with BSC by –0.2 mmol/l (95% CI –0.3 mmol/l to 0.0 mmol/l) ($p = 0.048$). This was driven by a reduction in low-density liproprotein (LDL) cholesterol of –0.15 mmol/l (95% CI –0.29 mmol/l to –0.01 mmol/l) ($p = 0.042$). At 12 months the average total and LDL cholesterol were lower than at baseline in both groups and although the CPAP group had a further reduction in total and LDL cholesterol from the 3-month assessment, the difference between groups at 12 months was not statistically significant; total cholesterol ($p = 0.51$) and LDL cholesterol ($p = 0.29$).

At 12 months there was a reduction in the systolic BP in the BSC group not seen in the CPAP group, which led to a difference between the groups of 3.7 mmHg (95% CI 0.2 mmHg to 7.3 mmHg) in favour of BSC, which was statistically significant ($p = 0.040$).

Cardiovascular events

New self-reported cardiovascular events were documented at 3 and 12 months and are shown in *Tables 22* and *23*. Atrial fibrillation was the predominant event, with more events being recorded in the BSC group, although overall the difference between groups was not statistically significant at 3 or 12 months ($p = 0.48$, $p = 0.72$).

TABLE 18 Cognitive function at 3 months

	BSC			CPAP				
Outcome measure	*n*	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 3, mean (SD)	Treatment effect (95% CI)	*p*-value
MMSE	123	28.5 (2.1)	28.7 (1.8)	120	28.2 (2.1)	28.3 (2.1)	–0.2 (–0.6 to 0.2)	0.25
DSS test	123	38.7 (11.1)	39.6 (11.6)	119	37.5 (11.9)	39.5 (11.2)	0.8 (–0.9 to 2.5)	0.36
TMT–B (seconds)	123	117.9 (58.9)	108.6 (49.7)	117	117.7 (55.0)	109.7 (42.7)	0.7 (–7.2 to 8.5)	0.87
Simple reaction time test								
Mean time (seconds)	95	382.9 (111.5)	394.4 (129.2)	102	379.5 (85.4)	380.4 (89.9)	–12.8 (–39.9 to 14.3)	0.35
Four-choice reaction time								
Number of correct answers	100	38.3 (2.3)	38.5 (1.9)	102	38.6 (2.3)	38.6 (1.9)	–0.1 (–0.5 to 0.4)	0.82
Mean time for correct answers (seconds)	100	680.8 (207.9)	666.6 (181.4)	102	682.3 (155.9)	699.4 (174.2)	32.0 (–0.7 to 64.8)	0.055

TABLE 19 Cognitive function at 12 months

	BSC			CPAP				
Outcome measure	*n*	Baseline, mean (SD)	Month 12, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)	Treatment effect (95% CI)	*p*-value
MMSE	116	28.5 (2.0)	28.5 (1.7)	113	28.3 (2.0)	28.5 (1.9)	0.1 (–0.3 to 0.5)	0.65
DSS test	116	39.4 (10.4)	40.6 (11.3)	113	37.2 (11.7)	40.0 (10.7)	1.1 (–0.6 to 2.7)	0.22
TMT–B (seconds)	115	113.7 (55.8)	107.6 (47.2)	111	119.9 (57.9)	116.6 (54.9)	6.2 (–3.4 to 15.8)	0.21
Simple reaction time test								
Mean time (seconds)	99	379.4 (108.1)	388.1 (108.1)	98	376.2 (84.6)	370.0 (94.6)	–16.4 (–39.1 to 6.2)	0.16
Four-choice reaction time								
Number of correct answers	100	38.5 (2.1)	38.4 (2.5)	99	38.6 (2.5)	38.7 (1.7)	0.3 (–0.2 to 0.8)	0.26
Mean time for correct answers (seconds)	100	681.9 (204.2)	688.4 (215.7)	99	678.8 (204.2)	688.1 (166.0)	1.8 (–33.6 to 37.2)	0.92

TABLE 20 Cardiovascular risk factors at 3 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 3, mean (SD)	Treatment effect (95% CI)	*p*-value
Systolic BP (mmHg)	123	141.3 (19.8)	137.4 (16.3)	120	137.5 (18.1)	136.3 (15.9)	0.7 (–2.5 to 3.8)	0.69
Diastolic BP (mmHg)	123	78.2 (12.6)	76.4 (11.0)	120	77.2 (10.2)	76.1 (10.0)	0.1 (–1.9 to 2.2)	0.91
Total cholesterol (mmol/l)	117	4.6 (1.1)	4.6 (1.1)	114	4.6 (1.1)	4.5 (1.0)	–0.2 (–0.3 to 0)	0.048
HDL (mmol/l)	116	1.29 (0.39)	1.28 (0.36)	110	1.18 (0.29)	1.18 (0.31)	–0.02 (–0.06 to 0.02)	0.44
LDL (mmol/l)	108	2.63 (0.87)	2.64 (0.91)	102	2.69 (0.98)	2.56 (0.89)	–0.15 (–0.29 to –0.01)	0.042
Triglycerides (mmol/l)	115	1.61 (0.88)	1.59 (0.77)	108	1.75 (0.88)	1.76 (1.00)	0.06 (–0.08 to 0.20)	0.38
Glucose (mmol/l)	119	6.2 (2.2)	6.2 (1.9)	112	6.3 (1.9)	6.3 (2.0)	0.1 (–0.3 to 0.5)	0.54
HbA_{1c} (mmol/mol)	111	46.6 (11.7)	47.2 (12.3)	109	46.2 (11.2)	46.5 (11.6)	–0.3 (–1.6 to 1.1)	0.70

HDL, high-density lipoprotein.

TABLE 21 Cardiovascular risk factors at 12 months

	BSC			CPAP				
Outcome	*n*	Baseline, mean (SD)	Month 12, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)	Treatment effect (95% CI)	*p*-value
Systolic BP (mmHg)	116	141.7 (20.3)	135.5 (17.3)	113	138.0 (18.2)	137.5 (15.6)	3.7 (0.2 to 7.3)	0.04
Diastolic BP (mmHg)	116	78.5 (12.9)	76.2 (12.0)	113	77.8 (10.6)	76.2 (9.9)	0.2 (–2.1 to 2.5)	0.84
Total cholesterol (mmol/l)	108	4.6 (1.1)	4.5 (1.0)	109	4.6 (1.1)	4.4 (1.1)	–0.1 (–0.3 to 0.1)	0.51
HDL (mmol/l)	106	1.28 (0.39)	1.25 (0.37)	106	1.19 (0.28)	1.18 (0.30)	0.01 (–0.03 to 0.06)	0.57
LDL (mmol/l)	101	2.61 (0.88)	2.55 (0.93)	100	2.66 (0.97)	2.50 (0.94)	–0.09 (–0.26 to 0.08)	0.29
Triglycerides (mmol/l)	105	1.62 (0.90)	1.59 (0.79)	106	1.75 (0.87)	1.74 (0.96)	0.06 (–0.10 to 0.22)	0.48
Glucose (mmol/l)	110	6.3 (2.2)	6.4 (2.4)	108	6.2 (1.8)	6.3 (1.8)	0.0 (–0.4 to 0.4)	0.93
HbA_{1c} (mmol/mol)	104	46.6 (11.8)	47.7 (14.9)	102	46.5 (11.2)	46.8 (12.5)	–0.9 (–3.1 to 1.4)	0.45

HDL, high-density lipoprotein.

TABLE 22 Cardiovascular events at 3 months

Adverse cardiovascular event	BSC			CPAP			Odds ratio (95% CI)	*p*-value
	n	Baseline, mean (SD)	Month 3, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)		
MI, *n* (%)	124	23 (19)	0	121	21 (17)	1 (1)		
Stroke, *n* (%)	124	4 (3)	0	121	2 (2)	0		
Transient ischaemic attack, *n* (%)	124	12 (10)	1 (1)	121	15 (12)	0		
New angina, *n* (%)	124	32 (26)	0	120	29 (24)	1 (1)		
New atrial fibrillation, *n* (%)	124	37 (30)	4 (3)	121	24 (20)	5 (4)		
New peripheral vascular disease, *n* (%)	124	3 (2)	0	121	1 (1)	0		
All adverse cardiovascular events, *n* (%)	124	60 (48)	5 (4)	121	56 (46)	7 (6)	1.54 (0.47 to 5.06)	0.48

TABLE 23 Cardiovascular events at 12 months

Adverse cardiovascular event	BSC			CPAP			Odds ratio (95% CI)	*p*-value
	n	Baseline, mean (SD)	Month 12, mean (SD)	*n*	Baseline, mean (SD)	Month 12, mean (SD)		
MI, *n* (%)	117	21 (18)	0	114	22 (19)	3 (3)		
Stroke, *n* (%)	117	3 (3)	0	114	1 (1)	0		
Transient ischaemic attack, *n* (%)	117	9 (8)	2 (2)	114	12 (11)	1 (1)		
New angina, *n* (%)	117	27 (23)	3 (3)	113	26 (23)	2 (2)		
New atrial fibrillation, *n* (%)	117	32 (27)	14 (12)	114	22 (19)	7 (6)		
New peripheral vascular disease, *n* (%)	117	3 (3)	0	114	1 (1)	1 (1)		
All adverse cardiovascular events, *n* (%)	117	56 (48)	17 (15)	114	51 (45)	14 (12)	0.87 (0.40 to 1.88)	0.72

Tertiary outcome

Of the 140 patients randomised to CPAP treatment, 120 (86%) reported that they were still using CPAP at 3 months and 99 (71%) at 12 months. Actual CPAP data were obtained in 117 patients at 3 months, with median usage of 1.52 hours/night [interquartile range (IQR) 0.19 to 5.12 hours], and 102 patients at 12 months, with median usage of 2.22 hours/night (IQR 0.10 to 5.09 hours). Assuming zero usage in those patients with missing data and who stopped treatment during follow-up gave a more conservative estimate of median CPAP use of 1.33 hours/night (IQR 0.13 to 5.0 hours) at 3 months and 1.26 hours/night (IQR 0.04 to 4.45) at 12 months. CPAP usage data are shown in *Table 24*.

Serious adverse events

There were 37 serious adverse events, of which 15 (in 12 patients) occurred in the CPAP group and 22 (in 13 patients) in the BSC group. They included two deaths, one in the CPAP group and one in the BSC group. All events were independently classified as unrelated to the trial. There was no suggestion of clinically important harm from CPAP use.

TABLE 24 Continuous positive airway pressure usage over 3 and 12 months

Time assessed	Over first 3 months	Over 12 months
n randomised	140	140
n (%) analysed	117 (84%)	102 (73%)
Median use (mean hours/night) (IQR)	01.52 (00.19–05.12)	02.22 (00.10–05.09)
Using CPAP > 4 hours/night, *n/N* (%)	41/117 (35)	36/102 (35)
Missing data and stopped CPAP, *n/N* (%)	7/140 (5)	12/140 (9)
Median use (hours/night) (IQR)[a]	01.33 (00.13–05.00)	01.26 (00.04–04.45)

a Including patients with missing data.

Self-reported side effects

This trial involved the use of an approved medical device which is the mainstay of treatment for OSAS in middle-aged populations. Therefore, the TSC did not expect any serious adverse events or adverse reactions of relevance to the device. Nonetheless, CPAP is associated with common side effects which were reported by the patients. The side effects were independently classified into categories, as suggested by the IDMC and TSC, and presented in *Table 25*. Treatment side effects are also incorporated in the SAQLI questionnaire.

TABLE 25 Self-reported side effects attributable to OSAS or its treatment

Side effect	BSC	CPAP
n	138	140
Possibly related to OSAS,* n *(%)		
Daytime sleepiness/morning headaches/snoring/raised haematocrit	4 (3)	2 (1)
Cardiac dysrhythmias (e.g. atrial fibrillation)	5 (4)	1 (1)
Other cardiovascular events (e.g. stroke, transient ischaemic attack, heart failure, angina)	5 (4)	2 (1)
RTAs	1 (1)	–
Probably related to CPAP,* n *(%)		
Interface-related issues (e.g. claustrophobia, dislike of mask, leaking air, red/watery eyes, sore skin, pressure uncomfortable)	–	33 (24)
Upper airway problems (e.g. dry mouth, runny or stuffy nose, sinus problems, nose bleeds)	–	47 (34)
Abdominal bloating, *n* (%)	–	4 (3)
Anxiety/dyspnoea related to CPAP	–	4 (3)
General inconvenience or intolerance of CPAP or accident using the CPAP machine	–	4 (3)
Possibly related to either OSAS or CPAP		
Disturbed sleep (e.g. insomnia, noisy equipment)	–	2 (1)
Social issues (e.g. partner disturbed, inconvenience)	–	2 (1)
Probably unrelated,* n *(%)		
Lower respiratory problems (e.g. cough, bronchitis, worsening asthma, pneumonia, 'chest infection')	5 (4)	6 (4)
Incidental medical conditions	19 (14)	21 (21)
Accidents (unrelated to sleepiness)	–	2 (1)
Upper respiratory tract infection	–	7 (5)

Chapter 4 Health economics

The evaluation of the cost-effectiveness evidence of CPAP for the treatment of OSAS in people aged 65 years and over comprises a systematic review of the existing cost-effectiveness evidence on CPAP, within-trial analysis based on individual patient data collected during the 12 months of the PREDICT, and decision-analytic modelling to extrapolate to a lifetime time horizon and incorporating relevant external evidence.

Systematic review of existing cost-effectiveness evidence on continuous positive airway pressure

This systematic review provides an overview of the existing cost-effectiveness evidence, as well as an assessment of the quality and relevance of the data from the perspective of the UK NHS, on whether or not CPAP is a cost-effective treatment for patients aged ≥ 65 years. *Appendix 3* reports the methods and detailed results of the systematic review, including summary data and extraction tables of the relevant studies. An overall summary of the cost-effectiveness evidence and key areas of uncertainty is provided below. The findings from the review provide the basis for the development of a new decision-analytic model reported in *Economic model*.

The systematic review on the existing cost-effectiveness evidence on CPAP for the treatment of OSAS found 10 relevant studies. Most studies used a Markov model to synthesise the available evidence;[20,111–115] health states for cardiovascular events and RTAs were typically included. The characterised health effects of CPAP included lower risk of RTAs,[20,111–117] work accidents,[116] cardiovascular events[20,112–114,116,117] and diabetes,[116] and direct improvements in HRQoL from reduced sleepiness (all 10 studies). The improvement in HRQoL was estimated by converting other measures of quality of life[118] or daytime sleepiness[20,114] into health utilities, obtained directly from patients in before-and-after studies[111–113,115,119] or from assumptions.[116,117] All studies concluded that CPAP is a cost-effective treatment for patients with OSAS. In general, the cost-effectiveness results were robust to alternative assumptions on parameter inputs with the exception of the health utility gain from treatment with CPAP.

The studies share two key limitations for the current decision problem:

1. None examined the cost-effectiveness of CPAP in patients aged ≥ 65 years.
2. All relied on indirect evidence to estimate the health utility benefit from treatment.

Although CPAP is likely to be beneficial in older people (as discussed in *Chapter 1*), the magnitude of such benefits cannot be inferred from the estimates obtained from younger populations. CPAP may be at least as cost-effective in older people, given their greater baseline risk of cerebrovascular events and the greater prevalence of age-related cognitive dysfunction, which CPAP could improve. On the other hand, CPAP may be less cost-effective, since older people generally suffer from other conditions which may affect sleep, such as Parkinson's disease, which are not affected by CPAP. In addition, CPAP may be less effective in reducing BP in older people given their reduced acute BP response to each arousal from sleep. Finally, older people are likely to drive less often than working-age people (or shorter distances) and therefore have a lower risk of RTAs.

The limitations of the studies discussed above support a de novo analysis of the cost-effectiveness of CPAP, particularly focused on older people, and the integration of health utility evidence reported directly from patients in PREDICT. The analysis has two components, a within-trial analysis based on PREDICT which examines the cost-effectiveness of CPAP over 1 year and a decision model extrapolating to the patients' lifetime and integrating external evidence.

Within-trial economic evaluation

Methods

Individual patient data from PREDICT were used to estimate health outcomes, costs and cost-effectiveness of CPAP in addition to BSC compared with BSC alone over 12 months. Costs were evaluated in pounds sterling at a 2012 price base from the UK NHS perspective. Health outcomes were expressed as QALYs. All analyses and modelling were undertaken in Stata 12.0.

Health outcomes

Health outcomes were expressed in QALYs using EQ-5D in the base case and SF-6D as an alternative scenario. Patients reported HRQoL by filling in EQ-5D questionnaires every month and using the SF-36 at baseline and at the 3-month and 12-month visits. EQ-5D scores are valued using the UK tariff.[120] SF-36 was translated into SF-6D using the Brazier *et al.*[121] algorithm. Patients who died had their HRQoL set to zero from the date of death. QALYs for each patient were calculated as the area under the curve, following the trapezium rule.[122] Differences in mean QALYs between the two patient groups were adjusted for HRQoL scores at baseline.[123]

Resource use and costs

Health-care resource use was recorded in the monthly diaries filled in by patients. Information recorded in the diaries included information on medication initiated or discontinued, GP visits, nurse visits, telephone calls to the GP and to NHS Direct, ambulance use, visits to the accident and emergency department, outpatient appointments, hospital overnight admissions, emergency admissions and total number of nights in hospital over the past month. It was assumed that resource use associated with the RTAs or home accidents that were recorded during the trial would have been recorded in the monthly diary. *Table 26* shows the unit costs applied to each resource use item in order to calculate the total cost per patient. Medication was not included in the total costs because the large majority of these were low-cost generics, use of which was unlikely to change the results.

TABLE 26 Unit costs for health-care resource use

Health-care resource	Unit cost	Reference/comments
Visits to the GP	£43	PSSRU unit costs 2012; 10.8b General practitioner[124]
Home visits from the GP	£110	PSSRU unit costs 2012; 10.8b General practitioner[124]
Visits to nurse	£58/hour	PSSRU unit costs 2012; 10.1 Community nurse.[124] Assumed 15 minutes appointment
Home visit from nurse	£70/hour	PSSRU unit costs 2012; 10.1 Community nurse.[124] Assumed 30 minutes for appointment and travel
Telephone call to GP	£26	PSSRU unit costs 2012; 10.8b General practitioner[124]
Calls to NHS Direct	£28	£25.53 (2007–8)[125] inflated using inflating indices in PSSRU 2012[124]
Ambulance[a]	£292	£263 PSSRU 2008 inflated using inflating indices in PSSRU 2012[126]
A&E visits	£108	NHS Reference Costs 2011–12 – A&E not leading to admitted[127]
Outpatient clinic	£106	NHS Reference Costs 2011–12 – Total outpatient attendances[127]
Hospital overnight admissions	£585	NHS Reference Costs 2011–12 – Non-elective (short stay) HRG data[127]
Emergency admissions	£157	NHS Reference Costs 2011–12 – A&E leading to admitted[127]

A&E, accident and emergency; HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit.
a The unit cost of calls to NHS Direct and ambulance services are obtained from the most up-to-date source available and inflated to 2012 prices using the health and social care inflating indices in the PSSRU unit cost book.[126]

Costs of continuous positive airway pressure treatment

The costs used in the cost-effectiveness analysis to estimate the average cost of treatment applied are shown in *Table 27*. The analysis followed an intention-to-treat strategy; therefore, only the patients allocated to CPAP were assumed to incur the cost of treatment. Patients allocated to BSC who switched to CPAP treatment were assumed not to incur the cost of treatment. Humidification was optional. No data were collected on the number of masks each patient received; therefore, the base case assumes that 90% of patients received one mask and 10% received two masks. The filter was supplied with the machine and it was assumed that it was changed every 6 months. The cost of filters was calculated as the average cost between the normal and the hypoallergenic filter. Patients who discontinue CPAP were assumed to return the machine (together with the humidifier, if applicable) to be re-used by another patient. The device's useful life was assumed to be 7 years for the CPAP machine and the humidifier, 1 year for the masks and 6 months for the air filters. This was based on the assumptions made for the previous cost-effectiveness analyses of CPAP reported in the systematic review and discussions with the clinical team. Therefore, treatment costs were expressed as an annual equivalent cost using the public sector discount rate of 3.5% for machines with a lifetime greater than 1 year.[99,129] These assumptions were varied in the sensitivity analysis.

Missing data

Data were missing or incomplete if patient failed to return a questionnaire, provided a partially complete questionnaire or was lost to follow-up (censored). Missing data at baseline were imputed with mean imputation.[130] Unanswered questions on resource use in the returned questionnaires were assumed to indicate that no resource use had taken place during that month. The remaining missing data were imputed, using multiple imputation with chained equations and predictive mean matching.[131] This approach assumed that data were missing at random, i.e. that the value of the missing data on costs and/or HRQoL could be predicted from the non-missing data. The multiple-imputed data sets constituted the data set used for the base case. *Appendix 3* provides more details on the strategy employed to deal with missing data. Assumptions were varied in the sensitivity analysis.

TABLE 27 Costs of CPAP treatment[128]

Item	Unit cost	Machine life
CPAP machine		
CPAP machine S9 AutoSet™	£430	7 years
Humidifier H5i™ and climate line	£165	7 years
Masks		
Mirage Quattro™ full-face mask	£120	1 year
Mirage Liberty™	£125	1 year
Mirage Swift™	£89	1 year
Mirage Micro™ nasal mask	£80	1 year
Filters		
Air filter (S9™), pack of 50	£8	6 months
Air filter, hypoallergenic (S9™), pack of 50	£50	6 months

All equipment in this table were manufactured by ResMed (UK) Ltd, Abingdon, Oxfordshire, UK.

Base-case analysis

The base-case analysis followed an intention-to-treat strategy, whereby patients were analysed according to allocation, irrespective of compliance with treatment. The cost-effectiveness of CPAP was evaluated by comparing the costs and QALYs in the two patient groups at 1 year, using conventional decision rules and estimating incremental cost-effectiveness ratios (ICERs) as appropriate.[132] The base-case analysis used EQ-5D to calculate QALYs whereas SF-6D was used in an alternative scenario. The probability that CPAP was cost-effective under the thresholds used by NICE (£20,000 and £30,000 per QALY gained) was calculated with semi-parametric bootstrapping.[133,134]

Sensitivity analysis

A number of alternative scenarios were considered in which the assumptions used as part of the base-case results were varied. These analyses were undertaken to assess the robustness of the base-case results to alternative assumptions. *Table 28* summarises the sensitivity analyses. For each element, the position in the base-case analysis is outlined, alongside the alternative assumption applied. These analyses were conducted for both the base-case scenario with QALYs calculated with EQ-5D and the alternative scenario with QALYs calculated from SF-6D.

Subgroup analysis

The aim of the subgroup analysis was to identify patient subgroups where the intervention was potentially more or less cost-effective than in the overall patient population. The clinical effectiveness presented in *Chapter 3* showed that CPAP reduced daytime sleepiness and that the treatment effect was significantly larger in patients with a higher baseline ESS score. No other treatment interactions were found. Therefore, subgroup analysis is presented for patients with more or less severe daytime sleepiness, as measured by ESS score at baseline. The same cut-off points as those used for the stratification in the randomisation process (ESS score of <13 and ESS score of ≥ 13) were used to define less severe (ESS score of <13) and more severe (ESS score of ≥ 13) OSAS. Each of the subgroups were analysed independently with the same analytic model used for the overall population.

TABLE 28 Details of the key elements of the base-case analysis and variation used in the sensitivity analysis

Scenario	Element	Position in base-case analysis	Variation in the sensitivity analysis
1	Costs of CPAP	The costs of the CPAP machine and the humidifier are annuitised over 7 years. Yearly replacement for masks. Filters replaced every 6 months	Frequent replacement scenario:[135] CPAP machine annuitised over 3 years. Masks replaced every 3 months. Filters replaced monthly
2	Time horizon	The time horizon for costs corresponds to the lifetime of the CPAP machine (7 years)	CPAP is assumed to be used for 1 year and discarded after that; therefore, the cost of the machine is not annuitised
3	Missing data	Missing data assumed to be missing at random	Complete-case analysis – missing data assumed to be missing completely at random
4	Missing data	Missing data assumed to be missing at random	Missing data imputed with mean interpolation
5	Missing data	Missing data assumed to be missing at random	Individuals with missing data have 25% greater costs or experience 25% lower HRQoL

Results

Health-related quality of life

The EQ-5D health utility values for each treatment group are shown in *Table 29*. The proportion of patients who answered the EQ-5D questionnaire at each month varied between 100% (CPAP group at baseline) and 66% (CPAP group at months 10 and 11). The proportion of missing data was similar across treatment groups. *Figure 9* shows the observed EQ-5D values over the trial for both patient groups. No clear pattern emerged. The CPAP group had greater mean EQ-5D scores at baseline and at months 2, 4–7, 9 and 12 (and lower scores in the other months); however, the differences were not statistically significant. Therefore, no clear treatment effect emerges from the comparison of EQ-5D scores between groups.

TABLE 29 European Quality of Life-5 Dimensions health utility values over the trial

	BSC				CPAP			
Month	*n*	%	Mean	SD	*n*	%	Mean	SD
0	136	98.55	0.680	0.242	140	100.00	0.693	0.249
1	116	84.06	0.687	0.246	112	80.00	0.684	0.280
2	100	72.46	0.685	0.258	98	70.00	0.700	0.292
3	121	87.68	0.704	0.251	121	86.43	0.672	0.301
4	101	73.19	0.679	0.259	97	69.29	0.692	0.284
5	101	73.19	0.660	0.267	97	69.29	0.671	0.328
6	109	78.99	0.663	0.255	103	73.57	0.677	0.295
7	105	76.09	0.652	0.271	97	69.29	0.687	0.276
8	104	75.36	0.683	0.268	88	62.86	0.668	0.311
9	109	78.99	0.650	0.275	95	67.86	0.682	0.287
10	102	73.91	0.694	0.254	92	65.71	0.647	0.318
11	99	71.74	0.647	0.286	92	65.71	0.656	0.310
12	119	86.23	0.680	0.264	115	82.14	0.689	0.301

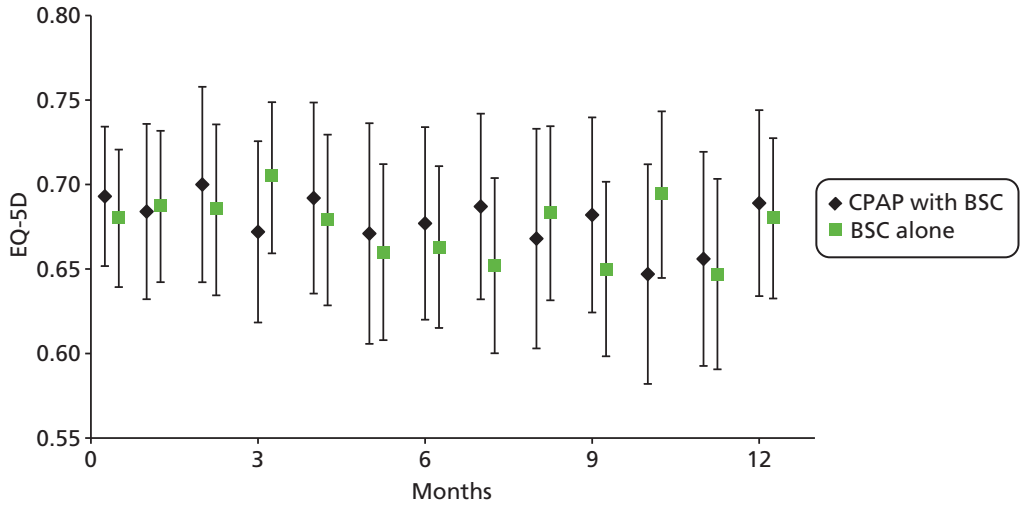

FIGURE 9 European Quality of Life-5 Dimensions health utility values over the trial. Figure shows mean (as a square or lozenge) and the 95% CI (as lines).

The SF-6D health utility values are shown in *Table 30* and *Figure 10*. The proportion of patients who answered the SF-36 questionnaire was higher than for the EQ-5D; this may have been related to the questionnaire being administered at the 3-month and 12-month clinic visit, while the EQ-5D was returned monthly by post. There was also less variability in the SF-6D health utility values than that observed in the EQ-5D. This may also have been related to the administration of the questionnaire or to the differences in the scoring algorithm. The difference between treatment groups was non-statistically significant for the SF-6D.

Health-care resource use and costs

The number and proportion of returned questionnaires on health-care resource are shown in *Table 31*. Baseline refers to the resource use in the month prior to enrolment. The proportion of returned questionnaires was similar across treatment groups and varied between 100% and 66%.

The resources used by each patient group [average number of times (SD) the resource was used] over the 12-month follow-up period are shown in *Table 32*. The estimates were obtained prior to multiple imputation of missing data. The group allocated to BSC alone had more contacts with the NHS but the differences are non-statistically significant. The most frequent contact was visits to GP (CPAP 6.93 vs. BSC 7.27 visits per patient). The second most frequent NHS contact were visits to the nurse (CPAP 3.36 vs. BSC 4.78 visits per patient), followed by outpatient appointments (CPAP 2.83 vs. BSC 3.65 per patient). Hospital overnight admissions were rare (CPAP 0.42 vs. BSC 0.55 per patient). There were 93 patients in the CPAP group who initiated medication (386 items) and 62 who discontinued medication (197 items), whereas in the BSC group 92 patients initiated medication (444 items) and 57 discontinued medication (192 items).

TABLE 30 Short Form questionnaire-6 Dimensions health utility values over the trial

	BSC				CPAP			
Month	*n*	%	Mean	SD	*n*	%	Mean	SD
0	137	99.28	0.659	0.092	138	98.57	0.661	0.088
3	125	90.58	0.661	0.088	123	87.86	0.681	0.087
12	118	85.51	0.653	0.096	113	80.71	0.679	0.111

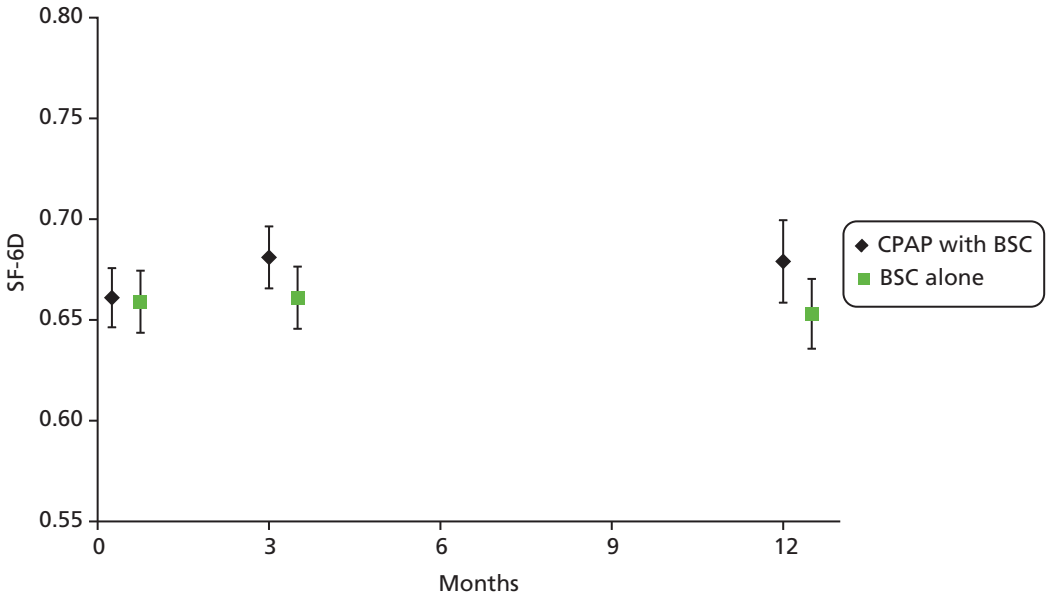

FIGURE 10 Short Form questionnaire-6 Dimensions health utility values over the trial. Figure shows mean (as a square or lozenge) and the 95% CI (as lines).

TABLE 31 Number and proportion of returned questionnaires on health-care resource use

	BSC		CPAP	
Month	*n*	%	*n*	%
Baseline	138	100.00	140	100.00
1	118	85.51	116	82.86
2	101	73.19	99	70.71
3	122	88.41	120	85.71
4	102	73.91	96	68.57
5	101	73.19	98	70.00
6	109	78.99	105	75.00
7	106	76.81	96	68.57
8	106	76.81	92	65.71
9	109	78.99	95	67.86
10	102	73.91	93	66.43
11	99	71.74	93	66.43
12	120	86.96	116	82.86

TABLE 32 Health-care resource use over the trial

	BSC		CPAP	
Type	Average per patient	SD	Average per patient	SD
Any contact with NHS	7.30	1.69	6.70	1.72
Visit to GP	7.27	3.20	6.93	2.94
GP home visit	0.32	0.67	0.18	0.47
Visit to nurse	4.78	3.23	3.36	2.16
Nurse home visit	0.27	0.80	0.14	0.51
GP telephone call	0.92	1.07	0.54	0.78
NHS direct telephone call	0.21	0.50	0.06	0.27
Ambulance	0.22	0.47	0.17	0.46
Accident and emergency	0.42	0.68	0.32	0.55
Outpatient clinic	3.65	2.48	2.83	1.99
Patients who stayed in hospital overnight at least once	0.42	0.64	0.33	0.57
Hospital overnight admissions	0.55	1.30	0.42	1.01
Emergency admissions	0.23	0.47	0.19	0.44
Nights in hospital	2.15	4.85	1.11	2.62

The health-care resource costs over the trial are shown in *Table 33*. These costs refer to the resource use data presented in *Table 32* and multiplied by the relevant unit costs (see *Table 26*). On average, patients randomised to CPAP incurred less cost, but the difference was not statistically significant. The highest costs were those related to outpatient appointments, hospital overnight admissions and visits to the GP. The SD shows how much dispersion there was around the average cost; in some cost categories the SD was greater than the mean (e.g. GP home visit, nurse home visit), indicating that there was a large variability in the costs incurred by each patient.

Costs of CPAP treatment

The average costs of CPAP treatment per patient (including the respective components) are shown in *Table 34*. All patients allocated to the intervention received a standardised CPAP machine (S9 Autoset™ ResMed (UK) Ltd, Abingdon, Oxfordshire, UK) and a mask. Eighty-two patients (59%) also received a humidifier. Patients who discontinued CPAP were assumed to return the machine (together with the

TABLE 33 Health-care resource costs over the trial

	BSC alone		CPAP	
Type	Average (£)	SD (£)	Average (£)	SD (£)
Visit to GP	312.62	137.71	298.03	126.56
GP home visit	35.57	73.41	20.26	51.98
Visit to nurse	69.27	46.78	48.79	31.39
Nurse home visit	9.35	27.85	5.04	17.69
GP telephone call	24.05	27.72	14.12	20.38
NHS Direct telephone call	5.95	13.94	1.55	7.51
Ambulance	64.79	136.53	50.76	133.72
Accident and emergency	45.40	73.27	34.23	59.88
Outpatient clinic	386.84	263.18	300.25	210.43
Hospital overnight admissions	321.17	757.68	246.78	590.14
Emergency admissions	35.82	74.40	30.57	68.88
Total costs associated with health-care resource use	1311	1009.44	1050	830.21

TABLE 34 Costs of CPAP treatment

Item	Cost element	Number	Average cost per patient (£)
A	Annual equivalent cost of CPAP machine	–	70.32
B	Annual equivalent cost of humidifier	–	26.98
C	Number (and proportion) of patients who received a humidifier	82 (59%)	–
D	Average annual equivalent cost of humidifier per patient (= B × C)	–	15.81
E	Average annual equivalent cost per patient (= A + D)	–	86.13
F	Average cost of masks	–	104
G	Average cost of masks assuming (10% of patients received 2) (= 1.1 × F)	–	114
H	Average cost per filter	–	0.58
I	Average cost of filters per patient per year (2 filters per year) (= 2 × H)	–	1.16
	Average cost of CPAP treatment per patient (= E + G + I)	–	201.14

humidifier, if relevant). Only eight patients allocated to the BSC group switched to CPAP treatment. Since the analysis follows intention to treat, these patients are assumed not to incur the costs of CPAP treatment. Given the small number of patients switching to CPAP treatment, this is unlikely to affect the results. The average cost of CPAP treatment was estimated at £201.14 per patient per year.

Cost-effectiveness analysis

The cost-effectiveness results for PREDICT are presented in *Table 35*. The analysis was conducted post multiple imputation and included the costs of CPAP treatment (£201.14) for those patients allocated to the CPAP group. Detailed costs and HRQoL post imputation are given in *Appendix 3*. The average cost per patient was £1363 (95% CI £1121 to £1606) for those allocated to CPAP and £1389 (95% CI £1116 to £1662) for those allocated to BSC alone. The accrued cost was, on average, –£35 (95% CI –£390 to £321) lower for those allocated to CPAP. The average QALYs obtained from EQ-5D health utilities were 0.680 (95% CI 0.638 to 0.722 QALYs) for the CPAP group and 0.666 (95% CI 0.627 to 0.705 QALYs) for those allocated to BSC alone. The average QALYs obtained from SF-6D health utilities for were 0.678 (95% CI 0.664 to 0.691 QALYs) for the CPAP group and 0.658 (95% CI 0.643 to 0.673 QALYs) for those allocated to BSC alone. The CPAP group experienced more EQ-5D QALYs [0.005 (95% CI –0.034 to 0.044 QALYs)] and more SF-6D QALYs [0.018 (95% CI 0.003 to 0.034 QALYs)]. The improvements in QALYs were small, albeit statistically significant, for the SF-6D. The improvement of 0.005 QALYs is equivalent to 2 days in full health and the improvement of 0.018 QALYs is equivalent to 7 days. Overall, CPAP appeared to have improved health outcomes as well as reduced overall costs to the NHS. Therefore, CPAP with BSC dominated BSC alone. In these situations, it is not appropriate to present ICERs.[132]

The cost-effectiveness planes for the base case with EQ-5D QALYs and the alternative scenario with SF-6D QALYs are shown in *Figure 11a* and *b*, respectively. The lines represent the cost-effectiveness thresholds conventionally used in the NHS (£20,000 per additional QALY gained). The simulations for the cost-effectiveness results using EQ-5D QALYs were evenly spread across the four quadrants while the simulations using SF-6D QALYs were mostly concentrated on the eastern quadrants, indicating that there was considerable uncertainty as to CPAPs health benefits, particularly those captured by EQ-5D, and whether or not it was cost-saving. The small improvement in health outcomes was more certain with SF-6D QALYs.

The cost-effectiveness acceptability curve for the base case (EQ-5D QALYs) and its alternative scenario with SF-6D QALYs is shown in *Figure 12*. The probability that the intervention was cost-effective at the thresholds conventionally used by NHS is 0.61 per QALY gained for the base case and 0.96 for the scenario with SF-6D QALYs. In the base case, the probability that CPAP was cost-effective plateaus at 0.60 as the cost-effectiveness threshold increased. This occurred because of the uncertainty around the improvement in EQ-5D QALYs observed during the trial, reflected in the 95% CI of –0.034 to 0.044. In contrast, the probability that CPAP was cost-effective was above 0.9 across the full range of cost-effectiveness thresholds with SF-6D QALYs. This is consistent with the scatter pattern in the cost-effectiveness plane (see *Figure 11*).

TABLE 35 Cost-effectiveness results (post multiple imputation) over the trial

	Costs		EQ-5D QALYs		SF-6D QALYs	
Treatment group	Average (£)	SE	Average	SE	Average	SE
CPAP	1363	£123	0.680	0.021	0.678	0.007
BSC	1389	£139	0.666	0.020	0.658	0.008
Incremental costs and QALYs						
CPAP with BSC – BSC alone	–35	£180	0.005	0.020	0.018	0.008

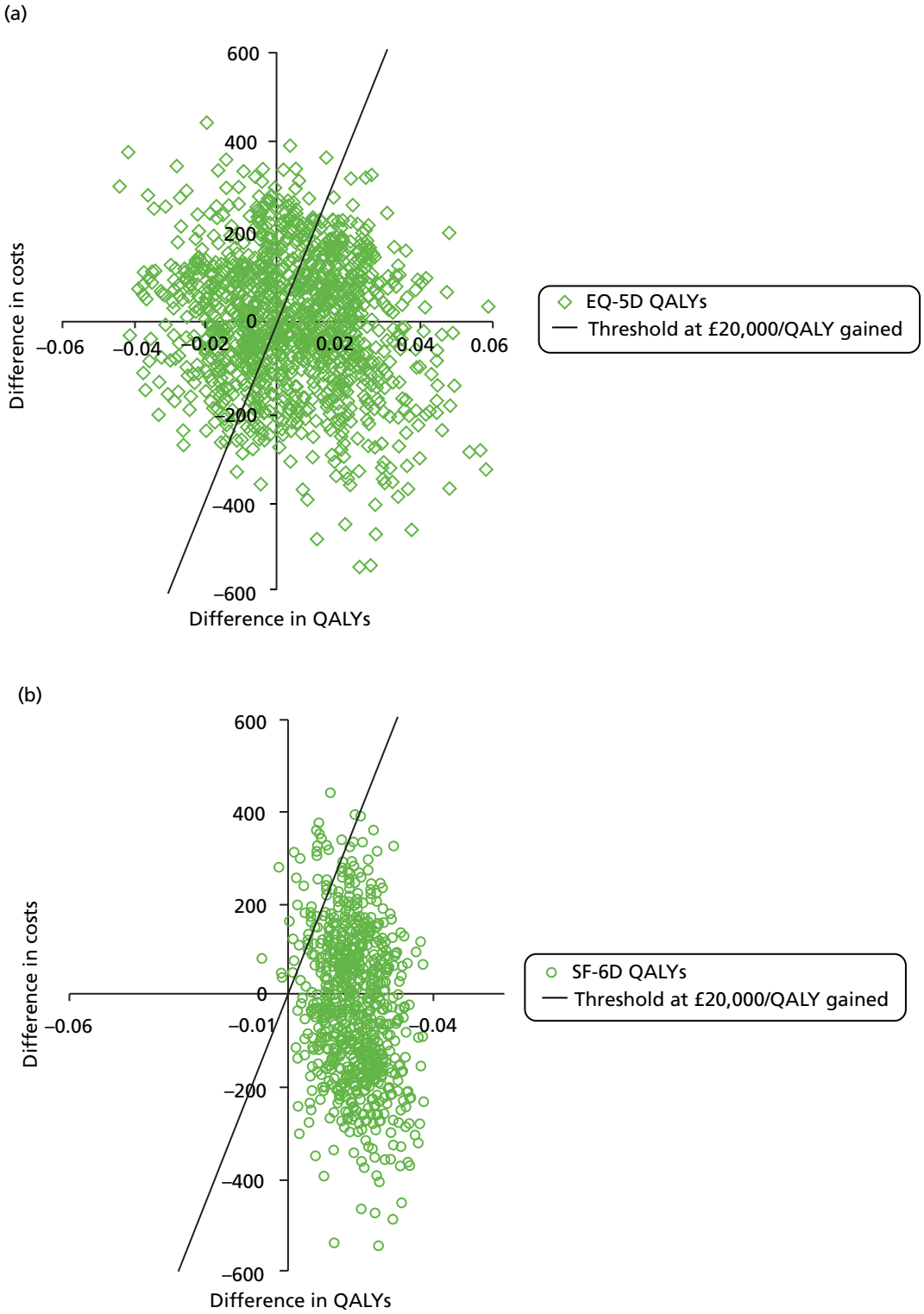

FIGURE 11 Cost-effectiveness plane for the overall population. (a) EQ-5D QALYs; and (b) SF-6D QALYs.

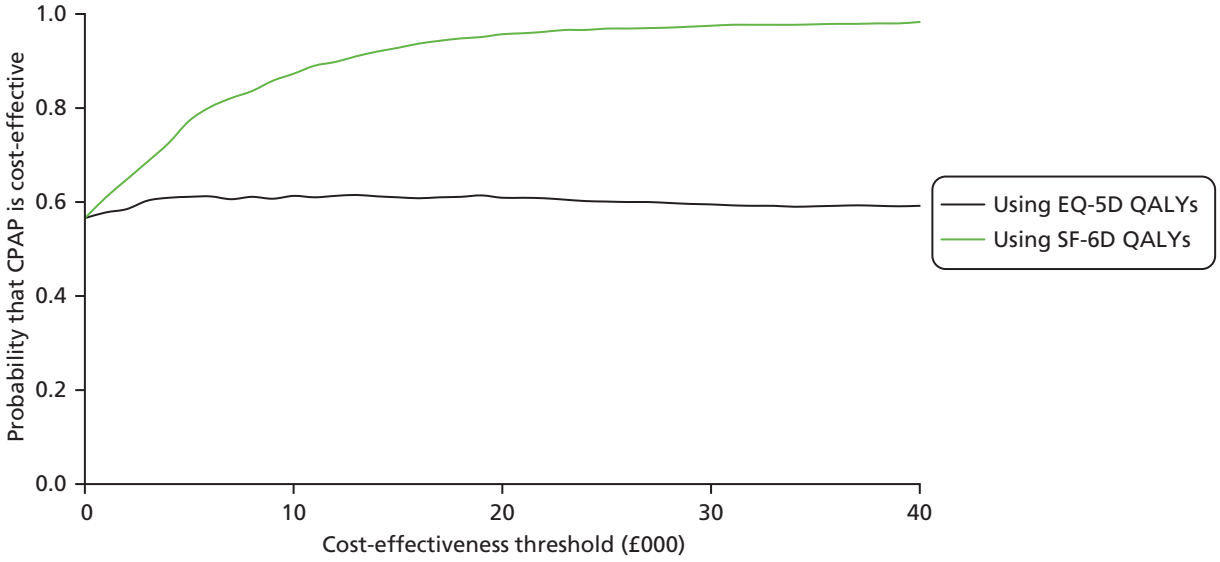

FIGURE 12 Cost-effectiveness acceptability curve.

Subgroup analysis

The results for the subgroups defined according to ESS score at baseline are shown in *Table 36*. There were 184 patients with ESS score of <13 (CPAP, $n = 88$; BSC, $n = 96$) and 94 patients with ESS score of ≥13 (CPAP, $n = 52$; BSC, $n = 42$). For the less severe OSAS subgroup, CPAP appears to be less costly and provide fewer QALYs than BSC; therefore, the ICER for BSC alone versus CPAP was £1118 per QALY gained for the base case with EQ-5D QALYs. CPAP dominated in the SF-6D QALYs scenario because it was associated with lower costs and greater QALYs; therefore, an ICER was not calculated. For the more severe OSAS subgroup, CPAP dominated BSC alone because it was associated with lower costs and better health outcomes in both the base case with EQ-5D QALYs and the scenario with SF-6D QALYs.

There was considerable uncertainty in these results because in both subgroups, similarly to the overall population, the differences in costs were small and not statistically significant, –£19 (95% CI –£475 to £438) for the less severe OSAS subgroup and £17 (95% CI –£520 to £555) for the more severe OSAS subgroup. The differences in QALYs were also small and not statistically significant. The less severe OSAS

TABLE 36 Cost-effectiveness results for subgroup populations (post multiple imputation)

	Costs		EQ-5D QALYs		SF-6D QALYs	
Treatment group	Average (£)	SE (£)	Average	SE	Average	SE
Subgroup ESS score of <13						
CPAP	1393	162	0.677	0.027	0.675	0.009
BSC	1440	179	0.684	0.023	0.660	0.10
Incremental costs and QALYs						
CPAP with BSC – BSC alone	–19	231	–0.017	0.025	0.018	0.010
Subgroup ESS score of ≥13						
CPAP	1313	188	0.686	0.035	0.682	0.012
BSC	1274	212	0.624	0.037	0.654	0.012
Incremental costs and QALYs						
CPAP with BSC – BSC alone	17	270	0.049	0.032	0.018	0.012

subgroup experienced a difference in EQ-5D QALYs of –0.017 (95% CI –0.066 to 0.033 QALYs) and in SF-6D QALYs of 0.018 (95% CI –0.002 to 0.038 QALYs). The more severe OSAS subgroup experienced positive differences for both EQ-5D and SF-6D QALYs, although not statistically significant, at 0.049 (95% CI –0.014 to 0.111) for EQ-5D QALYs and 0.018 (95% CI –0.006 to 0.043) for SF-6D QALYs. Thus, it is difficult to draw definite conclusions from this analysis given the level of uncertainty around the results. The EQ-5D QALYs appeared to follow the improvement in ESS score, which is more pronounced in the more severe OSAS subgroups (see *Table 8*). The improvement in SF-6D QALYs was similar in the two subgroups, although the differences in QALYs between CPAP and BSC alone were small across subgroups.

The cost-effectiveness planes for more severe (ESS score at baseline of ≥ 13) and less severe OSAS (ESS score at baseline of <13) are shown in *Figure 13a* and *c*, and *b* and *d*, respectively. As with *Figure 11*, results for EQ-5D QALYs are shown in *Figure 13a* and *c* and for SF-6D QALYs are shown in *Figure 13b* and *d*. The axis scales are the same to facilitate comparison. The results differed depending on ESS score at baseline and HRQoL instrument used to obtain QALYs. In the less severe OSAS population, the simulations for EQ-5D QALYs were mostly spread across the western quadrants, indicating decrements in health outcomes. The simulations for SF-6D QALYs were concentrated in the eastern quadrants, indicating positive gains in health. In the more severe OSAS population, most of the simulations were located in the eastern quadrants for both EQ-5D and SF-6D QALYs. In other words, we are more confident that CPAP was cost-effective in the more severe OSAS subgroup.

The cost-effectiveness acceptability curves for the subgroups are shown in *Figure 14*. The certainty around the cost-effectiveness of the intervention depended on the HRQoL instrument and the subgroup considered. In the less severe OSAS subgroup, the probability that CPAP was cost-effective decreased as the cost-effectiveness threshold increased for EQ-5D QALYs but increased for SF-6D QALYs. This reflected the distribution of the differences in QALYs presented in *Figure 13*. Using EQ-5D QALYs, the mean difference was close to zero but the majority of the simulations returned a decrement in QALYs between the treatment groups. In the cost-effectiveness acceptability curve, that decrement was compensated by the decrease in costs. However, as the threshold increased, the value placed on QALYs increased in relation to the costs savings. Therefore, for higher threshold values, CPAP was less likely to be cost-effective. Using SF-6D QALYs, the majority of simulations returned a gain in QALYs between treatment groups. This was because, as the threshold increased, the gains were valued, and the probability that CPAP was cost-effective increases. In the more severe OSAS group, the probability that CPAP was cost-effective increased as the threshold increased. This reflected the cost-effectiveness plane in *Figure 13*, where most of the simulations, for both EQ-5D and SF-6D QALYs, returned gains in health.

Sensitivity analysis

A selection of the results for the sensitivity analysis is presented in *Table 37* (see *Appendix 3* for additional information). The cost differences and QALY differences were small and close to zero in the majority of analyses, and this resulted in variable ICERs. Therefore, while the results were relatively consistent in terms of costs and QALYS, the cost-effectiveness conclusions were mixed. In two scenarios with EQ-5D QALYs and three with SF-6D, QALYs CPAP dominated BSC alone. In four scenarios with EQ-5D QALYs and three with SF-6D QALYs, CPAP had a positive ICER. In two of the scenarios with EQ-5D QALYs, the ICER was above the conventional thresholds of cost-effectiveness used by NICE of £20,000 and £30,000 per QALY gained.

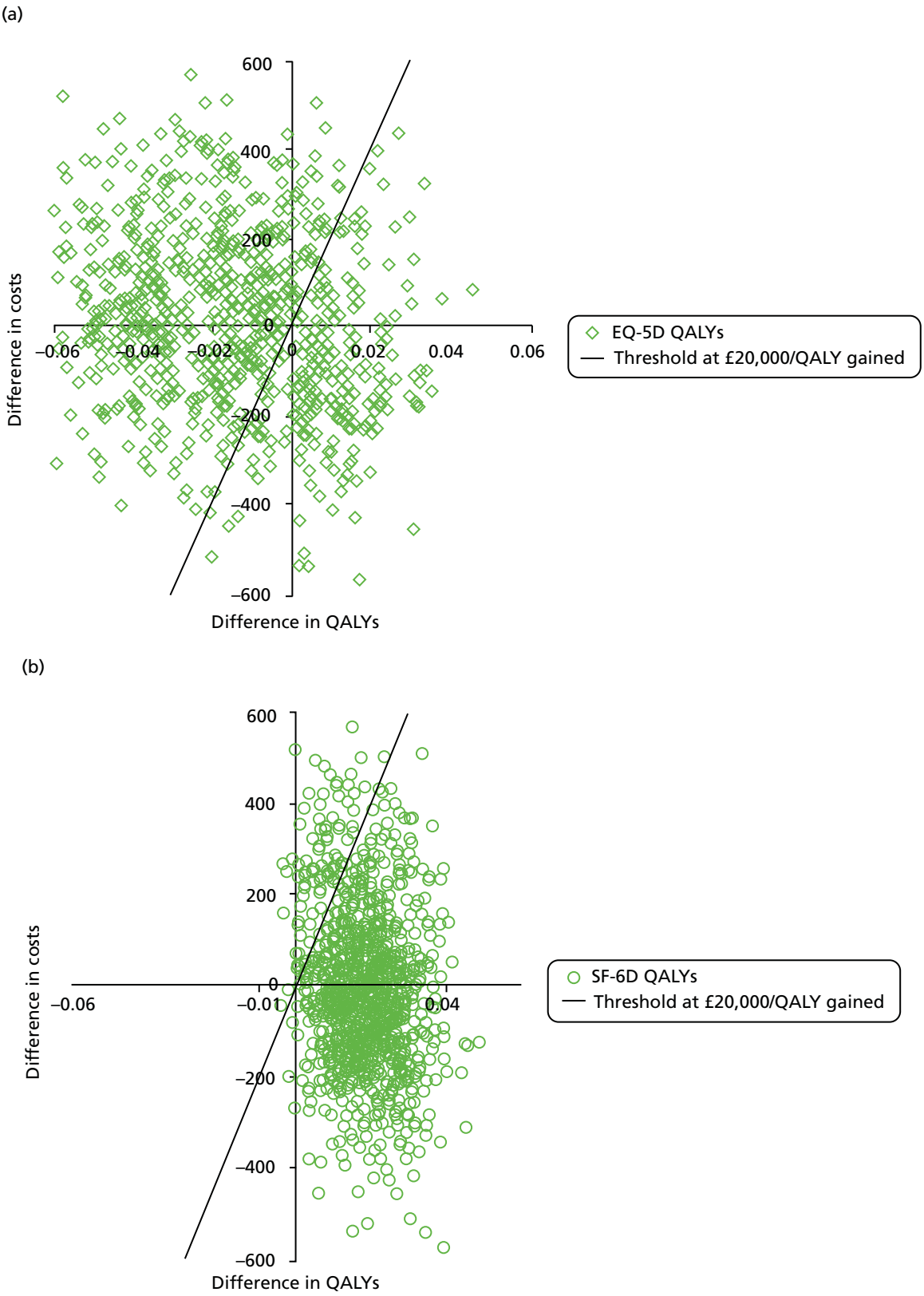

FIGURE 13 Cost-effectiveness plane for population subgroups. (a) ESS score of < 13 EQ-5D; (b) ESS score of < 13 SF-6D; (c) ESS score of ≥ 13 EQ-5D; and (d) ESS score of ≥ 13 SF-6D. (*continued*)

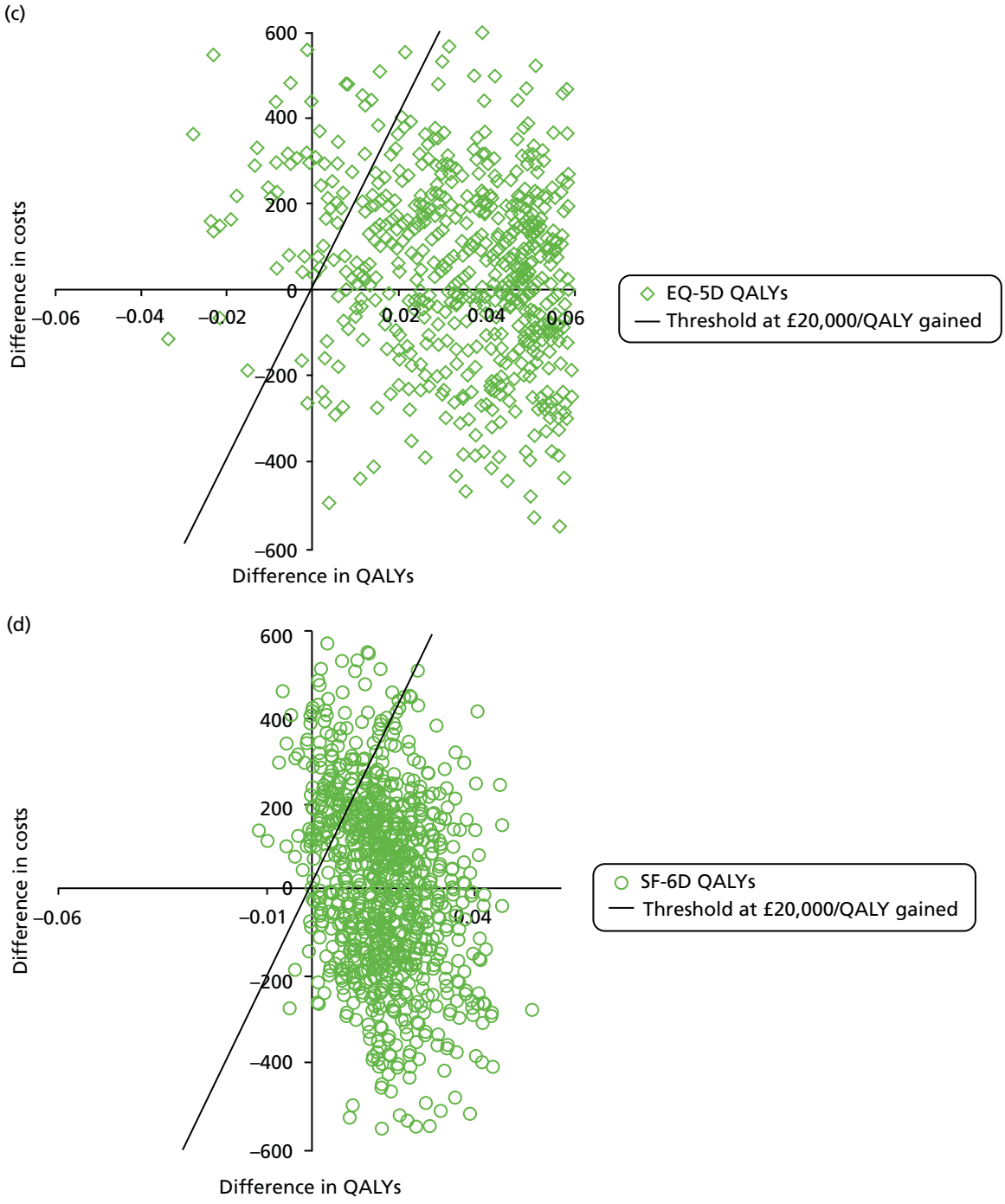

FIGURE 13 Cost-effectiveness plane for population subgroups. (a) ESS score of < 13 EQ-5D; (b) ESS score of < 13 SF-6D; (c) ESS score of ≥ 13 EQ-5D; and (d) ESS score of ≥ 13 SF-6D.

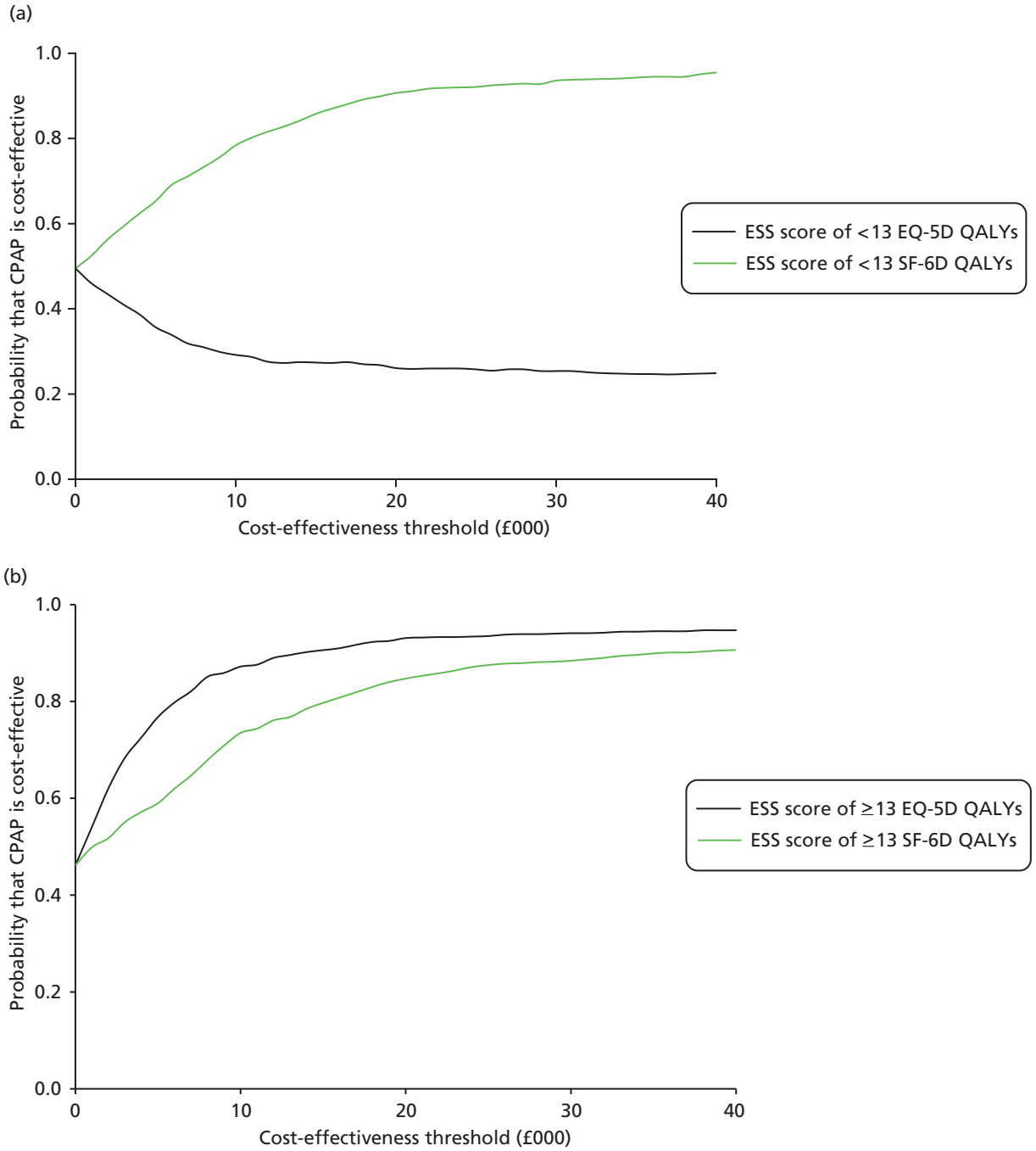

FIGURE 14 Cost-effectiveness acceptability curves for less severe OSAS population. (a) ESS score of < 13; and (b) ESS score of ≥ 13.

TABLE 37 Summary results of the sensitivity analysis

	Difference in costs		Difference in EQ-5D QALYs			SF-6D QALYs			Probability that CPAP is cost-effective at £20,000/QALY gained	
Scenario	Average (£)	SE (£)	Average	SE	ICER/EQ-5D QALYs (£)	Average	SE	ICER/SF-6D QALYs (£)	EQ-5D QALYs	SF-6D QALYs
Base case	***–35***	***180***	***0.005***	***0.020***	***D***	***0.018***	***0.008***	***D***	***0.61***	***0.96***
1: Frequent replacement scenario (CPAP costs = £608.95)	373	180	0.005	0.020	74,600	0.018	0.008	20,722	0.25	0.46
2: CPAP used for 1 year (CPAP costs = £710.16)	474	180	0.005	0.020	94,800	0.018	0.008	26,333	0.20	0.30
3A: Complete-case analysis (EQ-5D QALYs)	–258	258	0.010	0.029	D	NA	NA	NA	0.75	NA
3B: Complete-case analysis (SF-6D QALYs)	–201	247	NA	NA	NA	0.015	0.013	D	NA	0.91
4: Mean interpolation	43	201	0.006	0.018	7167	0.014	0.007	3071	0.55	0.81
5A: Missing not at random (costs)	–27	201	0.005	0.020	D	0.018	0.008	D	0.62	0.96
5B: Missing not at random (QALYs)	–35	180	–0.006	0.19	5833	0.012	0.009	D	0.42	0.85

NA, not applicable.
D indicates that CPAP dominates because it is associated with both lower costs and QALY gains.

Economic model

The ICER for CPAP was above the conventional thresholds of cost-effectiveness in scenarios 1 and 2, which assumed a higher treatment cost for CPAP. Scenario 1 assumed a greater frequency in the replacement of the machine and in the use of the consumables and scenario 2 assumed that the CPAP machine was used for only 1 year then discarded. In scenario 1, the CPAP and humidifier were assumed to be replaced every 3 years, the masks every 3 months and the filters monthly. The average cost of CPAP per patient per year tripled in scenario 1 from £201.14 in the base case to £608.94 and also more than tripled in scenario 2 to £710.16. This increase in the costs of CPAP resulted in an increase in the average difference in total costs, from –£35 (95% CI –£390 to £321) in the base case to £373 (95% CI £17 to £729) in scenario 1 and to £474 (95% CI £119 to £830) in scenario 2. The ICER for scenario 1 using EQ-5D QALYs was £74,600 and for scenario 2 was £47,800; for the same scenarios using SF-6D QALYs, it was £94,800 and £26,333, respectively. These results suggested that the cost-effectiveness of CPAP was highly sensitive to the costs of CPAP treatment.

Scenario 3 used only the data from patients who completed all questionnaires on HRQoL and costs. It assumed that these data were missing completely at random; that is, that the probability that data were missing was independent of both the observed and unobserved data. CPAP dominated BSC alone.

In scenario 4, missing data were imputed with the average of the observed data for each patient. The mean difference in costs changed slightly to £43 (95% CI –£353 to £440) while the differences in QALYs remained unchanged. Nevertheless, the change in the mean difference in costs between treatment groups resulted in a positive ICER of £7167 per EQ-5D QALY gained and £3071 per SF-6D QALY gained. This showed how small differences in costs or QALYs had a large impact on the results. Note that this scenario should be considered with caution, as it assumed that patients' costs and HRQoL were expected to remain constant over the trial, which may not be the case.

The 'missing not at random' scenarios explored how the results changed if missing data on HRQoL and costs were assumed to be systematically different from that of patients with similar characteristics but who returned the questionnaires. The difference in costs changed very slightly, to –£26 (95% CI –£422 to £369), with little impact on the results. The difference in EQ-5D QALYs changed more noticeably from 0.005 (95% CI –0.034 to 0.044) to –0.006 (95% CI –0.044 to 0.031) whereas the difference in SF-6D QALYs changed slightly from 0.018 (95% CI 0.003 to 0.034) to 0.012 (95% CI –0.006 to 0.03). As a result, assuming that patients with missing data experienced lower HRQoL reduced the probability that CPAP was cost-effective from 0.61 to 0.42 for EQ-5D QALYs and from 0.96 to 0.85 for SF-6D QALYs.

Introduction

The results of the within-trial analysis suggested that CPAP may be a cost-effectiveness alternative to BSC alone. However, there was a question of whether or not all of the relevant outcomes of CPAP treatment were captured within the 12-month follow-up period. For example, a potential long-term benefit of CPAP is the reduction in the risk of cardiovascular events [e.g. stroke and coronary heart disease (CHD)]. No difference in the incidence of these events was observed in PREDICT; however, RCTs, such as PREDICT, are unlikely to capture differences in the incidence of such rare events. In order to extrapolate results beyond the period of follow-up and to incorporate relevant external evidence, it is common to employ a decision model. Other studies examining the cost-effectiveness of CPAP have considered the effect of CPAP in reducing the risk of cardiovascular events, diabetes, and work and RTAs using evidence from a variety of sources (see *Systematic review of existing cost-effectiveness evidence on continuous positive airway pressure*). McDaid *et al.*[20] used intermediate outcomes such as reductions in BP and cholesterol to predict long-term risks of cardiovascular events using published risk models. Therefore, by employing a decision model, differences in BP and other risk factors observed within the trial could be translated into differences in the incidence of events, which in turn have an impact on costs and QALYs. Furthermore, if there does exist relevant external evidence, it can be brought to bear on the cost-effectiveness analysis so that it synthesises all of the available evidence.

For these reasons, a decision model was employed to formally assess the cost-effectiveness of CPAP for the treatment of OSAS in older patients over a lifetime time horizon. Health outcomes were expressed in QALYs. Costs took the NHS and Personal Social Services perspectives, expressed in pounds sterling at a 2011–12 price base. Both costs and health outcomes were discounted at a 3.5% annual discount rate, in line with the NICE reference case.

The cost-effectiveness of CPAP was evaluated by comparing the additional costs of CPAP in combination with BSC, with its additional benefits in terms of improvement in HRQoL. HRQoL was measured by both EQ-5D and SF-6D. The results are presented for both measures, but it should be noted that EQ-5D QALYs constituted the primary outcome of PREDICT. The cost-effectiveness of CPAP was estimated using conventional decision rules and reported as an ICER if applicable.[132] All results were probabilistic in that input parameters were entered as probability distributions and Monte Carlo simulation was used to propagate the uncertainty over 10,000 simulations. The probabilistic results were translated into cost-effectiveness acceptability curves and probabilities that CPAP was cost-effective under conventional thresholds used by NICE of £20,000 and £30,000 per QALY gained.[136] Subgroup analysis is presented for patients with more or less severe daytime sleepiness: ESS score of < 13 and ESS score of ≥ 13 (as for the within-trial analysis). Each of the subgroups were analysed independently in the same model.

Reviews for external evidence

Systematic review of the clinical effectiveness of continuous positive airway pressure

A systematic review was conducted to identify any additional external evidence on the effectiveness of CPAP in this population to supplement the data collected in PREDICT. The inclusion criteria were RCTs comparing CPAP with sham CPAP, BSC or usual care, and dental devices in patients with an average age of 60 years or older with OSAS and capacity to give informed consent.

Three studies were identified that met the inclusion criteria from 3560 unique titles (see *Appendix 3* for details of the review). The three studies included patients with cardiovascular conditions and compared CPAP therapy with sham CPAP[88] or no CPAP[89,90] for OSAS in the secondary care setting. None of the studies was conducted in the UK and none collected generic measures of health utility. The primary outcome was left ventricular ejection fraction in Egea *et al.*,[88] baroreflex sensitivity in Ruttanaumpawan *et al.*[89] and a number of neurological, quality of life, sleep-related and mortality outcomes in Parra *et al.*[90] Two studies[88,89] reported BP at baseline and at follow-up; however, both these studies focused on patients with chronic heart failure and their follow-up was short, at 3 and 1 months, respectively. In the Egea *et al.* study,[88] no statistically significant differences were found in BP. In the Ruttanaumpawan *et al.* study,[89] the reduction in average systolic BP at 1 month was statistically significant but the reduction in average diastolic BP was not.

The results of these three studies are difficult to generalise to the overall patient population with OSAS and aged 60 years and older, given their focus in patients with concomitant cardiovascular disease. Egea *et al.*[88] and Ruttanaumpawan *et al.*[89] included only patients with chronic heart failure and Parra *et al.*[90] included only patients who had had an ischaemic stroke. These patients are likely to be a smaller proportion of those with OSAS. In PREDICT, 18 (6%) of patients had chronic heart failure and 8 (3%) had had a stroke. If the effect of CPAP was systematically different for these patients, the effect of CPAP observed in the identified studies is not generalisable to the overall patient population. Consequently, these studies were not used to inform the effectiveness estimates in the model, and these were derived solely from the results of PREDICT.

Road traffic accidents

Another potential long-term benefit of CPAP is the reduction in RTAs. RCTs are unlikely to capture reductions in the rate of RTAs given their infrequency. For example, the rate of RTAs in drivers aged 60–69 years was 96 per 100,000.[137] Therefore, reviews of observational studies were examined for evidence in reductions in the rate of RTAs in older OSAS patients. Four systematic reviews were identified.[138–141] All of the studies included in these reviews evaluated the risk of RTAs in patients whose average age was below 60 years. Given the small number of events recorded in the trial and paucity of published evidence in this patient population, RTAs are not included in the model.

Linking intermediate outcomes to final events

Intermediate outcomes such as BP or blood cholesterol can be used to predict the risk of final events using published risk models. There is a large number of risk models published in the literature. The Framingham risk model for cardiovascular disease was selected because it has been extensively validated and was used in a prior evaluation of CPAP.[20,142,143] The Framingham risk model is based on the Framingham cohort, a large prospective cohort of US men and women aged 30 to 74 years and validated in multiple populations.[143] It calculates risk of fatal and non-fatal cardiovascular events for an individual within a certain age range based on smoking status, BP, blood cholesterol, diabetes status and whether or not there is electrocardiographic evidence of left ventricular hypertrophy. The limitation of the Framingham risk model is that it has not been validated for patients aged 75 years and older.

A summary of the treatment effects observed in PREDICT for intermediate outcomes is shown in *Table 38*. The effects on intermediate outcomes were small, generally not statistically significant and somewhat inconsistent. CPAP appeared to increase BP, which would increase the risk for cardiovascular events, but decreased total cholesterol and increases high-density lipoprotein cholesterol, which in turn would decrease the risk. Given the small size, uncertainty and inconsistency in the direction of effect, these outcomes were be included only as a scenario analysis.

TABLE 38 Selected results from PREDICT over 12 months

Outcome	Treatment effect (95% CI)
Systolic BP (mmHg)	3.7 (0.2 to 7.3)
Diastolic BP (mmHg)	0.2 (–2.1 to 2.5)
Total cholesterol (mmol/l)	–0.1 (–0.3 to 0.1)
HDL cholesterol (mmol/l)	0.01 (–0.03 to 0.06)
LDL cholesterol (mmol/l)	–0.09 (–0.26 to 0.08)
Triglycerides (mmol/l)	0.06 (–0.10 to 0.22)

HDL, high-density lipoprotein.

Adherence to continuous positive airway pressure therapy

Adherence to CPAP may affect the clinical effectiveness and cost-effectiveness of treatment. PREDICT recorded adherence to CPAP at 3 months and at 1 year from treatment initiation in terms of proportion of patients who reported using CPAP and average hourly usage per night (see *Chapter 3*, *Tertiary outcome*; *Table 24*). Of the 140 patients randomised to CPAP treatment, 120 (86%) at 3 months and 99 (71%) at 12 months reported that they were still using CPAP.

A recent systematic review on adherence to CPAP was used to extrapolate this parameter over time.[144] In a first stage, the studies included in the review were examined for their relevance in this patient population and whether or not data were provided on the proportion of patients using CPAP at one or more time periods from treatment initiation. Three studies evaluated compliance with CPAP use in patients with an average age of over 65 years: Russo-Magno *et al.*[145] in patients with an average age of 73 years, Bravata *et al.*[146] in patients with an average age of 66 years and Woehrle *et al.*[147] presented subgroup analysis in patients aged 60–70 years and patients 70 years of age and older.[145–147] However, none of these three studies reported the proportion of patients using CPAP at specified time points from treatment initiation. In a second stage, the studies included in the systematic review were examined for evidence on adherence at specified time points from treatment initiation. Two studies reported the proportion of patient using CPAP: McArdle *et al.*[148] examined CPAP use in yearly intervals up to 5 years in 1103 patients aged 43–58 years (average 50 years), Sin *et al.*[149] examined CPAP use in patients with an average age of 47.1 years at 2 weeks, 4 weeks, 3 months and 6 months. The reduction in adherence over time in McArdle *et al.*[148] was used to extrapolate the adherence at 1 year observed in PREDICT by assuming that adherence in the PREDICT patient population was reduced by the same proportion as the adherence in McArdle *et al.*

Final model

A cohort Markov model was developed to evaluate the cost-effectiveness of CPAP compared with BSC alone. The model tracked the health outcomes (health utility values, deaths) and costs over the cohort's lifetime. In the base case, the model consisted of two health states: OSAS (treated with CPAP or treated with BSC alone) and death (*Figure 15*). Cycle length was 1 year. CPAP was assumed to improve HRQoL and reduce NHS costs as observed in PREDICT (for more details see *Within-trial economic evaluation*). Adherence in the first year was obtained from PREDICT and assumed to deteriorate over time, as reported in McArdle *et al.*[148] The estimated of adherence used in the economic model is presented in *Table 39*. Adherence in McArdle *et al.* reduced by 10% in year 2, by 1% in year 3 and by 5% in year 4.[148] Applying these reductions to the adherence at 1 year observed in PREDICT yielded an adherence of 63.9% at year 2, 63.3% at year 3 and 60.1% at year 4. After year 4, adherence was assumed to remain constant.

In a scenario analysis, the model included four health states (OSAS, OSAS post CHD, OSAS post stroke and death) and two events (CHD and stroke). In this scenario, CPAP not only improved HRQoL and reduced NHS costs but also changed the risk for cardiovascular events. The patient cohort started in the OSAS state. At each 1-year cycle, patients were at risk of CHD and stroke. Following CHD or stroke, patients moved to the state post CHD or post stroke, respectively. The states of post CHD and post stroke had an elevated risk of death. The Framingham risk equation was used to link the effect of CPAP on intermediate outcomes (systolic BP, cholesterol) to cardiovascular events.

TABLE 39 Adherence with CPAP therapy modelled from previous studies

Adherence	PREDICT	McArdle *et al.*[148]	Reduction	Decision model
1 year	71%	84%	–	71%
2 years	–	74%	84% – 74% = 10%	71% × 90% = 63.9%
3 years	–	73%	74% – 73% = 1%	63.9% × 99% = 63.3%
4 years	–	68%	73% – 68% = 5%	63.3% × 95% = 60.1%

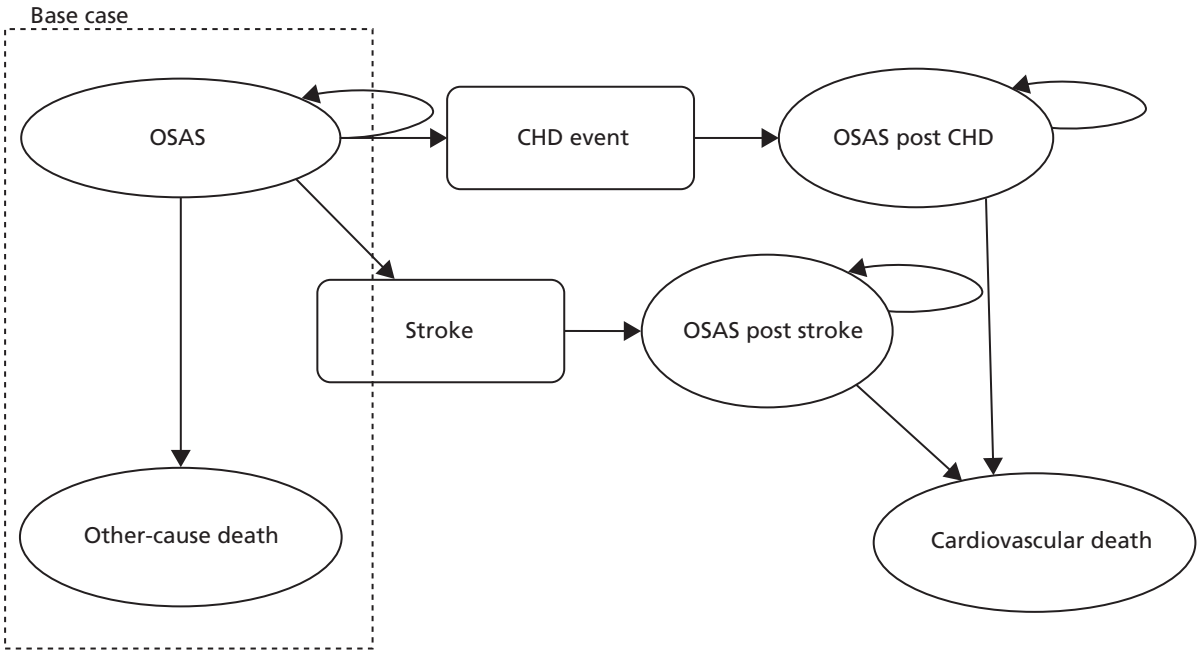

FIGURE 15 Diagram of model structure for the scenario analysis.

Health-related quality of life and quality-adjusted life-years

Health-related quality of life was expressed in terms of QALYs by quality adjusting the period of time for which the average patient was alive within the model using an appropriate health utility value. *Table 40* shows the health utility values used in the model. Health utility in the OSAS state corresponded to the average baseline EQ-5D in the patients that took part in PREDICT. The effect of CPAP during the first year corresponded to the improvement in EQ-5D QALYs observed in the trial at 1 year, adjusted for baseline, as presented in *Table 35*. The effect in subsequent years was adjusted for adherence assuming that

TABLE 40 Health utility values used in the model

	Mean		SD or SE			
Health state or event	EQ-5D	SF-6D	EQ-5D	SF-6D	Distribution	Source
OSAS untreated	0.687	0.660	0.245	0.090	Beta	PREDICT
CPAP effect in year 1	0.005	0.018	0.020	0.008	Normal	PREDICT
CPAP effect in year 2	0.0045	0.0162	0.020[a]	0.008[a]	Normal	Calculated (effect × 90%)
CPAP effect in year 3	0.0045	0.0160	0.020[a]	0.008[a]	Normal	Calculated (effect × 89%)
CPAP effect in year 4	0.0042	0.0152	0.020[a]	0.008[a]	Normal	Calculated (effect × 85%)
Age decrement	0.0003	NA	0.0002	NA	Normal	Sullivan *et al.*[150]
For the scenario with cardiovascular events						
Stroke decrement	0.1009		0.0123		Normal	Acute cerebrovascular disease[150]
CHD decrement	0.0557		0.0112		Normal	Acute MI[150]

NA, not applicable.
a Standard errors of CPAP effects years 2 to 4 assumed the same as in year 1.

reductions in adherence had a proportional impact on treatment effect. For example, a reduction in compliance of 10% from 31% to 27.9% reduced the effect of CPAP in health utility by 10% from 0.005 to 0.0045. The health utility decrements associated with age, CHD and stroke were obtained from the catalogue of EQ-5D scores developed by Sullivan *et al.*[150]

Cardiovascular events

In the scenario including cardiovascular events, the Framingham risk equations were employed to estimate the risk of events from the intermediate outcomes recorded in PREDICT.[20,143] The characteristics of the patient cohort for the scenario with cardiovascular events are presented in *Table 41*. These correspond to the average patient characteristics at baseline in PREDICT. *Table 42* presents the probability of a cardiovascular event based on the characteristics of the cohort at baseline. The probability was calculated for subgroups of patients by sex, smoking status and diabetes using only those patients with complete data for these variables at baseline. The risk for the PREDICT patient population was a weighted average of the risks for each subgroup, weighted by their relative proportions in the population.

All-cause death

In the model, patients are at risk of death at every cycle. Patients in the OSAS state experience an age-dependent risk of death, obtained from interim lifetables for England and Wales for the years 2009–11.[151] For the scenario including cardiovascular events, the age-dependent risk of death from causes other than cardiovascular was estimated using a cause elimination approach. Patients in the post-stroke or post-CHD OSAS group (who survived the cardiovascular event) were then at an elevated risk of death as in the McDaid *et al.* analysis, with a relative risk of 3.2 (95% CI 2.67 to 3.83)[152] for the post-CHD state and a relative risk of 2.3 (95% CI 2.0 to 2.7) for the post-stroke state.[153]

TABLE 41 Characteristics of the patient cohort for the scenario with cardiovascular events

Variables	Mean	SD
Age (years)	70.59	4.66
Systolic BP (mmHg)	139.01	18.92
Total cholesterol, mmol/l (mg/dl)	4.58 (177.02)	1.04 (40.35)
HDL cholesterol, mmol/l (mg/dl)	1.24 (31.00)	0.34 (13.11)

HDL, high-density lipoprotein.

TABLE 42 Probability of cardiovascular events at baseline (using characteristics presented in *Table 41*)

Sex	Male				Female				Overall
Smoking status	Yes	Yes	No	No	Yes	Yes	No	No	–
Diabetes	Yes	No	No	Yes	Yes	No	No	Yes	–
Number of patients	5	8	102	56	0	0	15	5	–
1-year probability of cardiovascular events									
CHD	0.053	0.041	0.027	0.036	NA	NA	0.012	0.024	0.030
Stroke	0.010	0.006	0.003	0.005	NA	NA	0.002	0.006	0.004
Death from CHD	0.013	0.011	0.006	0.007	NA	NA	0.001	0.007	0.006
Death from cardiovascular disease	0.014	0.011	0.006	0.008	NA	NA	0.003	0.008	0.007

NA, not applicable.

Resource use and costs

Resource use and costs can be split into two components: (1) those related to CPAP therapy and (2) those related to cardiovascular events, only applicable in the scenario including cardiovascular events. The within-trial analysis estimated that patients allocated to CPAP accrued on average £35 (95% CI –£390 to £321) lower costs (*Table 43*). This cost difference included the costs of CPAP and the costs associated with any health-care resource use. Therefore, this difference in costs was applied to the hypothetical patient cohort in the OSAS state. As with the improvement in health utility, the cost difference was adjusted for reduced adherence over time. For the scenario including cardiovascular events, costs associated with cardiovascular events were obtained from the McDaid *et al.* report and inflated to 2011–12 prices.[20,124,154]

Patient population

The model followed a hypothetical patient cohort that corresponded to the patients in PREDICT, that is patients aged 65 years and over with OSAS (see *Table 41* for the patients' characteristics at baseline).

Sensitivity analyses

The sensitivity analyses conducted in the model-based analysis are summarised in *Table 44*. All analyses were fully probabilistic. The sensitivity analyses aimed to explore the robustness of the results to the main assumptions and parameter inputs. Therefore, scenario analyses were performed for the effect of CPAP on cardiovascular risk outcomes and the cost of CPAP therapy. Univariate sensitivity analysis was conducted to the cost of the CPAP machine.

TABLE 43 Costs used in the model

Parameter	Cost		Distribution	Source
	Mean	SE		
Costs related to CPAP				
Costs in the OSAS state untreated	£1389	£139	Gamma	PREDICT, within-trial analysis (see *Table 10*)
Effect of CPAP on costs	–£35	£180	Normal	PREDICT, within-trial analysis (see *Table 10*)
Costs related to cardiovascular events				
Cost of fatal CHD event				
Price year 2004–05	3021	367	Normal	McDaid *et al.*,[20] Briggs *et al.*[154]
Inflated to 2011–12	3716	451		
Cost of non-fatal CHD event				
Price year 2004–05	9997	429	Normal	McDaid *et al.*,[20] Briggs *et al.*[154]
Inflated to 2011–12	12,296	528		
Ongoing cost of CHD				
Price year 2004–05	751	117	Normal	McDaid *et al.*,[20] Briggs *et al.*[154]
Inflated to 2011–12	924	144		
Inflation index from 2004–05 to 2011–12	285.7/232.3 = 1.23	NA	NA	PSSRU[124]
Acute cost of stroke (year 1)				
Price year 2004–05	9067	294	Normal	McDaid *et al.*,[20] Vergel *et al.*[155]
Inflated to 2011–12	11,152	362		
Ongoing cost of stroke (year 2 and beyond)				
Price year 2004–05	2392	282	Normal	McDaid *et al.*,[20] Vergel *et al.*[155]
Inflated to 2011–12	2942	347		

NA, not applicable; PSSRU, Personal Social Services Research Unit.

TABLE 44 Details of the key elements of the base-case analysis and variation used in the scenario analysis

Scenario	Element	Position in base-case analysis	Variation in the sensitivity analysis
1	CPAP used for 1 year	The costs of the CPAP machine and the humidifier are annuitised over 7 years. Yearly replacement for masks. Filters replaced every 6 months	CPAP is assumed to be used for 1 year and discarded after that; therefore, the cost of the machine is not annuitised. CPAP therapy costs £710.16 per patient
2	Cardiovascular effects with CPAP direct effects	Changes in the risk of cardiovascular events are not included in the base-case model	CPAP changes the risk of cardiovascular events as predicted by the Framingham risk equation through its effect on BP and cholesterol as observed in the PREDICT clinical trial. CPAP increases health outcomes and reduces costs are reduced in PREDICT
3	Cardiovascular effects only	Changes in the risk of cardiovascular events are not included in the base-case model	CPAP changes the risk of cardiovascular events as predicted by the Framingham risk equation through its effect on BP and cholesterol as observed in the PREDICT clinical trial. The direct effect of CPAP on costs and QALYs is not considered

Results

Base case

The results for the base case are presented in *Table 45*. CPAP reduced the average costs per patient by –£369 and improved health outcomes by 0.051 EQ-5D QALYs. The improvement for SF-6D QALYs was 0.182. Since CPAP reduced costs and improved health outcomes, it dominated BSC alone and an ICER is not calculated.

The distribution of average costs and average QALYs over the 10,000 simulations conducted for the probabilistic sensitivity analysis are shown in *Figure 16*. Similarly to the within-trial analysis, there was considerable uncertainty around the results using EQ-5D QALYs. In the analysis with SF-6D QALYs, most simulations were located in the eastern quadrants; the large majority were below the cost-effectiveness threshold, represented by the diagonal line.

TABLE 45 Cost-effectiveness results for the base case

Treatment	Average costs	Average EQ-5D QALYs	Average SF-6D QALYs
CPAP	£15,887	8.046	7.862
BSC	£16,216	7.994	7.680
Incremental costs and QALYs			
CPAP with BSC – BSC alone	–£329	0.051	0.182

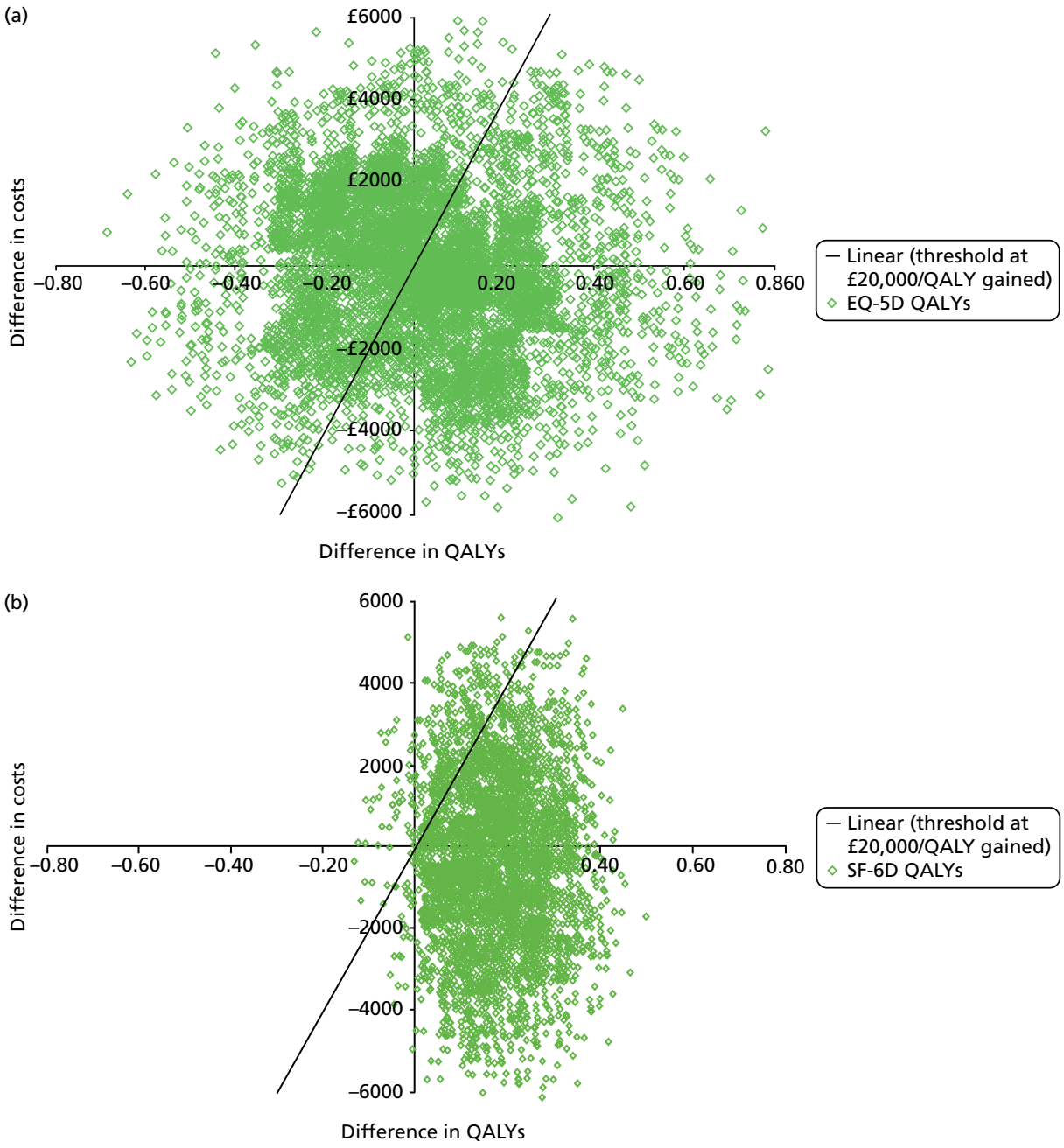

FIGURE 16 Cost-effectiveness plane for the model-based base-case analysis. (a) EQ-5D; and (b) SF-6D.

The probability that CPAP was cost-effective over a range of cost-effectiveness thresholds is shown in *Figure 17*. The uncertainty around the results observed in the cost-effectiveness planes above (see *Figure 16*) is reflected in the probability that the CPAP was cost-effective. In the EQ-5D analysis, the scatter of the simulations translated into a curve plateauing at 0.6. The SF-6D analysis indicated a greater probability that the CPAP was cost-effective across the range of thresholds. The probability that CPAP was cost-effective at the conventional thresholds used by NICE of £20,000 and £30,000 per QALY gained was 0.62 for EQ-5D QALYs and 0.95 and 0.97, respectively, for SF-6F QALYs. These results were consistent with those of the within-trial analysis.

Subgroup analyses

The cost-effectiveness results for the subgroup populations defined according to ESS score at baseline are shown in *Table 46*. In the less severe OSAS subgroup (ESS score of < 13 at baseline), the use of CPAP treatment reduced overall costs by £201. The effect on QALYs was dependent on the measure used: EQ-5D QALYs were reduced by 0.169 but SF-6D QALYs were increased by 0.181. Therefore, the ICER for the less severe OSAS subgroup using EQ-5D QALYs was £1189 per QALY gained. CPAP dominated in the SF-6D QALYs scenario. In the more severe OSAS subgroup, the use of CPAP treatment increased overall costs by £176 and both EQ-5D and SF-6D QALYs were increased. The ICERs were £360 per EQ-5D QALY gained and £967 per SF-6D QALY gained. These results were similar but in greater order of magnitude to the results of the within-trial analysis.

The cost-effectiveness planes for both population subgroups and by instrument used for obtaining QALYs, EQ-5D or SF-6D are shown in *Figure 18*. The same scale was used across the four plots to facilitate comparisons. In analysis of the less severe OSAS subgroup (ESS score of < 13 at baseline), using EQ-5D, there was considerable uncertainty on how CPAP affected costs and QALYs. In the analysis using SF-6D, some uncertainty around the effect on costs remained, but CPAP appeared to improve health outcomes across most of the simulations. In the more severe OSAS subgroup (ESS score of ≥ 13 at baseline), there was some degree of certainty that CPAP improved health outcomes, in terms of both EQ-5D and SF-6D. The uncertainty around the impact on costs remained.

The cost-effectiveness acceptability curve over a range of cost-effectiveness thresholds for both subgroups is shown in *Figure 19*. The curves were similar to the within-trial analysis. In the less severe OSAS subgroup, the probability that CPAP was cost-effective at £20,000 per QALY gained was 0.28 for the analysis with EQ-5D QALYs and 0.89 for the analysis with SF-6D QALYs. In the more severe OSAS subgroup, the probability that CPAP was cost-effective was 0.91 for the analysis with EQ-5D QALYs and 0.83 for the analysis with SF-6D QALYs.

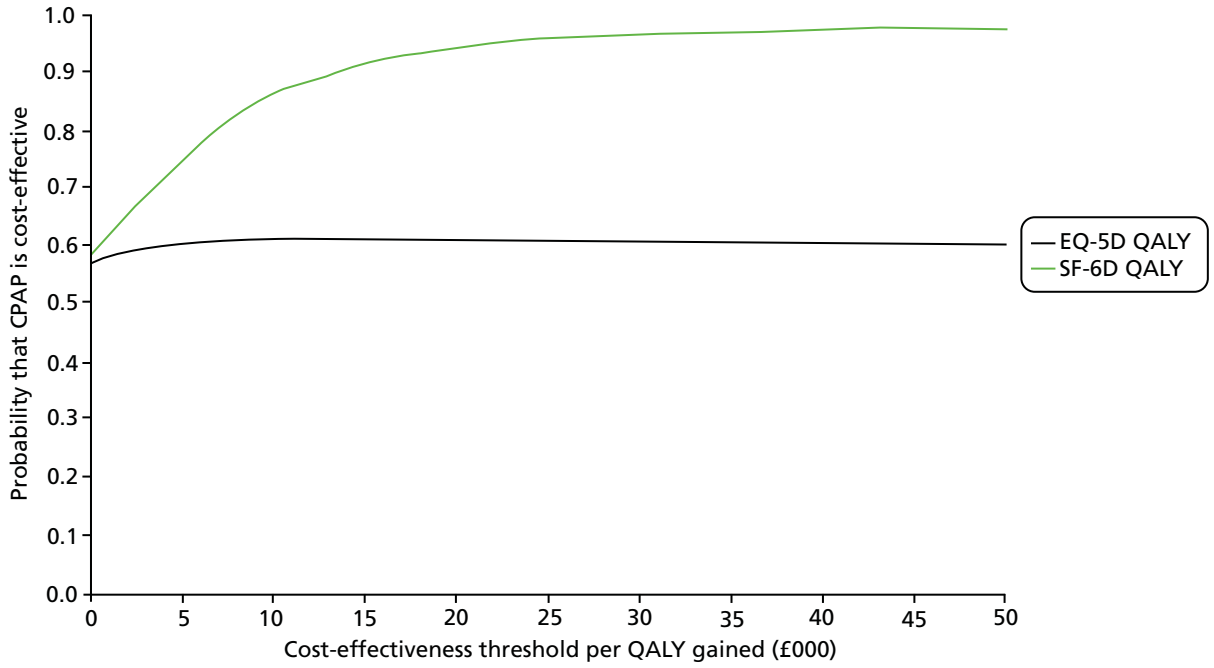

FIGURE 17 Cost-effectiveness acceptability curves for model-based base-case analysis.

TABLE 46 Cost-effectiveness results for subgroup populations

Treatment	Average costs	Average EQ-5D QALYs	Average SF-6D QALYs
Subgroup ESS score of < 13			
CPAP	£16,019	7.823	7.861
BSC	£16,221	7.992	7.679
Incremental costs and QALYs			
CPAP with BSC – BSC alone	–£201	–0.169	0.181
Subgroup ESS score of ≥ 13			
CPAP	£16,396	8.483	7.860
BSC	£16,216	7.994	7.678
Incremental costs and QALYs			
CPAP with BSC – BSC alone	£176	0.489	0.182

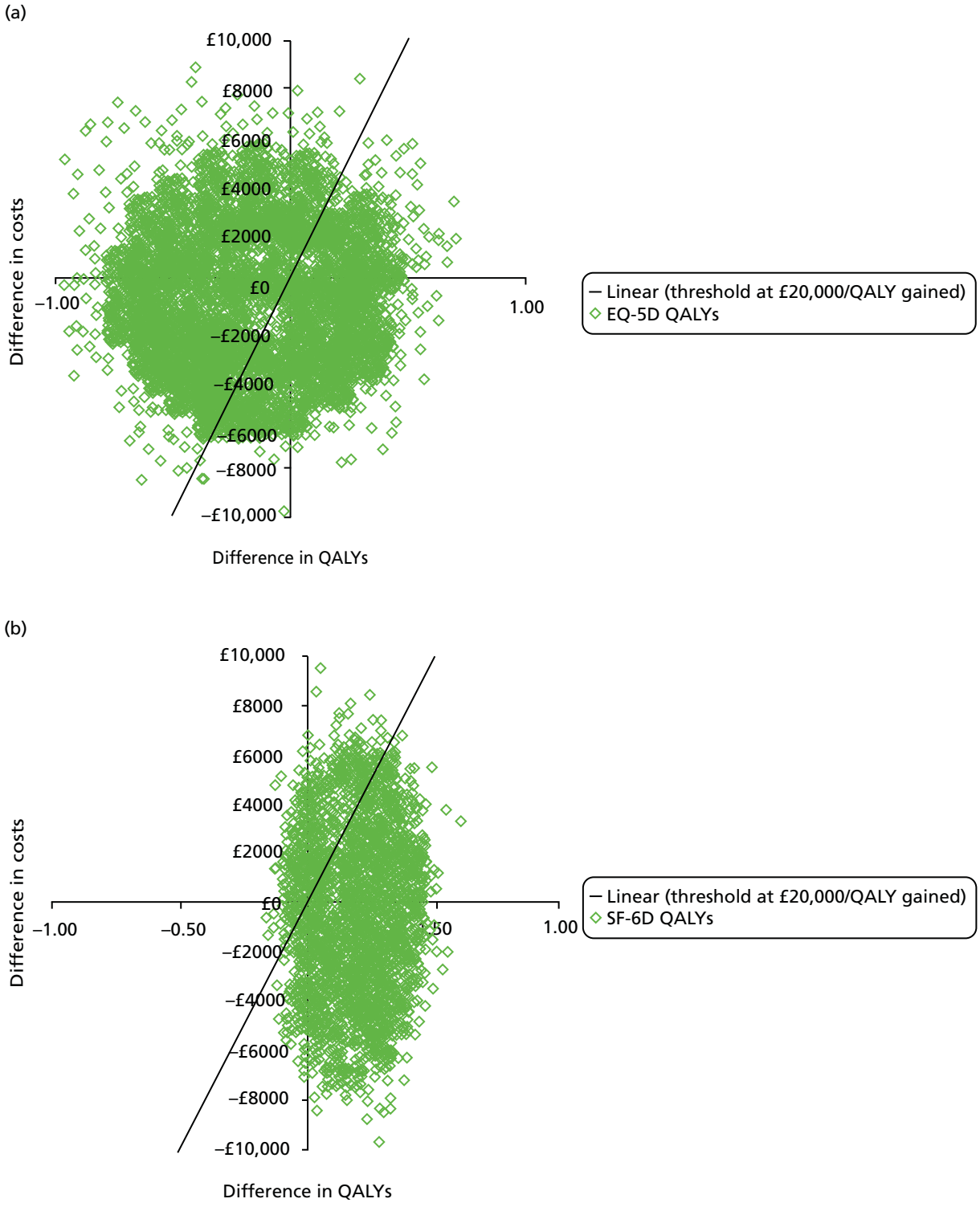

FIGURE 18 Cost-effectiveness plane for subgroup populations. (a) ESS score of < 13 EQ-5D; (b) ESS score of < 13 SF-6D; (c) ESS score of ≥ 13 EQ-5D; and (d) ESS score of ≥ 13 SF-6D. (*continued*)

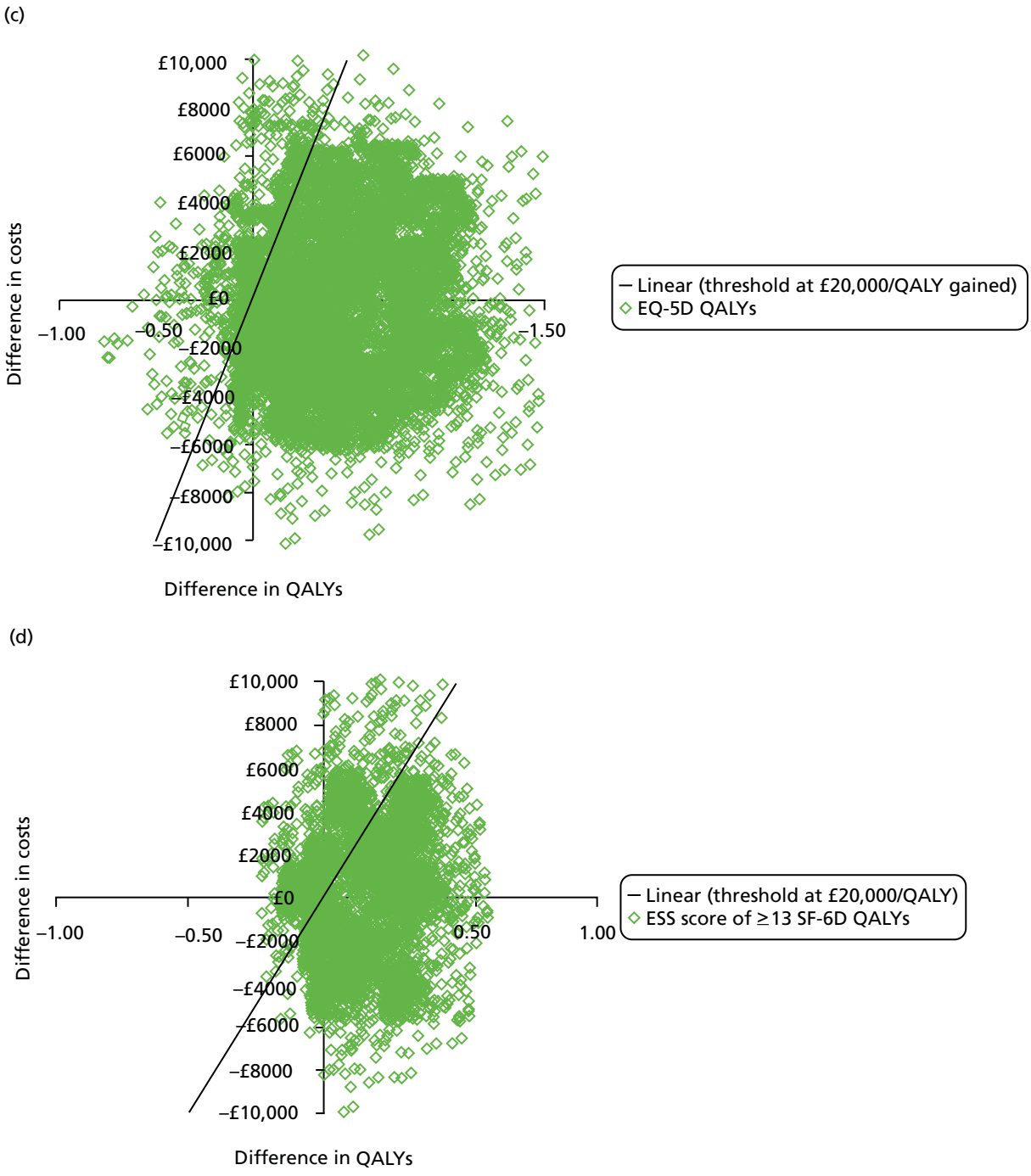

FIGURE 18 Cost-effectiveness plane for subgroup populations. (a) ESS score of < 13 EQ-5D; (b) ESS score of < 13 SF-6D; (c) ESS score of ≥ 13 EQ-5D; and (d) ESS score of ≥ 13 SF-6D.

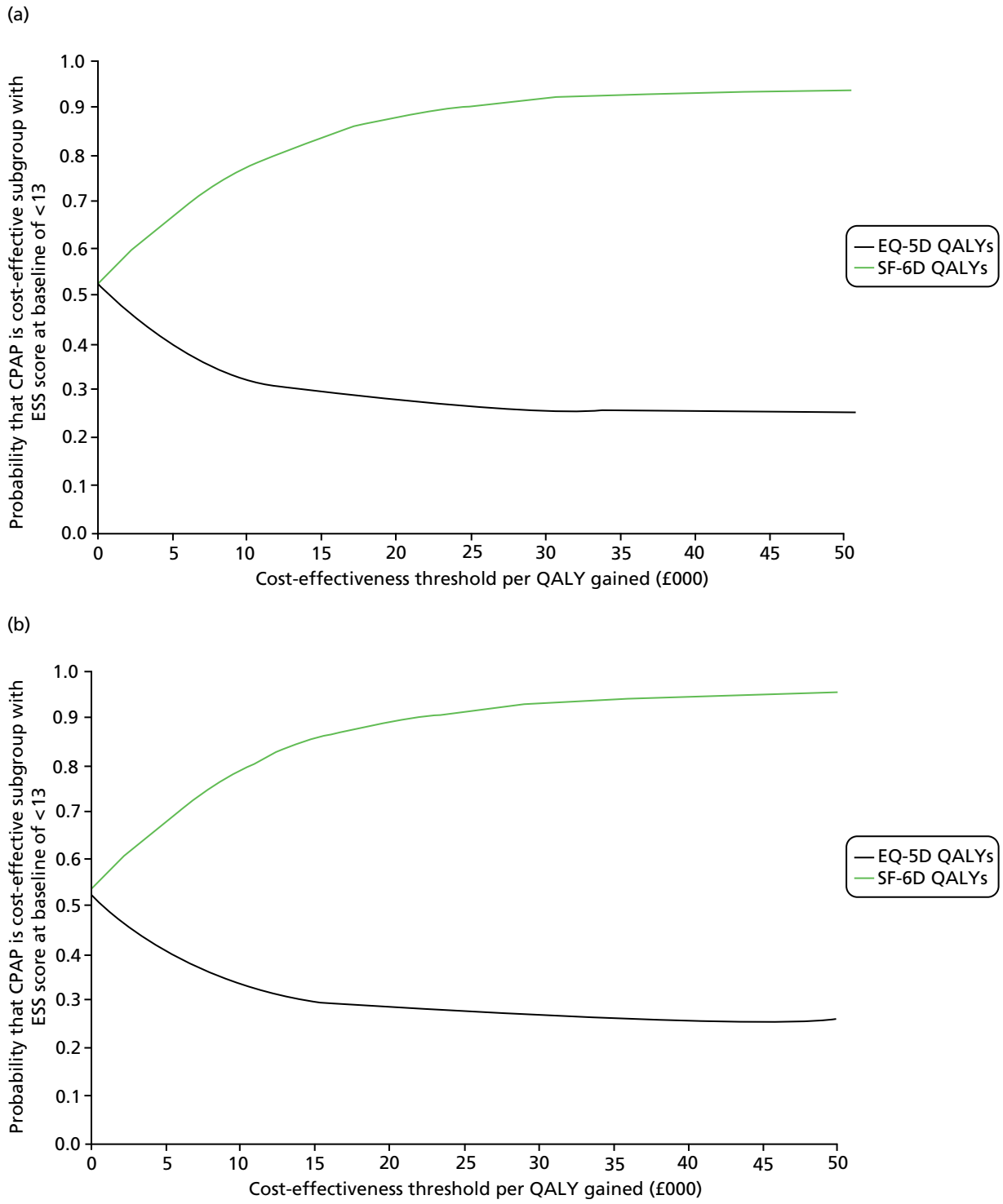

FIGURE 19 Cost-effectiveness acceptability curve for the subgroup (a) ESS score of < 13; and (b) ESS score of ≥ 13.

Sensitivity analysis

The results of the scenario analysis are shown in *Table 47*. See *Appendix 3* for more detailed results including average costs and QALYs for each treatment, cost-effectiveness planes and cost-effectiveness acceptability curves. In scenario 1, the costs of CPAP treatment were increased to £710.16 because of more frequent replacement of the machine and consumables. Therefore, the difference in costs in the first year increased from –£35 to £474 (see *Table 37*). This cost difference was extrapolated over the patients' lifetime in the model to £4785 (from –£329) in the base case. The probability that CPAP was cost-effective reduced from 0.62 to 0.20 when using EQ-5D QALYs and from 0.95 to 0.31 when using SF-6D QALYs. This was consistent with the findings of the within-trial analysis.

Scenario 2 included the effect of CPAP on cardiovascular risk predicted by the Framingham risk equations. The impact of including cardiovascular outcomes was very small. The difference in QALYs was reduced from 0.051 to 0.022 when using EQ-5D QALYs and from 0.182 to 0.139 when using SF-6D QALYs.

In scenario 3, only cardiovascular effects were considered; the cost and QALY difference observed at 12 months in PREDICT were not included. Over the patients' lifetime, the differences in costs and QALYs were very small and uncertain (–£10; EQ-5D QALYs, –0.024; SF-6D QALYs, –0.023). This reflects the small effect of CPAP in diastolic BP and cholesterol observed in the trial.

The impact of the cost of the CPAP machine on the EQ-5D ICERs and in the probability that CPAP is cost-effective is shown in *Figure 20*. Note that the cost of the CPAP machine was annuitised over 7 years using a discount rate of 3.5%. Therefore, if the cost of the CPAP machine was doubled from £430 to £860, the annuitised cost of the machine increased from £70.32 to £140.65. This cost should be added to the annuitised cost of the humidifier (£26.98 multiplied by the proportion of people who received humidifier, 0.59 = £15.81) and the cost of consumables (£115.16) to give a final therapy cost of £271.62. In this analysis, the ICER for CPAP was above £20,000 per QALY gained and the probability that CPAP was cost-effective was below 0.50 for a machine cost of £1290 (three times the base-case cost of £430). These results indicated that a key driver of cost-effectiveness was whether or not patients returned the machine rather than the cost of the machine itself.

TABLE 47 Cost-effectiveness results for the scenario analysis

Scenario	Difference in average costs	Difference in average EQ-5D QALYs	ICER/EQ-5D QALYs	Difference in average SF-6D QALYs	ICER/SF-6D QALYs	Probability that CPAP is cost-effective at £20,000/QALY gained	
						EQ-5D QALYs	SF-6D QALYs
Base case	***–£329***	***0.051***	***D***	***0.182***	***D***	***0.62***	***0.95***
1. CPAP used for 1 year (= £710.16)	£4785	0.051	£94,404	0.182	£26,599	0.20	0.31
2. Cardiovascular effects with effect of CPAP on costs and QALYs	–£327	0.022	D	0.139	D	0.58[a]	0.92[a]
3. Cardiovascular effects only	–£10	–0.024	£401	–0.023	£427	0.27[a]	0.28[a]

a Probability that CPAP is cost-effective presented for the most common subgroup (male patients who do not smoke and are not diabetic; 102 patients, 53.4% of patient population in the trial).
D indicates that CPAP dominates because it is associated with both lower costs and QALY gains.

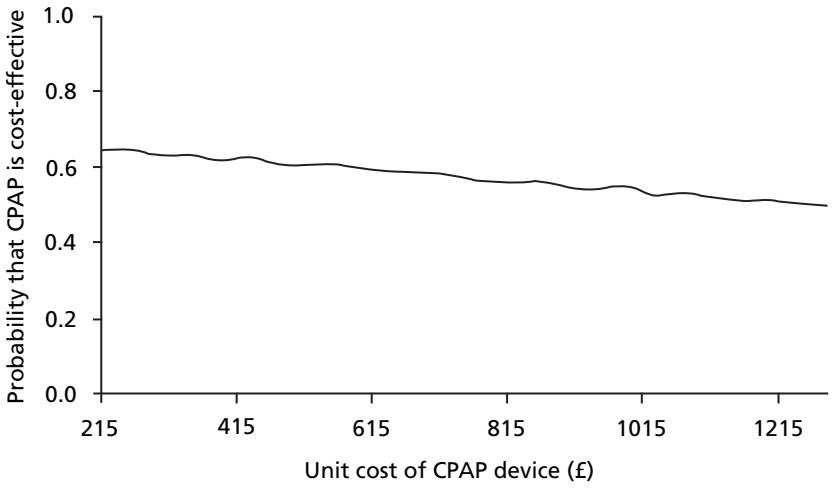

FIGURE 20 Impact of the unit cost of the CPAP machine on the probability that the CPAP therapy is cost-effective.

Discussion of the assessment of the cost-effectiveness

Continuous positive airway pressure treatment appeared to be a cost-effective alternative to BSC alone. CPAP decreased costs by a small amount and improved health outcomes. However, the differences in costs and health outcomes between the treatment groups were small and uncertain. The subgroup analysis by level of sleepiness suggested that CPAP was more likely to be cost-effective in the more severe OSAS subgroup of patients. These results were consistent across the within-trial and model-based analyses.

The key drivers of cost-effectiveness were the costs of CPAP treatment and the benefits of CPAP on HRQoL. Some patients may fail to return the machine following treatment discontinuation. In these patients, the CPAP machine is a sunk cost, as it does not benefit the patient and cannot be reissued to another patient. If CPAP machines are not fully utilised over the lifetime of the machine, on average, the cost per patient of CPAP treatment increases. In the extreme scenario that all patients discontinued treatment after 1 year and did not return the machine, the probability that CPAP was cost-effective at £20,000 per QALY gained was 0.20 for EQ-5D QALYs and 0.30 for SF-6D QALYS. The implication for clinical practice is that patients should be encouraged to return the CPAP machine if they cease to use it.

The benefits in HRQoL were small when measured by either EQ-5D or SF-6D, but the SF-6D results may seem more pronounced as the difference was statistically significant. The smaller amount of variability with the SF-6D compared with the EQ-5D may be related to the data collection process and/or the instrument itself. The EQ-5D was collected every month through a sleep diary, which was filled in by the patient at home and sent by post. The SF-36, from which SF-6D is derived, was collected less often during a clinic visit at baseline and at 3 months and 12 months. This may have influenced the reporting of HRQoL by patients, although this would have been the case for both the CPAP and the BSC groups. In addition, the EQ-5D and SF-6D questionnaires have some differences. The SF-6D uses 11 questions from the SF-36 health status measure divided over six health domains: pain (six levels), mental health (five levels), physical functioning (six levels), social functioning (five levels), role limitations (four levels) and vitality (five levels).[121] The EQ-5D comprises five questions, with three levels each, on mobility, self-care, usual activities, pain, and anxiety and depression.[156] The dimensions in SF-6D, particularly vitality, may render the SF-6D more sensitive to changes in sleepiness and sleep quality. PREDICT is the first trial to collect SF-6D and EQ-5D following treatment of OSAS; however, some studies have compared SF-36 with EQ-5D and found that SF-36 was more sensitive to the impact of CPAP on HRQoL.[153,155]

The impact of including cardiovascular outcomes on the cost-effectiveness of CPAP appeared to be negligible. This reflected the small difference in BP and cholesterol between patient groups observed in PREDICT. The increase in systolic BP would increase the risk of cardiovascular outcomes whereas the change in cholesterol would decrease it. Overall, and on balance, the change in these intermediate outcomes resulted in a small decrease in costs and QALYs. A limitation of this assessment was the incorporation of the impact of CPAP on cardiovascular outcomes. The Framingham risk equations have not been validated in a population older than 74 years of age. Therefore, the risk of cardiovascular outcomes may not have been correctly estimated. The direction of the bias is unclear and would have depended on whether the risk was under- or overestimated and on the effect of BP versus cholesterol on overall cardiovascular risk. CPAP would have been favoured if the combined effect of CPAP on BP and cholesterol decreased overall cardiovascular risk and the risk was overestimated or if the combined effect increased overall risk and risk was underestimated. Nonetheless, the impact of this bias was likely to be small, given the small change in costs and QALYs observed for the scenario with cardiovascular effects.

The cost-effectiveness analysis entailed three components to ensure appropriate consideration of all the relevant evidence: a systematic review of previous economic evaluations, a within-trial analysis using individual patient data collected in PREDICT and a model-based analysis incorporating the data collected in PREDICT with relevant external evidence. A systematic review on the clinical effectiveness of CPAP in older people confirmed that PREDICT was the sole source of evidence in this patient population. As it is considered that the CPAP treatment effects recorded in younger patients were not generalisable to older patients, this meant that PREDICT was the sole source of evidence of the treatment effects of CPAP included in the model-based analysis. Uncertainty around the cost-effectiveness results was quantified with a range of scenarios and sensitivity analyses in the within-trial and model-based analyses.

Areas of uncertainty included whether or not the savings in health-care costs are sustained over time and the differences between EQ-5D and SF-6D QALYs. The savings in health-care costs are small and uncertain; however, on average, these were enough to offset the cost of CPAP treatment. The savings may reflect the effect of CPAP on health-care resource use. Patients on CPAP may experience fewer adverse effects caused by their OSAS than patients on BSC alone and use the NHS less often as a result. Alternatively, the average saving per patient may be as result of chance and an artefact of the trial being underpowered to detect differences in costs.

The differences in the improvements in QALYs observed with EQ-5D and SF-6D were another area of uncertainty and a key driver of cost-effectiveness. As discussed, these differences may be related to the failure of the questionnaires in capturing the impact of sleepiness on quality of life or to the differences in the frequency and setting of the administration. Future research should explore the differences between EQ-5D and SF-6D as well as how different methods to collect HRQoL data impact on the results.

Chapter 5 Discussion

Main findings

Positive Airway Pressure in Older People: a randomised controlled trial was designed to assess the clinical efficacy of CPAP in older people with OSAS at 3 months and its cost-effectiveness over 12 months. CPAP improved sleepiness after 3 months by 2.1 points on the ESS compared with BSC. The beneficial effects were maintained at 12 months, and the magnitude of the improvements was similar to those seen in middle-aged patients with equivalent disease severity.[20] This subjective improvement in sleepiness was corroborated by the improvement in objective sleepiness at 3 months.

Continuous positive airway pressure also improved quality of life, both generic and disease-specific. CPAP-related improvement was statistically significant for the QALYs calculated with the SF-6D but not with the EQ-5D, equating to 1 week and 2 days, respectively. The CPAP group also accrued marginally lower health-care costs than BSC alone over 12 months. Overall, the economic benefit of CPAP was linked to the reduced health-care usage, offsetting the cost of the equipment, making it a cost-effective alternative to BSC for the treatment of OSAS in older people. The discrepancy between the two QALY measures could be a result of the EQ-5D being a less sensitive measure of the changes in health status attributed to sleepiness than the SF-36 (from which the SF-6D is derived).[12]

Additional findings

Secondary outcomes related to cognitive function did not show any difference between the two groups despite reductions in sleepiness in the CPAP group. However, the baseline cognitive scores were often within the age-adjusted normative range, which may have resulted in a ceiling effect. Cognitive dysfunction is well recognised in middle-aged OSAS patients[14,157] and is potentially linked to changes in brain morphology.[158] However, the impact of OSAS on cognitive function, separate from its effects on sleepiness and vigilance, is debated.[159,160] In older people with OSAS, the benefits of CPAP could be reduced because the capacity for neuronal recovery is less, owing to a combination of neurodegeneration associated with ageing and the life-long effects of OSAS.[57]

The cardiovascular risk factors showed a small reduction in total cholesterol at 3 months, which was driven by a reduction in the LDL component. These findings are similar to those in a more severe and sleepier OSAS population, following 1 month of treatment with CPAP.[161] CPAP resulted in no improvement in BP. In the BSC group there was a small improvement in the systolic BP at 12 months. This finding echoes the results of a recent RCT of cardiovascular risk in mild asymptomatic patients[162] in which CPAP usage, more specifically low usage, seemed to slightly raise BP. We speculate this could be a result of the BSC group following the BSC advice more closely.

Other secondary outcomes which showed no statistically significant difference between the two groups at 3 and 12 months were mood, frequency of nocturia and accidents. Interestingly, the patients in this trial had a relatively low prevalence of depression compared with a recent study.[8] We speculate that the expected lack of improvement in nocturia with CPAP may have been because of the multifactorial nature of this symptom in older people.[163]

Comparison with other trials

A review of the clinical effectiveness of CPAP therapy in older people revealed three RCTs (from a possible 3560 titles) assessing the efficacy of CPAP treatment in OSAS patients with an average age of 60 years or older and the capacity to give informed consent. These studies included patients with cardiovascular conditions and compared CPAP therapy with sham CPAP[88] or no CPAP.[89,90] None of the studies assessed daytime sleepiness or collected generic measures of health-care usage and they were not conducted in a secondary-care setting. The primary outcomes were left ventricular ejection fraction,[88] baroreflex sensitivity,[89] a number of neurological, quality-of-life and sleep-related effects and mortality.[90] Two studies reported BP at baseline and at follow-up;[88,89] however, both of these studies focused on patients with chronic heart failure and their follow-up was short, at 3 months and 1 month, respectively. In the Egea *et al.*[88] study, no statistically significant differences were found in BP. In the Ruttanaumpawan *et al.*[89] study, the reduction in average systolic BP at 1 month was statistically significant but not the reduction in average diastolic BP. Overall, the results of these three studies are difficult to generalise to PREDICT, given their focus in patients with concomitant cardiovascular disease. Egea *et al.*[88] and Ruttanaumpawan *et al.*[89] included only patients with chronic heart failure and Parra *et al.*[90] included only patients who had had an ischaemic stroke.

Treatment adherence

The CPAP adherence was low at 3 and 12 months, which is likely to have diluted any treatment effect between the groups.[164] Indeed, exploratory analyses revealed that the treatment effect was larger in patients with more frequent CPAP use. The mean CPAP usage and the percentage of patients using CPAP at 12 months were similar to another UK RCT, albeit one of a shorter duration in patients with minimally symptomatic OSA.[162]

The CPAP machines used in PREDICT were autoadjusting and, based on previous studies, it is unlikely that the autoadjusting machines were the cause of less frequent CPAP use.[165–167] On the other hand, we adopted a clinical approach to initiating and managing CPAP treatment, which may have resulted in a less frequent CPAP use, compared with a more intensive trial protocol.[15] However, with the approach that was adopted in this study, we have ensured that the PREDICT outcomes reflect clinical practice in the UK, which in turn has strengthened the validity and applicability of the health economic assessment. An additional factor that may have contributed to the low frequency of CPAP use in older people is reduced social support. We do not know how many patients were married, a factor that has been reported to be associated with increased CPAP compliance;[168] however, just over half the patients slept alone.

Strengths and weaknesses

Positive Airway Pressure in Older People: a randomised controlled trial was designed as a pragmatic trial, recruiting older OSAS patients with comorbidity from geographically diverse areas throughout the UK. The findings are, therefore, relevant to what would be seen in clinical practice. Additionally, one of the unique elements of the trial design was the simultaneous cost-effectiveness evaluation, as well as the analysis of clinical effectiveness, measured over a relatively long time period. Finally, the high follow-up rates of patients attending at 3 and 12 months (over 80%) was impressive considering the duration of the trial.

A possible limitation of the trial was that sham CPAP was not used; therefore, as it was a physical device trial, the treatment allocation for the individual patients could not be concealed. The treatment allocation was concealed as far as possible from the member of the research team completing follow-up assessments. However, we reasoned that any placebo effect there might have been in the CPAP group would be expected to have disappeared by 12 months and that patients using CPAP might have expected an improvement but they would not have known by how much. Moreover, the results of the OSLER test and the observation of a therapeutic dose–response relationship between the treatment effect and CPAP use support a real effect.

Generalisability

With respect to generalisability, PREDICT did not focus on asymptomatic older people with OSA, and, although it could be argued that the patients studied had a relatively low mean ESS score at baseline, they were sufficiently symptomatic to seek treatment. At the other end of the disease spectrum, the exclusion of highly symptomatic OSAS patients in whom CPAP was considered mandatory is likely to have diminished the effect size. Patients with a higher baseline ESS score had a greater treatment effect in the exploratory analysis. Equally, the marginal improvement in cost-effectiveness was greater in the more symptomatic patients.

Continuous positive airway pressure prescribed for the symptom of excessive sleepiness due to OSAS in older people is more effective than BSC alone and no more expensive than BSC. The beneficial treatment effect is greater in patients with a higher ESS score prior to treatment and additionally in those the patients who used the CPAP treatment more.

Implications for health care

Clinical guidelines play an important role in improving health care for people with long-term conditions; however, it is well recognised they often fail to address the effects of comorbidity and polypharmacy.[169] There is also an inequality of research in older people with OSAS[170] and PREDICT addresses this. The high-quality data from this trial will add to the knowledge of age-related changes, improve the generalisability of research findings and help inform best practice in the clinical management of a population that is growing older. The results of this study clearly support the use of CPAP for the treatment of OSAS in older people.

Implication for future research

Adherence to treatment is a recognised concern, particularly in multimorbid patients; despite this, few studies have investigated how adherence could be promoted. Suggested research priorities for future research are:

- To focus on the optimisation of CPAP delivery, especially in older patients. Can changes in health-care delivery improve adherence? Stratifying older patients with OSAS according to comorbidities and social factors to assess the clinical effectiveness and cost-effectiveness of CPAP treatment could further inform the delivery of care. Given uncertainty surrounding use of EQ-5D further work could be undertaken to assess quality-of-life measures this group of patients.
- To define patient-centred outcomes for treatment of OSAS in women and in ethnic groups, both of whom are currently under-represented in clinical trials.
- To identify potential biomarkers sleepiness and cognitive function that would enable early detection, which could be used in studied to inform when in the disease cycle treatment is needed to avert central nervous system sequalae.
- To explore the hypothesis that OSA in different groups may have different causes anatomically and physiologically, with different consequences.

This last point remains to be explored and may be fundamental to the understanding and targeting of treatment of the disorder.

Conclusion

- PREDICT has been the longest and most comprehensive controlled treatment trial in older OSAS patients to date, assessing both the therapeutic and economic impact of CPAP treatment.
- PREDICT has addressed the lack of research in older people with OSAS.
- The results of PREDICT clearly show that CPAP reduces symptoms of excessive daytime sleepiness in older patients with OSAS, as it does in middle-aged populations, and that these clinical benefits are associated with reduced health-care utilisation.

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Alison McMillan drafted the first and subsequent versions of this report, with supervision by **Mary J Morrell** and the other authors, who reviewed and approved the final submitted report.

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Publications

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Appendix 1 Statistical and health economic analysis plans

Oxford Respiratory Trials Unit

MRC Clinical Trials Unit

HTA

Imperial College London
Royal Brompton & Harefield NHS Trust
Biomedical Research Unit

PREDICT

Positive Airway Pressure in Older People: A Randomised Controlled Trial

PREDICT

STATISTICAL ANALYSIS PLAN

Version 1.1

Version	Date	Comments
0.1	06/04/2011	First draft
0.2	09/05/2011	Updated following SAP meeting
0.21	14/06/2011	Minor updates prior to TSC meeting
0.3	08/03/2012	Multiple Imputation section added
0.4	02/04/2012	Updates following SAP meeting
0.5	13/04/2012	Minor changes before finalising
1.0	19/04/2012	Final draft of plan
1.1	10/06/2013	See appendix for details of changes

NHS Lothian

The University of Edinburgh

CHE Centre For Health Economics

UKCRN UK Clinical Research Network

Contents

1. INTRODUCTION

This document details the planned statistical analyses for an investigator-blind, randomised controlled trial that compares continuous positive airway pressure plus best supportive care (CPAP) against best supportive care only (BSC) for treatment of obstructive sleep apnoea hypopnoea syndrome (OSAHS) in patients aged 65 and over.

Full details of the background to the trial and its design are presented in the trial protocol.

The analyses described in this document will be performed by the designated statistician at the MRC Clinical Trials Unit. All data will be analysed using STATA version 12.

The trial statisticians responsible for writing this document in discussion with the co-chief investigators and other principal investigators and conducting the final analyses are:
Daniel Bratton, MRC CTU
Andrew Nunn, MRC CTU.

2. DESIGN

2.1 Summary

This study is a two-arm, investigator-blind, parallel group, multi-centre randomised controlled trial. A total of 270 participants will be recruited to the study and followed-up for 12 months. At baseline participants will be randomised to receive CPAP plus BSC (active) or BSC only (control).

The co-primary endpoints are:

1. the therapeutic outcome of change in Epworth Sleepiness Scale score between the mean of the scores at months 3 and 4 and the baseline score
2. the cost efficiency of CPAP therapy calculated through the impact of CPAP on health-related quality of life and health service utilisation over 12 months of follow-up.

2.2 Inclusion Criteria

- Age $\geq$65 years
- A clinical diagnosis of OSAHS: $\geq$ 4% Oxygen desaturation index > 7.5 events/hour and an Epworth sleepiness scale $\geq$ 9
- Ability to give written informed consent

2.3 Exclusion Criteria

- Previous exposure to CPAP therapy
- Arterial oxygen saturation <90% on room air
- FEV_1 / FVC <60%

- Substantial problems with sleepiness driving (in those who are still driving)
- Currently using HGV or PSV driving licence (where applicable - annual application is required for drivers > 65 years)
- Shift work
- Any very severe complication of OSAHS such that CPAP therapy is mandatory
- Inability to give informed consent or comply with the protocol e.g. the patient must be able to see to be able to participate in the wakefulness test
- Enrolled in another intervention study

2.4 Randomisation

Once a participant has given written consent to the trial, an enrolment form is completed and the participant is randomised using the telephone computerised randomisation service of the MRC CTU. Randomisation is by minimisation with a random element of 80%. The minimisation criteria are:

- Subjective day time sleepiness (Epworth sleepiness score, > 13 or ≤ 13)
- Functionality (Townsend disability index, >1 or ≤1)
- Recruiting centre

3. OUTCOME MEASURES

3.1 Primary outcome measures

Difference between the two treatment arms in:

- Subjective Sleepiness: the mean change in the mean of the Epworth Sleepiness Scale (ESS) scores measured at months 3 and 4 compared to baseline. The ESS assesses the tendency to fall asleep during eight typical daytime scenarios (1). Each component is given a score of 0, 1, 2 or 3 to represent no, slight, moderate or high chance of dozing respectively. The ESS score is then the sum of its eight components. If at least one of the components is missing the ESS will also be set to missing. Should non-integer values be given, these should be included in the sum and the final ESS rounded up to the next integer.
- Cost effectiveness at 12 months: Described by the EQ-5D, valued using UK population tariffs. This will be used to estimate the cost per QALY gained by providing CPAP in comparison to Best Supportive Care. The analysis will incorporate health care utilisation, including in patient and out patient hospital visits and GP visits during the trial. The cost-effectiveness analysis will be performed by the Centre for Health Economics, University of York and a separate analysis plan will be written for this outcome.

3.2 Secondary outcome measures

Difference between the two treatment arms in:

- Subjective sleepiness: the mean of the ESS scores measured at months 10, 11 & 12 compared to baseline

In addition, the change from baseline in the following outcomes will be analysed at 3 and 12 months:

Difference between the two treatment arms in:

- Objective sleepiness: OSLER (Oxford Sleep Resistance Test). This test assesses a patient's ability to resist sleep for 40 minutes. Two tests are conducted at each visit (baseline, 3m and 12m) and the average time taken to fall asleep at each visit will be used for analysis.
- Self reported health status (quality of life and mood):
  - Short Form 36 questionnaire (SF-36) consists of 36 quality of life related questions. Answers to questions are condensed into 8 summary scores which can be reduced further to the mental component summary (MCS) and physical component summary (PCS) scores. Each summary score will be calculated using the formulae proposed by Jenkinson et al (2). Should any of the 36 questions not be answered, the MCS and PCS will be set to missing along with any of the 8 summary scores which are dependent on the missing answers.
  - Sleep Apnoea Quality of Life Index (SAQLI; a disease specific sleep apnoea questionnaire which includes CPAP side effects). The SAQLI is scored by averaging the answers to 14 sleep apnoea related questions and, if applicable, adjusting for side effects attributable to CPAP therapy (see 10.1). Should any of the answers to 14 questions be missing, the SAQLI will also be set to missing)
  - Hospital Anxiety & Depression Scale (HADS). The anxiety and depression aspects of the HADS will be scored by summing the scores from the relevant questions, each of which is scored on a 0-3 scale (7 questions for each aspect).
- Functional index of activities of daily living: Townsend Disability Index (TDI). Each of the 9 items of the TDI is scored with either 0 (Yes, with no difficulty), 1 (Yes, with some difficulty) or 2 (No, need help). Items are then summed to give a total score (3). If at least one of the components is missing the TDI will also be set to missing.
- Frequency of nocturia: The average number of times that patients get up to pass urine at night is reported at the study visits
- Mobility: The Timed up and go test measures, in seconds, the time taken by an individual to stand up from a standard arm chair, walk a distance of 3 metres, turn, walk back to the chair and sit down. There is no upper time limit and the time in seconds is rounded up or down to a whole second.
- Road, and domestic accidents: the number of domestic accidents are self-reported at the follow-up visits (3 and 12 months). The proportion of patients experiencing each accident and any accident will be analysed.
- Cognitive function: Mini-mental state score, Trail making B time, Digit Symbol Substitution test score and simple and four-choice reaction time (see section 0 for a description of these tests).
- Cardiovascular Risk factors: systolic and diastolic blood pressures (SBP & DBP), fasting glucose, fasting lipids, HbA1c.
- Adverse cardiovascular events: Myocardial infarction, stroke, transient ischemic attack, new angina, new atrial fibrillation and new peripheral vascular disease. At each follow-up visit (3 and 12 months) patients report whether they have been newly diagnosed or experienced any of these events since the last visit.

The proportion of patients experiencing any adverse cardiovascular event listed above will be compared between treatment arms.

3.3 Tertiary outcome measures

- Treatment compliance: Measured objectively by smartcards in the machines and downloaded at 3 and 12 month clinic visits.

4. COGNITIVE FUNCTION TESTS

- The Mini Mental State Examination (MMSE) is a widely used screening tool for cognitive function. The MMSE provides a measure of orientation, registration (immediate memory), short-term memory (but not long-term memory) as well as language functioning. It is scored out of 30. Scores of 25-30 are considering normal; 18-24 indicate mild-to-moderate impairment; scores of 17 or less indicate severe impairment.
- The Trail Making Test B (TMT-B) provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. It requires individuals to draw a line sequentially connecting 25 encircled numbers and letters, distributed on a piece of paper alternating between numbers and letters (e.g. 1, A, 2, B, 3, C etc.). The score represents the amount of time required to complete the task. Performance on the TMT decreases with increasing age and lower levels of education.
- The Digit Symbol Substitution is a coding exercise. It requires an individual to copy a code at the top of the piece of paper. Each symbol in the code corresponds to a single digit number. The individual must write each code under each number and complete as many as possible in 90 seconds. The total number they get correct in this time is recorded.
- The simple and four choice reaction time is a two part test which measures reaction time and the number of correct responses and errors and is completed on a computer. The first test measures the time to react to a symbol appearing in a white box on the screen by pressing any button on a keyboard. The second part requires the individual to respond to the symbol appearing in any 1 of 4 white boxes at random. They have to respond using the allocated key on the keyboard.

5. SAMPLE SIZE CALCULATIONS

The primary analysis will be the difference between the two treatment arms in the mean change of the Epworth Sleepiness Score (ESS) from baseline to the mean of the 3 and 4 month scores. In the recent NICE/HTA Technology Appraisal of CPAP for OSAHS in middle-aged patients (4), the effect of CPAP treatment on the difference in ESS in middle-aged patients with mild sleep apnoea was -1.07 (SD 2.4). The inclusion criterion for this trial lies in the range of "moderate" sleep apnoea by OSAHS severity, but since sleepiness is often less pronounced in older people, power calculations are performed assuming a treatment response similar to that seen in mild disease in the middle-aged. A mean change of 1 point on the ESS is the minimum clinically significant change since it is indicative of one symptom state shift on one domain of

the score. To detect a one point change in Epworth score (SD of change 2.4), requires 244 patients randomised in a 1:1 ratio (alpha=0.05, power 90%).

In previous randomised trials with a similar design a loss to follow-up rate of 5% was found. Since PREDICT is a 12-month trial we have assumed the loss to follow-up rate will be 10%. Patients who cease CPAP therapy will be followed-up through the normal trial systems. Therefore, the sample size for this trial will be 270 patients in total randomised in a 1:1 ratio.

6. ANALYSIS PRINCIPLES

6.1 Minimisation factors

Randomisation will be by minimisation with a random element of 80%. The minimisation factors are:

- Epworth sleepiness score, ESS (13 or less, or above 13)
- Townsend disability index, TDI (1 or less, or above 1)
- Recruiting centre

All analyses will be adjusted for these factors to optimise power and reduce bias. The ESS and TDI will be entered into models as fixed effects continuous variables. Recruiting centre will be adjusted for using random effects in order to avoid dropping centres that may only recruit a single patient.

6.2 Other covariates

Age, gender, ODI and BMI will also be adjusted for in addition to the minimisation factors in an additional analysis of the primary efficacy endpoint.

6.3 Other principles

- All analyses will be intention-to-treat incorporating all randomised patients who have data recorded on the outcome of interest (complete case analysis).
- No adjustments for multiple testing will be made, but cautious interpretations will be made of statistically significant secondary outcomes due to the large number of secondary analyses being performed.

7. ANALYSIS DETAILS

7.1 Patient flowchart

Patient throughput, from those screened for entry through those who are eligible (meet all inclusion criteria and no exclusion criteria) for the trial will be reported. The throughput of patients from those eligible to be randomised to those that are included in the ITT primary analyses will be summarised in a CONSORT flowchart.

The number of patients who are excluded at screening (failure to satisfy inclusion and exclusion criteria, refusal to participate), discontinued from treatment, and discontinued from follow-up will be reported.

7.2 Baseline characteristics

Baseline characteristics will be summarised by treatment arm. Categorical variables will be summarised by number and percentage in each category and continuous variables will be summarised by mean and standard deviation or by median, 25th and 75th percentiles as appropriate. No formal statistical tests will be performed since any differences should be the result of chance rather than bias.

7.3 Primary endpoint analysis

Primary effectiveness outcome

The mean of the 3 and 4 month ESS scores will be calculated for each patient and used as the follow-up ESS score. Should either score be missing, the single observed score will be used in the analysis. If both scores are missing the patient will be excluded from the primary analysis. Any 3 or 4 month ESS scores which are obtained before 2 months or after 5 months of follow-up has been completed will be excluded from the analysis. The difference between the follow-up ESS and the ESS used for randomisation will then be calculated for each patient and compared between treatment groups using a multivariable linear regression model. The analysis will be adjusted for the minimisation factors as outlined in section 6.1.

7.4 Secondary endpoint analyses

ESS

The mean of the observed 10, 11 and 12 month ESS scores will be calculated for each patient and will be taken to be the 12 month subjective sleepiness score. Similar principles to those described in section 7.3 for calculating the mean score will be used. The difference between the two treatment arms in the change in subjective sleepiness at 12 months compared to baseline will then be analysed using a multivariable linear regression model adjusting for the minimisation factors.

OSLER

Each patient participates in two OSLER tests at baseline, 3m and 12m. Kaplan-Meier plots will be used to summarise the mean time taken to fall asleep (the event of interest) at baseline, 3 and 12 months. The difference in the mean time taken to fall asleep at each follow-up visit compared to baseline will be compared between treatment groups using multivariable linear regression models. Analyses will be adjusted for the mean time taken to fall asleep at baseline in addition to the minimisation factors.

Other continuous outcomes

Continuous outcomes (SF36, SAQLI, HADS, TDI, cognitive function tests, cardiovascular risk factors, mobility test, frequency of nocturia) will be analysed using multivariable regression models and will be adjusted for their corresponding baseline score/measurement and the minimisation factors. Non-normal (skewed) data should not be an issue and can be analysed using this method due to the implications of the Central Limit Theorem that for a large sample size the mean will be approximately normally distributed.

Binary outcomes

For binary outcomes (accidents, adverse cardiovascular events) the odds of experiencing the outcome will be compared between treatment arms using logistic regression. The comparison of the odds of patients having an accident (at home or while driving) will be adjusted for the accident history at baseline (whether had an accident at home in the month before enrolment or while driving in the three months before enrolment). All analyses with be adjusted for the minimisation factors.

7.5 Tertiary endpoint analyses

Treatment usage is taken to be the mean number of hours that CPAP is used per night during follow-up (total number of hours used divided by total number of days follow-up). CPAP usage will be summarised using the median and 25th and 75th percentiles since the data are likely to be skewed.

Patients who have stopped CPAP during follow-up and are missing adherence data will be assumed to have zero hours/night usage. The number of patients stopping CPAP or swapping to CPAP from BSC will be summarised along with reasons.

7.6 Sensitivity analyses

Patients who are randomised to the control and who start CPAP therapy during follow-up may dilute the results of the ESS comparisons. Sensitivity analyses of the primary and secondary ESS outcomes will be performed in which ESS observations in control arm patients will be excluded from analysis if CPAP therapy is started before the visit at which the observation is recorded.

7.7 Multiple Imputation

Under the Missing at Random (MAR) assumption

The missing at random (MAR) assumption assumes that the probability that the missing data depends on the values of the observed data but does not depend on the values of the missing data.

Under the MAR assumption multiple imputation can be used to impute missing ESS scores over follow-up and produce an unbiased analysis on all randomised individuals. The plausibility of the MAR assumption will be explored by comparing observed data in those patients with and without the outcome of interest.

All 12 ESS follow-up scores will be entered into an imputation model along with the minimisation variables and the variables listed in section 6.2. Imputations will be performed separately within treatment groups. CPAP compliance at the 3 month and 12 month visits will also be included in the imputation model for the CPAP arm. For each treatment arm fifty imputation models will be created using the 'ice' command in Stata. In analyses secondary to those described above the primary and secondary ESS outcomes will be reanalysed on the imputed datasets and the results combined using Rubin's rules.

Sensitivity Analysis

The MAR assumption is untestable and may be inappropriate so the probability that data are missing could depend on values of the missing data (missing not at random, MNAR). The ESS outcomes will therefore be reanalysed on all randomised individuals under a range of "missing not at random" scenarios. This will be done using the

formula $\Delta=\Delta_{CC} + (\delta_1 p_1 - \delta_0 p_0)$, where Δ_{CC} is the adjusted treatment effect in the complete case scenario (primary analysis), p_1 and p_0 are the proportion of missing outcomes, and δ_1 and δ_0 are the differences between the mean unobserved outcomes and mean observed outcomes in the CPAP and Best Supportive Care arms respectively. The standard error for Δ is approximately equal to the standard error for Δ_{CC} and so a confidence interval and p-value for Δ can be calculated.

Positive and negative values of δ_1 and δ_0 will be considered and varied simultaneously and separately. The resulting Δ will be displayed graphically with its confidence interval. The aim of this technique is to determine how sensitive the observed results are to different assumptions on the unobserved outcomes in the two treatment arms.

8. EXPLORATORY ANALYSES

8.1 Effect of CPAP adherence on ESS

Patients who were allocated to the CPAP arm at randomisation will be split into tertiles by their average CPAP usage in the last month of follow-up before the 3 month visit. Each group will then be compared to the BSC arm in a single model on the change in the primary ESS outcome. The minimisation variables will be adjusted for. A global test will be used to determine whether the treatment effect in each of the three CPAP groups differs.

A similar analysis will take place on the secondary ESS outcome, splitting patients into tertiles by their average CPAP usage in the last 3 months of follow-up before the 12 month visit.

The effect of CPAP usage on ESS at each timepoint will also be modelled using multivariable fractional polynomial models (5) adjusting for the minimisation variables. Since the BSC arm will not have compliance data the mean change in ESS in this arm will be displayed on the fractional polynomial plot.

8.2 Subgroup analyses

The effect of CPAP therapy on the primary ESS outcome will be compared separately by age, BMI and ESS and ODI at baseline. Each baseline variable will be categorised by its quartiles. The treatment effect in each subgroup will be estimated and compared using a global test for interaction. A continuous treatment effect plot will also be obtained from a fractional polynomial model (`mfpi` command in STATA) to show the treatment-covariate interaction in more detail (5, 6). The results from the two methods of analysis should be consistent; however, should the two models not agree this may be an indictor of an erroneous fractional polynomial model and so the results from the subgroup analysis will be used.

The effect of CPAP therapy on cognitive function (simple and four-choice reaction time) will be estimated in drivers and non-drivers. The treatment effects in the two subgroups will be formally tested for equality using an interaction test. Age and gender will also be adjusted for in this analysis.

Sleepiness during driving (whether nodded off whilst driving or pulled off the road due to sleepiness) will be compared at 3 and 12 months between treatment arms by driving habits (frequency of short local journeys and frequency long motorway journeys). Logistic regression models will be used.

Any reported road traffic accidents will be described in detail, with specific reference to the number of hours driving per week/month and the frequency of short local journeys vs motorway journeys > 1 hour.

In all subgroup analyses the minimisation variables will be adjusted for.

8.3 Exploratory analyses

Monthly diaries

A longitudinal analysis of the effect of CPAP therapy compared to BSC over the whole follow-up period will be performed by using the ESS scores from the monthly diaries. A multilevel model for repeated measures will be used with ESS as the response variable and month and baseline ESS as fixed effects with participant-specific and month-specific random intercepts (with the latter nested within the former). The model will make the assumption that all study visits and monthly diaries are completed on the expected dates. An unstructured covariance matrix will be used. From the model a plot of the treatment effect and its 95% CI at each month will be constructed.

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10. APPENDIX

10.1 Short SAQLI scoring manual

The Short Sleep Apnea Quality of Life Index (Short SAQLI) measures the effects of sleep apnea on a person's quality of life. The Short SAQLI has two parts; part I is completed by all subjects, but part II is completed by patients only if their sleep apnea condition has been treated.

Short SAQLI – Part I Scoring (Pre-Treatment)

A. Domains:
The 14 questions represent four quality of life domains.
Domain A – Questions #1,2,3,4 – Daily Activities
Domain B – Questions #5,6,7,8 – Social Interactions
Domain C – Questions #9,10,11 – Emotions
Domain D – Questions #12,13,14 – Symptoms

B. Scoring for Questions # 1 - 14:
Each questions has 7 response options that are scored as follows:

Score		Rating
7	=	not at all / no difficulty
6	=	a small amount
5	=	a small to moderate amount
4	=	a moderate amount
3	=	a moderate to large amount

2 = a large amount
1 = a very large amount

C. Total Score Calculation:
Add the individual scores for each of the 14 questions and divide the total by 14.

Short SAQLI – Part I and Part II Scoring (Post-Treatment)

A. The 14 questions in Section I represent four quality of life domains. The 4 questions in Section II represent treatment related problems.

Section I
Domain A – Questions #1,2,3,4 – Daily Activities
Domain B – Questions #5,6,7,8 – Social Interactions
Domain C – Questions #9,10,11 – Emotions
Domain D – Questions #12,13,14 – Symptoms

Section II
Domain E – Questions #15,16,17,18 – Treatment Related Side Effects

B. Scoring for Questions #1 - 14:
Each question has 7 response options that are scored as follows:

Score		Rating
7	=	not at all / no difficulty
6	=	a small amount
5	=	a small to moderate amount
4	=	a moderate amount
3	=	a moderate to large amount
2	=	a large amount
1	=	a very large amount

C. Scoring for Questions #15 – 17:
Each of these questions has 7 response options that are scored as follows:

Score		Rating
0	=	no problem
1	=	a small problem
2	=	a small to moderate problem
3	=	a moderate problem
4	=	a moderate to large problem
5	=	a large problem
6	=	a very large problem

D. Scoring for Question #18:
This score provides a weighting mechanism to reflect the trade-off between treatment related side effects compared with treatment benefits. It is scored as follows:

Score		Rating
0.25	=	no problem compared to the benefits
0.50	=	a small problem compared to the benefits

0.75 = a small to moderate problem compared to the benefits
1.00 = about equal
1.00 = a moderate to large problem
1.00 = a large problem
1.00 = a very large problem compared to the benefits

E. Total Score – Calculation:
Step 1: Add the individual scores for each of questions #1 - 14.
Step 2: Add the individual scores for each of questions #15 - 17 and multiply this total by the weighting factor (score) for question #18.
Step 3: Subtract the Step 2 (questions #15-18) score from the Step 1 (questions #1-14) score.
Step 4: Divide the Step 3 score by 14.

Effect of Treatment:
Subtract the pre treatment total SAQLI score from the post treatment total SAQLI score.

10.2 Changes from version 1 to version .1.1

- The analysis of the OSLER (secondary outcome) has been simplified to allow an easier and more clinically meaningful interpretation of the results. An analysis using a survival model (as in version 1) is not necessary as censoring is not an issue and so treating OLSER time as a continuous measure is appropriate
- Exploratory treatment interaction analyses with baseline ODI and baseline ESS have been added
- Several exploratory analyses in section 8.3 have been removed

11. SIGNATURES OF APPROVAL

Date: 10/06/2013
Version: 1.1

Signatures

Name	Trial Role	Signature	Date
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Andrew Nunn	Trial Statistician		

Oxford Respiratory Trials Unit

PREDICT

Positive Airway Pressure in Older People: A Randomised Controlled Trial

HEALTH ECONOMIC ANALYSIS PLAN

Version 1

Version	Date	Comments
1	16/11/2011	Final draft

1. INTRODUCTION

This document details the planned health economic analysis for an investigator-blind, randomised controlled trial that compares continuous positive airway pressure plus best supportive care (CPAP) against best supportive care only (BSC) for treatment of obstructive sleep apnoea hypopnoea syndrome (OSAHS) in patients aged 65 and over. Full details of the background to the trial and its design are presented in the trial protocol. The aim of the health economic analysis is to estimate the relative cost-effectiveness of CPAP compared with BSC in this patient population.

In general, cost-effectiveness analyses that include only the results of a single trial can form an incomplete analysis with limited usefulness for decision makers (Sculpher et al 2006). The concerns with such analyses are that they do not use all relevant evidence, that there is often a limited number of comparators and a restricted time horizon (dictated by the follow-up of the trial). Nevertheless, in some cases, a cost-effectiveness analysis based on a single study is appropriate. There may be no previous studies in which CPAP has been compared with BSC in patients with OSAHS who are aged over 65. Therefore it could be argued that there is no additional evidence comparing the efficacy of CPAP with BSC in this patient group. However, previous studies that have assessed the effectiveness of CPAP or other interventions for OSAHS in younger patients may provide additional information for particular cost or health outcomes that are not expected to differ according to patient age. Therefore the health economic analysis may incorporate information from additional data sources outside of the PREDICT trial.

In some studies, the follow-up period of the trial may be adequate to capture the differential costs and benefits of the intervention and comparators. However, in this instance, the time horizon of one year may be insufficient to capture all the costs and benefits associated with the treatment of a condition such as OSAHS with possible long-term sequelae. The PREDICT trial may provide information on surrogate outcomes at 12 months (e.g. the impact of CPAP on cardiovascular function or neurocognitive decline), that could be associated with long-term benefits (e.g. a reduction in cardiovascular events or improved cognitive function). Any impact of a reduction in sleepiness on the incidence of rare events, such as road traffic accidents among patients that drive, may also be difficult to characterise within a trial-based analysis.

For these reasons the primary analysis will extrapolate, using a decision analytic model. This decision analytic model will combine data from the PREDICT trial with information from additional sources where appropriate, in order to estimate mean costs and outcomes over a lifetime time horizon, and to calculate an incremental cost effectiveness ratio (ICER) in terms of incremental cost per quality adjusted life year (QALY) gained.

The analyses described in this document will be performed by a health economist at the Centre for Health Economics, University of York in collaboration with statisticians at the MRC Clinical Trials Unit. The health economist responsible for writing this document in discussion with the co-chief investigators and other principal investigators and conducting the final analyses are:
Susan Griffin, CHE; Mark Sculpher, CHE.

2. DESIGN

2.1 Summary

This study is a two-arm, investigator-blind, parallel group, multi-centre randomised controlled trial. A total of 270 participants will be recruited to the study and followed-up for 12 months. At baseline participants will be randomised to receive CPAP plus BSC (active) or BSC only (control).

The co-primary endpoints will be:

1. Change in Subjective Sleepiness recorded as a mean Epworth Sleepiness Scale (ESS) measured at the end of months 3 and 4, answering the question 'does CPAP work at 3 months?'
2. Change in health related quality of life: Described by the EQ-5D, valued using UK population tariffs. This will be used to estimate the cost per QALY gained by providing CPAP in comparison to Best Supportive Care. The analysis will incorporate health care utilisation, including inpatient and outpatient hospital visits and GP visits during the trial.

3. OUTCOME MEASURES

3.1 Primary health economic outcome measure

Difference between the two treatment arms in cost effectiveness to be estimated within a decision analytic model. This will be used to estimate the cost per QALY gained by providing CPAP in comparison to BSC. Data from the PREDICT trial will be used to inform the parameters in the decision analytic model relating to:

- Health related quality of life, which will be characterised utilising EQ-5D data collected during the trial, valued using UK population tariffs. The analysis will make use of EQ-5D data collected at all time points within the trial in order to estimate quality-adjusted survival using the area under the curve approach.
- Health service costs, which will be characterised in terms of health care utilisation, including inpatient and outpatient hospital visits, GP visits and medication use collected during the trial.
- Treatment costs for CPAP, which will be characterised in terms of the equipment and support supplied to patients in the PREDICT trial, to be informed by clinical opinion.

3.2 Secondary health economic outcome measures

An alternative source of data from the PREDICT trial will be used to inform parameters in the decision analytic model relating to:

- Health related quality of life, which will be characterised utilising SF-36 data collected during the trial to estimate the SF-6D, valued using UK population tariffs.

4. CALCULATION OF PARAMETER VALUES

- The five components of the EQ-5D can be assigned level 1, 2 or 3. The resultant health states described by the EQ-5D will be scored using UK value set estimated in Dolan et al. 1997. If at least one of the components is missing the EQ-5D will also be set to missing.
- A sub-set of 11 items from the SF-36 form the SF-6D. The health states described by the SF-6D will be scored using the UK value set for cost-utility analyses (Model 10) estimated in Brazier et al. 2002. If at least one of the components is missing the SF-6D will also be set to missing.
- Descriptive statistics will be reported for change in EQ-5D and SF-6D scores at 12 months.
- Unit costs for the resource use items recorded on the patient questionnaire will be derived from sources relevant to the UK NHS. GP and hospital visits will be costed according NHS Reference Costs, medication will be costed according to the British National Formulary.
- The cost of CPAP equipment determined by UK price lists for machines, masks and sundries.
- The cost of sleep studies and nurse time required by treatment with CPAP to be determined by expert/clinical opinion.
- Costs will be expressed in current year GBP. The Health Service Cost Index will be used to adjust costs to the current price year where necessary.
- Descriptive statistics will be reported for each resource use item.
- Where multiple sources of information exist that could be used to inform a single parameter value these will be assessed for heterogeneity and, where appropriate, pooled using meta-analytic techniques.

5. DECISION ANALYTIC MODEL

A Markov model describing a series of health states and health events experienced by patients with OSAHS, according to their treatment, will be developed. This model will be used as the basis for extrapolating the costs and health outcomes to a more appropriate time horizon. A similar model was developed for a cost-effectiveness analysis of CPAP for the treatment of younger patients with OSAHS (Weatherly et al. 2009). The uncertainty around the parameter values in the decision analytic model will be fully characterised and propagated through to the model results by conducting probabilistic sensitivity analysis. This is achieved by characterising parameter values using distributions (parametric or empirical based on bootstrapping) rather than point estimates. The decision analytic model is then evaluated multiple times, each time selecting a new random draw from the assigned distributions, producing a distribution of model outputs.

The strategies of CPAP versus no CPAP therapy will be evaluated using standard cost-effectiveness analysis. If one strategy is not found to be dominant (i.e. less costly and more effective) in comparison to the other, then an ICER will be determined. The ICER will be based on the mean costs and mean QALYs estimated within the probabilistic sensitivity analysis of the decision model. Uncertainty around cost-effectiveness will be described using cost-effectiveness acceptability curves which describe the probability that an intervention is cost-effective (Fenwick et al. 2001).

The primary analysis of the decision analytic model will include only those outcomes recorded in the PREDICT trial relating to change in health-related quality of life and health care resource utilisation associated with CPAP relative to BSC. Secondary analyses will incorporate additional health states such as cardiovascular and cerebrovascular events, cognitive function and road traffic accidents. The risk of cardiovascular and cerebrovascular events will be informed by linking the change in cardiovascular risk factors, such as blood pressure, observed within the PREDICT trial to longer term outcomes using existing published risk equations. The risk of road traffic accidents will be informed by linking the change in sleepiness observed within the PREDICT trial to risk of accidents using previously published studies.

A discount rate of 3.5% per annum will be applied to both costs and QALYs in line with NICE guidance.

6. ANALYSIS PRINCIPLES

6.1 Sub groups

The cost-effectiveness of CPAP may differ according to baseline patient characteristics. Sub-groups will be defined according to baseline disease severity or other baseline characteristics that would be known when assigning treatment where these may influence the expected ICER of CPAP relative to BSC. Definition of sub-groups will be informed by clinical opinion, but may include for example, Epworth sleepiness score, ESS (e.g. 13 or less, or above 13) and Townsend disability score, TDS (e.g. 1 or less, or above 1). The decision analytic model will be re-evaluated for all relevant sub-groups.

6.2 Scenario analyses

The use of a decision analytic model can introduce uncertainty around the assumptions used, including the health states described, the selection of data sources and the methods used to combine multiple data sources. These aspects of modelling uncertainty will be explored using scenario analysis. The decision analytic model will be re-evaluated utilising alternative assumptions in order to assess the sensitivity of the ICER to these modelling assumptions.

6.3 Multiple Imputation

- Patterns of missing data will be presented
- Sensitivity to missing data will be assessed by comparing the characteristics of patients with missing items to those with complete data. The assumption that data are "missing completely at random" will be assessed by checking whether complete cases differ systematically from the original sample (Briggs et al. 2003).
- If the assumption of "missing completely at random" is inappropriate regression analysis can be used to adjust for data that are "missing at random". Multiple imputation of missing items will be undertaken in Stata using the "ice" command.
- Where multiple imputation is undertaken, the estimation of parameter values within the decision model will be based on the appropriate pooled statistic from analyses on each of the multiply imputed datasets.

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Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 2001;10:779-89

8. SIGNATURES OF APPROVAL

Date:
Version:

Signatures

Name	Trial Role	Signature	Date
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Mark Sculpher	Health economist		

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Independent data monitoring committee

Chairperson Professor Tim Peto, Professor John Gibson and Professor David Wright.

Trial management

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Jack Quaddy and Assunta Sabia (ORTU).

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Dr Martin Allen, Andrew Bain, Nathalie Bryan and Ann Cooper.

Swindon (Great Western Hospital)
Dr Andrew Stanton, Sam Backway and Sue Meakin.

Taunton (Musgrove Park Hospital)
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Appendix 3 Appendix to the economic chapter

Systematic review of existing cost-effectiveness evidence

Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of CPAP against any comparator in the treatment of OSAS. Full details of the search strategies are reported in *Appendix 4*. The search strategies were based on those conducted by McDaid *et al.*[20] for the HTA report on CPAP devices for the treatment of OSAS. Since the systematic review of existing cost-effectiveness evidence in McDaid *et al.*[20] included studies up to 2006, our searches were run for studies published from January 2006 to April 2012. The economic evaluations included in the systematic review in McDaid *et al.*[20] were also included in the current systematic review.[111,113,118,119]

The systematic review included full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses). Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer. The information is summarised within the text, alongside a detailed critique of the included studies and their relevance to the UK NHS. The findings from the review provide the basis for the development of a new decision model.

Results

Figure 21 presents a flow diagram summarising the identification and selection of studies. A total of 3560 unique records were identified from the systematic literature searches, of which seven subsequently met the inclusion criteria.[20,111,112,114–117] In addition, three additional studies were identified from the previous HTA on the subject.[113,118,119] *Table 48* reports a brief summary of the studies. More detailed data extraction summary tables are presented at the end of this section.

All studies except Gander *et al.*[116] evaluated the cost-effectiveness of CPAP from a health-care or third-party payer perspective. Gander *et al.*[116] estimated the economic burden of OSAS from a societal perspective and, as a secondary analysis, presented an estimate of the ICER for treating OSAS compared with no treatment. Three studies were conducted in the UK,[20,112,118] 3 in the USA,[111,114,117] two in Canada,[115,119] one in New Zealand[116] and one in Spain.[113]

All studies compared CPAP with no treatment, and two also compared CPAP with dental devices.[20,114] Gander *et al.*[116] bundled CPAP together with dental devices and surgery under the treatment intervention. Pietzsch *et al.*[117] evaluated both the diagnostic options and CPAP treatment compared with no treatment. The time horizon employed was 5-years in six studies.[111,113–115,118,119] A lifetime horizon was used in three studies.[20,113,117] Alternative time horizons were used by three studies: 1 year in Gander *et al.*,[116] 10 years in Pietzsch *et al.*[117] and 14 years in Guest *et al.*[112]

In six studies, the patient population consisted of a cohort of middle-age men with moderate to severe OSAS.[20,112,113,117–119] Three studies presented results for a patient cohort with moderate to severe OSAS, which were calculated from averaging the results from six patient subgroups defined by sex and age. In Ayas *et al.*[111] the cohort was aged between 25 and 54 years; in Tan *et al.*[115] the cohort was aged between 30 and 59 years; and in Sadatsafavi *et al.*[114] the cohort was aged between 25 and 64 years. Gander *et al.*[116] included patients aged between 30 and 59 years with any level of OSAS severity. Only McDaid *et al.*[20] and Pietzsch *et al.*[117] conducted subgroup analysis. Subgroup populations were defined by age, sex and disease severity by McDaid *et al.*[20] and by age, sex and disease prevalence by Pietzsch *et al.*[117] Note that no study looked specifically at patients aged 60 years and over.

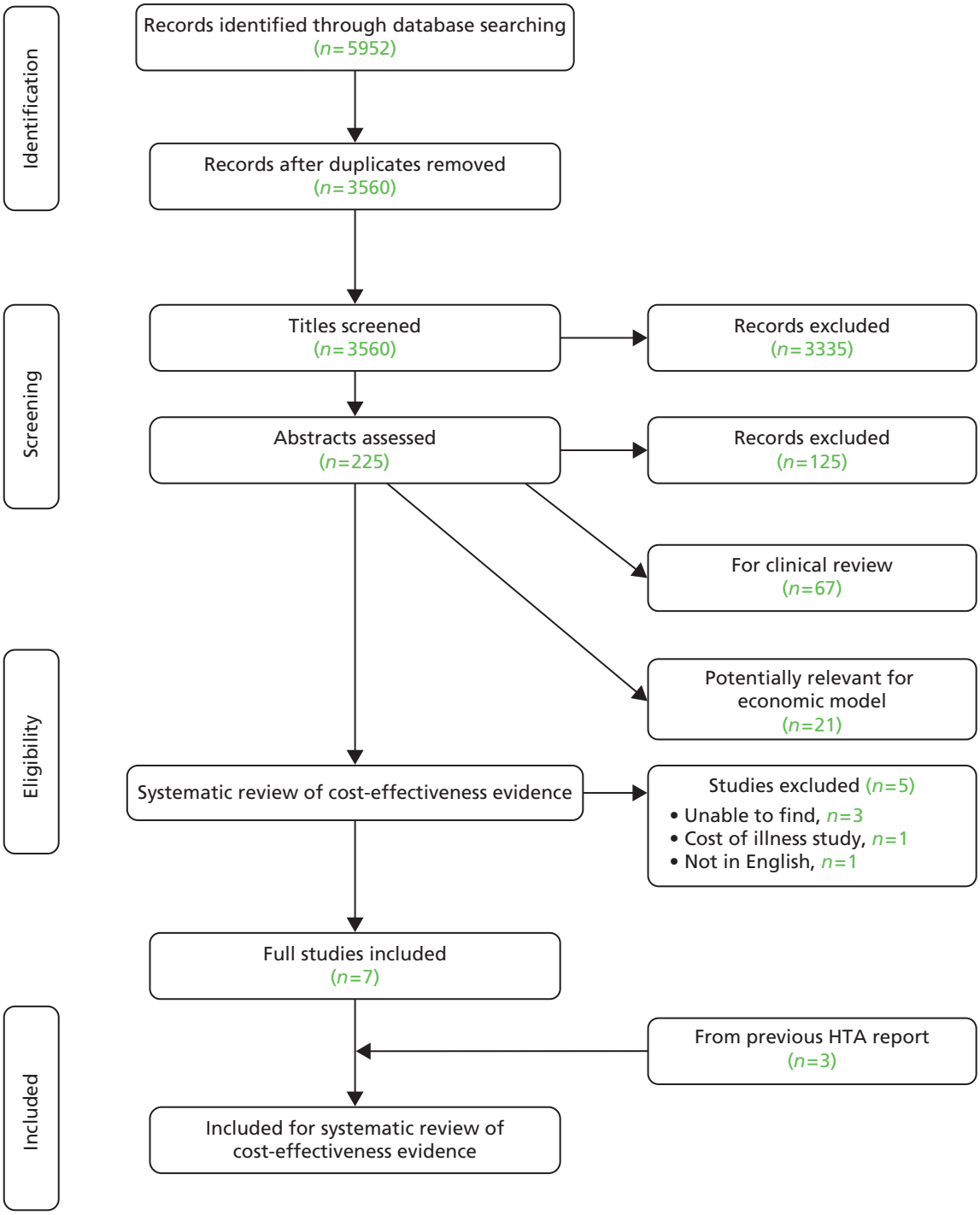

FIGURE 21 Flow diagram showing number of studies identified and included in the review of cost-effectiveness of CPAP.

TABLE 48 Summary of cost-effectiveness studies assessing CPAP included in the systematic review

First author (year)	Perspective	Country	Population	Comparators	Results
Chilcott (2000)[118]	Third-party payer	UK	Middle-age patients referred to sleep clinic	No treatment	ICER = £3200/QALY
Tousignant (2003)[119]	Third-party payer	Canada	Middle-aged patients (average age = 57 years)	No treatment	ICER between CAN$3397/QALY and CAN$9792/QALY; ICER without three outliers = CAN$18,637/QALY
Mar (2003)[113]	Third-party payer	Spain	50-year-old male with moderate to severe OSAS, defined by AHI > 30 events/hour and ESS score of > 10	No treatment	ICER 5-years = €7861/QALY; ICER lifetime = €4938/QALY
Ayas (2006)[111]	Third-party payer and societal	USA	Patients with moderate to severe OSAS (AHI ≥ 15 events/hour), aged between 25 and 54 years, drivers	No treatment	Third-party payer ICER = US$3354/QALY; societal ICER = US$314/QALY
Tan (2008)[115]	Third-party payer and societal	USA	Patients with moderate to severe OSAS, aged between 30 and 59 years, drivers	No treatment	Third-party payer ICER = CAN$3626/QALY; societal ICER = CAN$2979/QALY
Guest (2008)[112]	Third-party payer	UK	55-year-old patient with severe OSAS (AHI > 30 events/hour) and ESS score of ≥ 12	No treatment	CPAP dominates no treatment. Probablilty that CPAP is cost-efficient at £20,000/QALY is 0.99
McDaid (2009)[20]	Third-party payer	England and Wales	50-year-old male	Dental devices and no treatment	ICER = £3899/QALY; Probability cost-efficient at £20,000/QALY = 0.80
Sadatsafavi (2009)[114]	Third-party payer	USA	Patients with moderate to severe OSAS (AHI ≥ 15 events/hour), aged between 25 and 64 years	Dental devices and no treatment	ICER = US$27,540/QALY
Gander (2010)[116]	Societal	New Zealand	Patients between 30 and 59 years	No treatment	ICER = NZ$506.79/QALY
Pietzsch (2011)[117]	Third-party payer	USA	50-year-old male with moderate to severe OSAS	No treatment	ICER = US$16,172/QALY over 10 years and US$15,915/QALY for lifetime

AHI, Apnoea–Hypopnoea Index.

In order to synthesise the available evidence and extrapolate over the chosen time horizon, most studies employed a decision-analytic model. A Markov model was employed in six studies.[20,111–115] Gander *et al.*[116] used a decision tree. Pietzsch *et al.*[117] used a decision tree for the diagnostics pathway and a Markov model for subsequent treatment decisions. McDaid *et al.*[20] used the structure first proposed by Mar *et al.*[113] of a Markov model with four health states [OSAS event-free, post stroke, post CHD and dead] and three events (CHD, stroke and RTAs). Guest *et al.*[112] used a similar model, but including a health state following the RTA event. Tan *et al.*[115] used the same model as Ayas *et al.*,[111] which has an event-free OSAS state and six health states post RTA, corresponding to increasing levels of injury or death. Sadatsafavi *et al.*[114] used the same structure for the RTA component of the model but included post-MI and post-stroke health states. The Markov model in Pietzsch *et al.*[117] had five health states: event-free, hypertension, post MI, post stroke and dead. Patients were at risk of developing clinical hypertension and of experiencing an MI, stroke and RTA. The decision tree in Gander *et al.*[116] modelled the long-term consequences of increased costs owing to diabetes, cardiovascular disease, RTAs and work accidents in the untreated patients. Tousignant *et al.*[119] quality-adjusted the life expectancy of the patients included in the study, estimated based on Canadian lifetables, to calculate the cost-effectiveness of CPAP over a lifetime horizon. Chilcott *et al.*[118] synthesised data obtained from a review of the literature.

In line with the various model structures employed, treatment effectiveness was incorporated across the studies differently. A lower risk of RTAs was considered by eight studies.[20,111–117] Six studies included a reduction in cardiovascular events.[20,112–114,116,117] Gander *et al.*[116] included a reduction in the risk of diabetes and in the risk of work accidents. McDaid *et al.*[20] was the only study which incorporated a reduction in daytime sleepiness, as measured by ESS scores. Most studies based the effectiveness estimates in observational data on patients with moderate to severe OSAS. Seven studies assumed that CPAP reduces the risk of the various events to that of the general population and took the baseline risk of events in the untreated patients from observational studies.[111–117] McDaid *et al.*[20] obtained data on the effectiveness of CPAP in reducing ESS score and BP from a bivariate meta-analysis of RCTs and on the reduction in RTAs from observational evidence.

All studies included the benefits of CPAP in terms of HRQoL. Chilcott[118] converted SF-36 data into health utility weights using the Brazier *et al.*[121] algorithm. Tousignant *et al.*[119] obtained health utility values before and after CPAP treatment directly from patients receiving CPAP with a standard gamble exercise, although the before treatment scores were valued retrospectively. Mar *et al.*[113] administered the EQ-5D instrument to patients before and after CPAP treatment; these values were also used by Guest *et al.*[112] Ayas *et al.*[111] and Tan *et al.*[115] sourced health utility weights from Chakravroty *et al.*,[171] which evaluated HRQoL before and after treatment with a standard gamble exercise. McDaid *et al.*[20] developed a mapping function relating ESS score with EQ-5D and SF-6D, in which a reduction by 1 point in the ESS score was found to correspond to an improvement in health utility of 0.01. Sadatsafavi *et al.*[114] used this relationship in their model. Gander *et al.*[116] assumed a QALY gain of 5.4, based on data from the Sleep Alliance and Tousignant *et al.*,[119] although it is unclear how this estimate was obtained. Pietzsch *et al.*[117] used data from the US Medical Expenditure Panel Survey to estimate that age- and sex-specific HRQoL in terms of EQ-5D was reduced by 16% in untreated OSAS patients and by 7% in OSAS patients treated with CPAP.

Across all studies, the results of the cost-effectiveness analysis led the authors to conclude that CPAP was a cost-effective treatment for patients with OSAS. The ICERs were lower than the typical willingness to pay for an additional QALY used in each of the countries considered, and in Guest *et al.*[112] CPAP was found to be associated with reduced costs and increased health benefits compered with no treatment. In general, the ICERs were robust to alternative assumptions on parameter inputs with the exception of the HRQoL gain from treatment with CPAP. HRQoL gain due to CPAP treatment had the greatest impact on the ICER for all studies that included this parameter in their sensitivity analysis.[20,111,113–115,117]

Data extraction tables

TABLE 49 McDaid *et al.* data extraction table

Study details	McDaid *et al.* (2009)[20]
Economic evaluation type	Cost–utility analysis
Intervention	CPAP
Comparator(s)	Dental devices Conservative management (no treatment)
Outcomes	Primary outcome: incremental cost per QALY gained
Currency (year)	Pounds sterling (2005)
Study design	Markov model
Perspective	Third-party payer (NHS and Personal Social Services)
Setting	England and Wales
Patient population	Base case: 50-year-old male. Base-case results were estimated as the weighted average of the results according to average ESS score (mild – ESS score = 7, moderate – ESS score = 13 or severe – ESS score = 16) Subgroup analyses were conducted by sex, OSAS severity (as measured by ESS) and other relevant baseline characteristics.
Time horizon	Lifetime
Model structure	Four health states: • OSAS • OSAS post CHD • OSAS post stroke • Death Three types of events: • CHD • Stroke • RTA Cycle length: 1 year The model records the ESS score of the patient cohort as time progresses

Treatment effectiveness and sources	CPAP and dental devices:
	• Reduce sleepiness as measured by ESS. ESS score was linked to HRQoL weights via mapping functions
	  ○ Bivariate random-effects meta-analysis pooled on ESS score and systolic BP
	• Reduce BP, which in turn reduces the risk of cardiovascular events (stroke and CHD)
	  ○ No evidence on the relative effect of CPAP versus devices for BP. Same ratio as observed for ESS was applied
	  ○ Framingham risk equations converted BP into risk of cardiovascular events
	• Reduce RTAs
	  ○ Meta-analysis of before-and-after studies on effect of CPAP on RTAs. A systematic review did not identify studies on the effect of dental devices on RTAs

continued

TABLE 49 McDaid *et al.* data extraction table (*continued*)

Study details	McDaid *et al.* (2009)[20]
Resources used and costs and sources	Cost of the interventions included: cost of the devices, staff time, and overheads Cost associated with cardiovascular events Cost of RTA Published sources and manufacturer's submission on auto-CPAP device
HRQoL and sources	Health outcomes expressed in terms of QALYs • For the OSAS (with and without CPAP) health states, HRQoL weights obtained from mapping ESS score to EQ-5D and SF-6D using three sets of individual patient data ○ An increase in 1-point in ESS score is associated with disutility of 0.01 for both SF-6D and EQ-5D • HRQoL decrements associated with stroke, CHD and age were based on Sullivan *et al.*[150] • HRQoL decrement associated with RTA was based on the EQ-5D reported in the Health Outcomes Data Repository, which recorded EQ-5D data for individuals 6 weeks after their inpatient episode for injuries sustained from an RTA
Compliance	Long-term compliance was based on an observational study. Patients discontinuing treatment were assumed to return immediately to the levels of ESS score, BP and utility associated with no treatment
Mortality	All-cause mortality obtained from UK lifetables adjusted for deaths due to stroke and CHD Relative risk of death for patients experiencing stroke were adjusted upwards using factors published in the literature
Adverse events from treatment	None
Subgroup analysis	Subgroup analysis by baseline severity of OSAS as measured by ESS score: • Mild – mean ESS score = 7 • Moderate – mean ESS score = 13 • Severe – mean ESS score = 16 Subgroup analysis by age: • Cohort aged 35 years and 65 years old
Discounting	3.5% for costs and health outcomes
Results	Base case (males aged 50 years): • ICER CPAP vs. dental device = £3899/QALY • ICER dental device vs. no treatment = £2000/QALY • Probability cost-effective for £20,000/QALY for CPAP = 0.80 and for dental device = 0.20 Scenario (females aged 50 years) • ICER CPAP vs. dental device = £4335/QALY • ICER dental devices vs. no treatment = £2432/QALY Probability cost-effective for £20,000/QALY for CPAP = 0.78 and for dental device = 0.21

TABLE 49 McDaid *et al.* data extraction table (*continued*)

Study details	McDaid *et al.* (2009)[20]
Assessment of uncertainty	All results are presented probabilistic Scenario analysis: • Change in ESS score linked to SF-6D rather than EQ-5D • Relative risk reduction for cardiovascular events based on diastolic BP rather than systolic BP • Exclusion of cardiovascular events from model • Exclusion of cardiovascular events and RTAs from model • APAP machine with 5-year life span and humidifier Alternative sources of treatment effects
Conclusions	CPAP is more cost-effective than dental devices and conservative management for patients with OSAS Issues in the generalisability to younger or older populations, particularly because of comorbidities
Key cost-effectiveness drivers	HRQoL benefit associated with the reduction in ESS score as a result of CPAP Rate of RTAs
Uncertainties	• Translation of health benefits in terms of ESS score to HRQoL scores • Effect of CPAP on RTAs • Effect of CPAP on cardiovascular outcomes • Effectiveness and cost-effectiveness of CPAP in patients with mild disease • Comparative effectiveness of dental devices in mild and severe disease populations
Conflicts of interest	None

TABLE 50 Pietzsch *et al.* data extraction table

Study details	Pietzsch *et al.* (2011)[117]
Economic evaluation type	Cost–utility analysis
Intervention	Diagnostics: full-night polysomnography, split-night polysomnography and unattended portable home monitoring Treatment: CPAP
Comparator(s)	No diagnostic technology No treatment
Outcomes	Incremental costs per QALY
Currency (year)	US dollar (2008)
Study design	Decision tree (for diagnostic strategies) and Markov model (for treatment)
Perspective	Third-party payer
Setting	USA
Patient population	Base case: 50-year-old male with a prevalence of moderate to severe OSAS of 50% Sensitivity analyses considered women, alternative ages and alternative levels of OSAS prevalence
Time horizon	10-years and lifetime

continued

TABLE 50 Pietzsch *et al.* data extraction table (*continued*)

Study details	Pietzsch *et al.* (2011)[117]
Model structure	The decision tree splits the cohort into four groups: • True-positive diagnosis • True-negative diagnosis • False positive • False negative The Markov model has five health states: • Well • Hypertension • Post MI • Post stroke • Death Death can occur as a result of: • Motor vehicle accident • MI • Stroke • Other causes Events: • Motor vehicle accident (fatal or non-fatal) • MI (fatal or non-fatal) • Stroke (fatal or non-fatal) Develop clinical hypertension
Treatment effectiveness and sources	Cardiovascular: • Age- and sex-specific baseline incidence rates for MI, stroke and hypertension were estimated by fitting curves to the age- and gender-specific rates reported in large population studies (British Heart Foundation Statistics,[172] Brown *et al.*,[173] Hollander *et al.*,[174] Cutler *et al.*[175]) • CPAP use reduces the risk of MI, stroke and the incidence of hypertension to general population levels RTAs: • The annual probability of RTAs in individuals without OSAS was estimated from 2006 data published by the US Department of Transportation • The effect of untreated OSAS on the incidence rates of RTAs, MI, stroke and hypertension were estimated from the literature[7,24] (Marin *et al.*,[176] Barbe *et al.*,[177] O'Connor *et al.*[178]) CPAP reduces the risk of motor vehicle accidents to general population levels
Resources used and costs and sources	Direct health-care costs only: • Age-specific baseline health-care costs based on average US expenditures (Meara *et al.*[179]) and a one-time cost of end-of-life care (Hogan *et al.*[180]) • Incremental costs associated with the treatment of hypertension, an acute cardiovascular event or life after an acute cardiovascular event were based on Stuart *et al.*,[181] Taylor *et al.*,[182] Kauf *et al.*[183] and Qureshi *et al.*[184] • Health-care costs associated with non-fatal and fatal RTAs were based on a US Department of Transportation study (Blincoe *et al.*[185]) • The costs of diagnostic testing and CPAP treatment were based on national average 2008 Medicare reimbursement rates

TABLE 50 Pietzsch *et al.* data extraction table (*continued*)

Study details	Pietzsch *et al.* (2011)[117]
HRQoL and sources	QALYs HRQoL values were derived from the self-reported health of participants in the Medical Expenditure Panel Survey, as measured by EQ-5D: • An individual age-specific baseline HRQoL was decreased by a factor of 16% for patients who had suffered an MI, 21% for those who had suffered a stroke, and 4% for those suffering from hypertension • Baseline HRQoL was obtained from combining two studies which measured HRQoL in patients with severe[119] and moderate to severe (Chakravorty *et al.*[186]) OSAS patients. Baseline HRQoL was estimated at 16% lower than the average for that age for untreated OSAS and 7% lower for treated OSAS. HRQoL for treated false-positive individuals is 2% lower than average
Mortality	All-cause mortality obtained from US lifetables adjusted for deaths due to stroke and MI
Compliance	Assumption that 10.2% of patients decline therapy, as observed in a study with 353 patients diagnosed with moderate OSAS[7] CPAP compliance stabilises after 4 years at 68%, as observed in a study of long-term CPAP compliance[113]
Adverse events from treatment	None
Subgroup analysis	None
Discounting	3% for costs and benefits
Results	CPAP therapy: • ICER = US$16,172/QALY gained over 10 years and US$15,915/QALY gained over a lifetime • CPAP reduces the 10-year risk of motor vehicle collisions by 52%, the 10-year expected number of MIs by 49% and the 10-year risk of stroke by 31% • Within the range tested, compliance did not affect cost-effectiveness significantly (ICER = US$15,769/QALY for perfect compliance and US$16,112/QALY for double the quit rate and refusal rate) Diagnostics strategies: • The preferred diagnostic strategy is FN-PSG, with an ICER of US$17,131/QALY gained. Results little sensitive to OSAS prevalence and sex
Assessment of uncertainty	Scenarios tested: • Change in baseline risks • Efficacy of therapy • Costs • Utilities ICER was most sensitive to higher CPAP costs and lower HRQoL gain from treatment
Conclusions	CPAP is more cost-effective than dental devices and conservative management for patients with OSAS Issues in the generalisability to patients with mild disease or higher than average baseline risks for cardiovascular events
Key cost-effectiveness drivers	CPAP costs and HRQoL benefits from treatment
Uncertainties	Generalisability of costs across jurisdictions Assumptions around the effectiveness of CPAP
Conflicts of interest	None

TABLE 51 Ayas *et al.* data extraction table

Study details	Ayas *et al.* (2006)[111]
Economic evaluation type	Cost–utility analysis
Intervention	CPAP
Comparator(s)	Conservative management (no treatment)
Outcomes	Primary outcome: incremental cost per QALY
Currency (year)	US dollar (2003)
Study design	Markov model
Perspective	Third-party payer (US) and societal
Setting	USA
Patient population	Base case: • US drivers aged between 25 years and 54 years who were newly diagnosed with moderate to severe OSAS, which was classified as having an AHI ≥ 15 events per hour ○ Weighted average of the results for six patient groups defined by age (25–34 years, 35–44 years, and 45–54 years) and sex
Time horizon	5-year
Model structure	Markov model: • OSAS, with or without CPAP • Injured in RTA with Maximum Abbreviated Injury Scale scores 1 (minimal injury) to 5 (most severely injured) ○ RTA survivors with Maximum Abbreviated Injury Scale score 5 were assumed to be unable to drive afterwards and were at no risk of subsequent RTA • Dead

Treatment effectiveness
And sources
	• CPAP improves HRQoL and reduces the probability of a RTA
	  ○ Random-effects meta-analysis of eight observational studies in which actual RTAs were observed in patients before and after CPAP initiation
	  ○ Assumption: the RTA rate is OSAS patients who receive CPAP is equivalent to that of the general population
	• The annual probability of RTA in individuals without OSAS was determined using RTA data for 2003 from the National Highway Traffic Safety Administration

Resources used and costs and sources	Base case: direct health-care costs • CPAP-related costs and medical visits for initiation and follow-up: Medicare reimbursement rates for 2004 • Lifetime direct health-care costs due to RTAs: based on a technical report from the National Highway Traffic Safety Administration (Blincoe *et al.*[185]) Scenario – societal perspective: • Lifetime non-health-care costs owing to RTAs: insurance, legal and productivity, also based on the technical report by Blincoe *et al.*[185] Productivity losses valued in terms of lost wages, lost benefits and costs incurred from having to hire a person to accomplish the same tasks Assumed that standard CPAP machine has a life expectancy of 5 years

TABLE 51 Ayas *et al.* data extraction table (*continued*)

Study details	Ayas *et al.* (2006)[111]

HRQoL and sources	• Base case: published study by Chakravorty *et al.*[186] in patients with OSAS, before and after CPAP therapy
	  ○ Standard gamble demonstrated an increase in utility from 0.32 to 0.55 (difference = 0.23) before and after CPAP
	• Sensitivity analysis: EQ-5D before and after CPAP reported by Mar *et al.*[113] and by Jenkinson *et al.*[187]
	  ○ Mar *et al.*:[113] 0.738 before and 0.811 after (difference = 0.073)
	  ○ Jenkinson *et al.*:[187] 0.78 before and 0.83 after (diference = 0.05)
	• HRQoL weights for the consequences of RTA were obtained using the Functional Capacity Index as per Graham *et al.*[188]

Compliance	• Assumed 70%, based on McArdle *et al.*:[148] ○ Non-compliant patients incurred rental costs for the device and the cost of a single visit to their doctor over a 3-month period but did not benefit from the device over the period
Mortality	US lifetables
Adverse events from treatment	None included
Subgroup analysis	None
Discounting	3% for costs and health outcomes
Results	Base case (third-party payer): ICER for CPAP was $3354/QALY Societal: ICER for CPAP was $314/QALY
Assessment of uncertainty	Univariate sensitivity analysis: • ICER estimates were robust to the parameters tested • Perspective and HRQoL weights had the greatest influence. ICER increased more than tenfold if third-party payer perspective is used compared with societal. ICER increased more than fivefold if EQ-5D estimates were used rather than standard gamble Probabilistic sensitivity analysis
Conclusions	CPAP is a cost-effective use of health-care resources from both the health-care payer and the societal perspective
Key cost-effectiveness drivers	HRQoL benefit from CPAP therapy
Uncertainties	• CPAP effectiveness: ○ The cost-effectiveness results were sensitive to alternative estimates of HRQoL before and after CPAP • Other benefits from CPAP therapy have not been included, such as those related with reductions in BP and associated reductions in cardiovascular disease
Conflicts of interest	None

AHI, Apnoea–Hypopnoea Index.

TABLE 52 Sadatsafavi *et al.* data extraction table

Study details	Sadatsafavi *et al.* (2009)[114]
Economic evaluation type	Cost–utility analysis
Intervention	CPAP
Comparator(s)	Dental devices Conservative management (no treatment)
Outcomes	Primary outcome: incremental cost per QALY gained
Currency (year)	US dollar (2004)
Study design	Markov model
Perspective	Third-party payer (US)
Setting	USA
Patient population	Base case: patients with moderate to severe OSAS (AHI ≥ 15 events per hour) Results obtained from a weighted average of results stratified by age (25–34, 35–44, 45–54 and 55–64 years) and sex
Time horizon	5 years
Model structure	Four health states: • At risk of cardiovascular events and RTAs • Post MI • Post stroke • Dead Events: MI, stroke and RTA Cycle length: 1 year

Treatment effectiveness and sources	CPAP and dental devices reduce risk of cardiovascular events and RTAs
	
	• Risk reduction assumed proportional to the effect on AHI
	• Assumption tested in the sensitivity analysis
	
	Baseline rate of events
	
	• RTAs:
	
	  ○ Annual probability of RTA calculated using data from the National Highway Traffic Safety Administration for 2005
	  ○ Severity of RTAs was taken from a technical report on the economic impact of RTAs for 2000[185]
	  ○ Increased risk of RTA in untreated patients taken from a meta-analysis of before and after studies on RTAs in OSAS patients before and after CPAP
	
	• Cardiovascular events:
	
	  ○ The incidence of MI and stroke in treated patients assumed equivalent to incidence in patients without OSAS
	  ○ Incidence of MI in patients without OSAS obtained from Framingham risk equations[143]
	  ○ Incidence of stroke in patients without OSAS was based on the age- and sex-specific incidence of stroke in 1996 in the USA[189]
	  ○ The relative risk of events in untreated patients with OSAS was taken from a large observational study[176]
	  ○ Women were assigned lower cardiovascular risks as per Greenberg-Dotan *et al.*[190]

TABLE 52 Sadatsafavi *et al.* data extraction table (*continued*)

Study details	Sadatsafavi *et al.* (2009)[114]

Resources used and costs and sources	Base case: third-party payer perspective:
	• Direct health-care costs only:
	  ○ Costs of treatment: CPAP and OSAS
	  ○ Direct health-care costs as a result of RTA from a technical report by the US Department of Transportation
	  ○ Lifetime cost of RTA is uniformly distributed over the average of 40 years
	• CPAP and dental devices have an expected useful life of 5 years
	• Cost of stroke and MI based on Sarasin *et al.*[191]
	  ○ Cost of stroke includes hospitalisation, inpatient rehabilitation and ongoing treatment for all stroke survivors
	• Cost of MI includes the cost of hospitalisation and annual treatment cost

HRQoL and sources	Health outcomes expressed in terms of QALYs
	• Increase in HRQoL due to CPAP and dental devices
	  ○ An increase in 1-point in ESS score is associated with disutility of 0.01 for both SF-6D and EQ-5D based on McDaid *et al.*[192]
	  ○ Change in ESS score owing to CPAP and dental devices was obtained from a random-effects meta-analysis of RCTs comparing
	• HRQoL decrement due to cardiovascular events
	  ○ Published literature (Pickard *et al.*,[193] Bradley *et al.*,[194] Mahoney *et al.*[195])
	• HRQoL decrement due to RTAs
	  ○ As per Ayas *et al.*[111]

Compliance	Assumed that compliance is equal for dental devices and CPAP. McArdle *et al.*:[148] adherence of 84% at 1 year and 68% at 5 years
Mortality	US lifetables
Adverse events from treatment	None
Subgroup analysis	None
Discounting	3% for costs and health outcomes
Results	• ICER CPAP vs. dental device = US$27,540/QALY • ICER dental device vs. no treatment = US$2940/QALY
Assessment of uncertainty	ICER robust to scenarios considered except: • Zero utility gain from dental devices – ICER (dental device vs. no treatment) increases to US$16,988/QALY • Utility gain from dental device equal to that of CPAP – ICER (CPAP vs. dental device) increases to US$155,539/QALY • Cost-effectiveness depends on compliance
Conclusions	CPAP is more cost-effective than dental devices and conservative management for patients with OSAS
Key cost-effectiveness drivers	Gain in HRQoL associated CPAP and dental devices Effect of CPAP and dental devices on RTAs and cardiovascular events
Uncertainties	HRQoL benefits associated with CPAP and dental devices Compliance to therapy
Conflicts of interest	None

AHI, Apnoea–Hypopnoea Index.

TABLE 53 Tan *et al.* data extraction table

Study details	Tan *et al.* (2008)[115]
Economic evaluation type	Cost–utility analysis
Intervention	CPAP
Comparator(s)	Conservative management (no treatment)
Outcomes	Primary outcome: incremental cost per QALY
Currency (year)	Canadian dollar (2005)
Study design	Markov model
Perspective	Third-party payer (US) and societal
Setting	USA
Patient population	Base case: • British Colombia drivers between 30 years and 59 years of age who were newly diagnosed with moderate to severe OSAS • Results calculated as a weighted average of six patient groups defined by age (30–39, 40–49, and 50–59 years) and sex. Patient characteristics from a sample of patients diagnosed at Vancouver General Centre from 2003–2004 ($n = 132$)
Time horizon	5 year
Model structure	As per Ayas *et al.*[111]
Treatment effectiveness and sources	As per Ayas *et al.*[111] The annual probability of RTA in individuals without OSAS was determined using RTA data for 1997 from the Insurance Corporation of British Colombia. These were assumed to apply to patients treated with CPAP

Resources used and costs and sources	Base case: third-party payer perspective:
	• Direct health-care costs only:
	  ○ Costs of CPAP based on the data obtained from authors' referral centre in Vancouver
	  ○ Initiation and two follow-up visits – costs obtained from 2004 Medical Services Plan Physician Fee Guide by the British Columbia Medical Association
	  ○ Direct health-care costs as a result of RTA from a report on the economic burden of unintentional injuries in Canada (SMARTRISK[196])
	• Scenario – societal perspective:
	• Lifetime societal costs due to RTAs causing injuries and property damage, based on SMARTRISK,[196] Vodden *et al.*[197] and Mercer *et al.*[198]

HRQoL and sources	As per Ayas *et al.*[111]
Compliance	As per Ayas *et al.* [111]
Mortality	Canadian lifetables
Adverse events from treatment	None included
Subgroup analysis	None
Discounting	3% for costs and health outcomes
Results	Base case (third-party payer): ICER for CPAP was CAN$3626/QALY Societal: ICER for CPAP was CAN$2979/QALY

TABLE 53 Tan *et al.* data extraction table (*continued*)

Study details	Tan *et al.* (2008)[115]
Assessment of uncertainty	Univariate sensitivity analysis: • ICER estimates were robust to the parameters tested • HRQoL weights had the greatest influence. ICER increased more than fivefold if EQ-5D estimates were used rather than standard gamble • Probabilistic sensitivity analysis
Conclusions	CPAP is a cost-effective use of health-care resources from both the health-care payer and the societal perspectives
Key cost-effectiveness drivers	HRQoL benefit from CPAP therapy
Uncertainties	• CPAP effectiveness: • The cost-effectiveness results were sensitive to alternative estimates of HRQoL before and after CPAP • Other benefits from CPAP therapy have not been included, such as those related with reductions in BP and associated reductions in cardiovascular disease
Conflicts of interest	None

TABLE 54 Guest *et al.* data extraction table

Study details	Guest *et al.* (2008)[112]
Economic evaluation type	Cost–utility analysis
Intervention	CPAP
Comparator(s)	Conservative management (no treatment)
Outcomes	Expected costs and QALYs with CPAP and no treatment Expected percentage of patients surviving at 14 years Expected percentage of event-free surviving patients at 14 years
Currency (year)	UK pound sterling (2005)
Study design	Markov model
Perspective	Third-party payer (NHS)
Setting	UK
Patient population	55-year-old patient with severe OSAS as defined by an AHI > 30 (events/hour) and daytime sleepiness (ESS score of ≥ 12)
Time horizon	14 years
Model structure	Health states: • Event-free untreated • Event-free treated • Stroke • Cardiovascular event • RTA • Post stroke, cardiovascular event or RTA Cycle length: 1 year Patients post stroke can no longer drive

Treatment effectiveness and sources	• Risk of cardiovascular events
	
	  ○ The cumulative annual risk of fatal and non-fatal cardiovascular and cerebrovascular events in patients with and without CPAP was based on the study by Marin *et al.*[176] and extrapolated from 12 to 14 years using an exponential regression
	  ○ The ratio of developing CHD to stroke in untreated patients was 1 : 1.13 and in treated patients 1 : 1, based on Mar *et al.*[113]
	
	• Risk of RTAs
	
	  ○ The risk of an RTA in treated patients is the same as in the general population, which was based on Department of Transport statistics
	  ○ Department of Transport statistics also provided the distribution of different severities of RTAs
	  ○ The model assumes that the risk of an RTA in untreated patients was 2.6 times greater than in treated patients, based on the average of the relative risks reported in two studies[199,200]

Resources used and costs and sources	Third-party perspective: direct health-care costs only: • Resource use estimated obtained from clinicians • Expected useful life of CPAP device assumed 7 years • Costs of RTAs obtained from Department of Transport statistics • Costs of cardiovascular events assumed equivalent to hospital costs of an episode of MI and home-based cardiac rehabilitation

TABLE 54 Guest *et al.* data extraction table (*continued*)

Study details	Guest *et al.* (2008)[112]
HRQoL and sources.	Health outcomes expressed in terms of QALYs. HRQoL weights were obtained from a Spanish study reporting EQ-5D values before and after CPAP treatment:[113] • 0.738 for untreated, 0.811 for treated • 0.590 for non-fatal stroke in untreated, 0.649 for non-fatal stroke in treated (estimated) • 0.664 for non-fatal cardiovascular event in untreated and 0.730 for treated (estimated) • 0.701 for non-fatal RTA in untreated and 0.771 for non-fatal RTA in treated (estimated)
Compliance	Assumed that 74% of patients are compliant during the first year of treatment, that 3.8% of patients discontinue after second year, and the discontinuation rate declines exponentially over the remaining time horizon
Mortality	Not reported other from cardiovascular event, stroke or RTA
Adverse events from treatment	None
Subgroup analysis	None
Discounting	3.5% for costs and health outcomes

Results	• Expected QALYs:
	
	  ○ Untreated = 7.22
	  ○ Treated = 8.09
	
	• Expected costs
	
	  ○ Untreated = £10,645.02
	  ○ Treated = £9672.25
	
	• CPAP dominates no treatment
	• Probability that CPAP is cost-effective at £20,000/QALY = 0.99

Assessment of uncertainty	Probabilistic sensitivity analysis
	
	Threshold analysis:
	
	• CPAP is no longer dominant if:
	
	  ○ Compliance falls below 60% in the first year of treatment
	  ○ The risk reduction of having a cardiovascular/cerebrovascular event falls to 60% of the base-case value
	  ○ The cardiovascular event : stroke ratio among untreated OSAS patients raises above 1 : 0.9

Conclusions	CPAP is less costly and more effective than conservative management for patients with OSAS after a minimum of 2 years of treatment
Key cost-effectiveness drivers	From the results presented, compliance and cardiovascular benefits from CPAP. However, results for alternative assumptions around the HRQoL gain from CPAP were not presented
Uncertainties	Benefits from CPAP in terms of HRQoL gain, reduction in cardio/cerebrovascular events and reduction in RTAs Compliance over time
Conflicts of interest	The study was sponsored by ResMed (UK) Ltd, manufacturers of a CPAP device

AHI, Apnoea–Hypopnoea Index.

TABLE 55 Gander *et al.* data extraction table

Study details	Gander *et al.* (2010)[116]
Economic evaluation type	Combination of cost of illness, cost–benefit and cost–utility analysis
Intervention	CPAP
Comparator(s)	No treatment
Outcomes	Total costs, costs per category Incremental costs per QALY
Currency (year)	New Zealand dollar (not reported)
Study design	Decision tree
Perspective	Societal
Setting	New Zealand
Patient population	Patients with OSAS aged between 30 and 59 years. Prevalence obtained from the population in the Wellington region was 5.61% (95% CI 2.62% to 8.60%)
Time horizon	1 year
Model structure	Decision tree starting at when patients develop symptoms: • Patients may seek or not seek treatment (20%) • Of those who seek treatment, the GP may consider that action is not necessary or may refer to the hospital screening clinic (50%) • Of those referred to the screening clinic, a proportion will be referred to the sleep clinic (70%) • Of those referred to the sleep clinic, some will be diagnosed as not having OSAS (30%), some will be given conservative therapies (9%), other CPAP or dental appliances (60%) or surgery (1%) • People with OSAS who did not seek treatment were considered at risk of RTAs, other accidents, diabetes and cardiovascular disease

Treatment effectiveness and sources	• Risk of RTAs
	  ○ The incidence of RTAs and other accidents was estimated from 2005 Accident Compensation Corporation claims
	  ○ The odds ratio for RTAs for untreated OSAS was obtained from a pooled meta-analysis of studies comparing RTAs rates for people with and without OSAS (Sassani *et al.*[201])
	  ○ The odds ratio for other accidents for untreated OSAS was obtained from a study reporting the OR for being involved in a work place accident over a 10-year period for men who reported snoring and workplace sleepiness compared with those who did not, adjusted for age, weight, BMI, years of work and workplace exposure (Lindberg *et al.*[202])
	• Diabetes
	  ○ The incidence of diabetes was taken as the average prevalence in the total population (4.1%)
	  ○ The odds ratio for developing diabetes was based on the study by Sassani *et al.*[201]
	• Cardiovascular disease
	  ○ The incidence of cardiovascular disease was taken as the average prevalence in the total population (9.0%)
	  ○ The odds ratio for cardiovascular disease was obtained from Peppard *et al.*[18]

TABLE 55 Gander *et al.* data extraction table (*continued*)

Study details	Gander *et al.* (2010)[116]
Resources used and costs and sources	Costs were categorised as direct health-care, direct non-health care, indirect and intangible costs: • Treated OSAS direct health-care costs included GP consultation, respiratory medicine clinic, sleep clinic diagnosis, appliances and surgery (if required) • Untreated OSAS direct health-care costs included health-care costs from RTA, from other accident, diabetes and cardiovascular disease medication • Treated OSAS direct non-health care: private motor vehicle transport for treatment and diagnosis • Untreated OSAS direct non-health care: RTA and other accidents • Untreated OSAS indirect non-health care: productivity losses, RTA, other accident • Untreated OSAS intangible cost: death from RTA or other accident • Only incremental costs were included
HRQoL and sources	Cost–utility analysis assumes a per case QALY gain of 5.4 (0.10 to 8.00) and that 20% of patients are treated The source of QALY gain is Sleep Alliance and Tousignant *et al.* (1994)
Compliance	Not considered
Mortality	Not considered
Adverse events from treatment	None
Subgroup analysis	None
Discounting	None required (time horizon = 1 year)
Results	• Expected total costs • Untreated = NZ$341.23 per patient • Treated = NZ$730.14 per patient ○ The incremental total cost per case treated was NZ$506.79/QALY gained
Assessment of uncertainty	Monte Carlo simulations to obtain 95% CIs
Conclusions	Treating OSAS is a cost-effective use of resources
Key cost-effectiveness drivers	OSAS prevalence is a key determinant of total costs
Uncertainties	Generalisability of input parameters, mostly referring to a severe population, to the overall OSAS population
Conflicts of interest	None

TABLE 56 Mar *et al.* data extraction table

Study details	Mar *et al.* (2003)[113]
Economic evaluation type	Cost–utility analysis
Intervention	Nasal CPAP
Comparator(s)	No treatment
Outcomes	Incremental costs per QALY
Currency (year)	Euro (2000)
Study design	Markov model
Perspective	Third-party payer
Setting	Spain
Patient population	50-year-old male patient with moderate to severe OSAS, defined by an AHI > 30 (events/hour) and ESS score of > 10
Time horizon	5 years and lifetime
Model structure	Four health states: • OSAS with or without treatment • Post stroke • Post CHD • Death Three events: • Stroke • CHD • RTA Cycle length of 1 year

Treatment effectiveness and sources	Patients with untreated OSAS are at an increased risk of stroke, CHD and RTA. Patients with treated OSAS are at the same risk as the general population
	For the calculation of relative risks for CHD and stroke, authors assumed that patients with AHI > 30 have an increase in diastolic arterial pressure of 3.6 mmHg, based on Young *et al.*[203] and applying the relationship presented by MacMahon *et al.*[204]
	• CHD
	  ○ Relative risk (untreated patients) = 1.185
	• Stroke
	  ○ Relative risk (untreated patients) = 1.353
	  ○ Sources of data for risk of stroke and CHD and relative risk because of OSAS
	  ○ Young *et al.*,[203] Pankow *et al.*[205] and Mar *et al.*[206]
	• RTA
	  ○ Relative risk (untreated patients) = 8.1
	  ○ Based on Teran-Santos *et al.*[5] and Cassel *et al.*[207]

Resources used and costs and sources	Costs included were those of diagnosis and treatment of OSAS and the costs attributable to cardiovascular morbidity

TABLE 56 Mar *et al.* data extraction table (*continued*)

Study details	Mar *et al.* (2003)[113]
HRQoL and sources.	HRQoL with and without treatment: • Before and after (post 3 months) patient survey conducted by authors • HRQoL post stroke and post CHD • Quality-adjustment factors of 0.8 for stroke and 0.9 for CHD, based on 27 factors
Compliance	10% dropout rate from treatment in the first year. This had an impact on costs but not on health outcomes
Mortality	Mortality from events • Based on mortality rates for stroke, CHD, RTAs and all-cause death from the Basque Country
Adverse events from treatment	Not considered
Subgroup analysis	None
Discounting	3% for both costs and effects
Results	• ICER (5 years) = €7861/QALY • ICER (lifetime) = €4938/QALY
Assessment of uncertainty	Univariate sensitivity analysis: • Age, sex, increased risk of stroke in untreated patients, HRQoL benefit, benefit of CPAP on BP, drop-out rate, costs, discount rate, inclusion of polysomnography as a diagnostic • Results were sensitive to HRQoL benefit from treatment
Conclusions	Treatment of OSAS with nasal CPAP is a cost-effective use of resources The key clinical benefit from treatment is the improvement in HRQoL, which is also where the evidence base is strongest
Key cost-effectiveness drivers	HRQoL benefit from treatment
Uncertainties	Generalisability to patients with less severe OSAS, since estimates of effectiveness and HRQoL benefit were obtained from patients with severe OSAS Treatment effectiveness and HRQoL benefit, owing to the observational nature of the data used
Conflicts of interest	None

AHI, Apnoea–Hypopnoea Index.

TABLE 57 Chilcott *et al.* data extraction table

Study details	Chilcott *et al.* (2000)[118] – from McDaid *et al.* (2009)[20]
Economic evaluation type	Cost–utility analysis
Intervention	Nasal CPAP
Comparator(s)	No treatment
Outcomes	Incremental costs per QALY
Currency (year)	UK Pound sterling (not reported)
Study design	Review synthesis. Effectiveness estimates based on results from two before-and-after studies
Perspective	Third-party payer
Setting	UK
Patient population	Patients referred to a sleep clinic. Typically middle-aged
Time horizon	5 years
Model structure	Not applicable
Treatment effectiveness and sources	Three studies[12] using before and after initiation of CPAP
Resources used and costs and sources	Resources related with investigation, diagnostic, treatment and follow-up. Unit costs and resource use reported separately
HRQoL and sources.	Health outcomes expressed in terms of QALYs The gain in HRQoL was 0.12 QALYs (95% CI 0.09 to 0.16 QALYs) over 1 year HRQoL values generated via SF-36 survey using the Brazier *et al.*[121] algorithm. Societal preferences were applied using time trade-off and standard gamble
Compliance	10% dropout rate from treatment in the first year. This had an impact on costs but not on health outcomes
Mortality	–
Adverse events	–
Subgroup analysis	None
Discounting	6% for costs and 1.5% for health benefits
Results	CPAP was estimated to be more costly and more effective than no treatment. The ICER for CPAP at 1 year was £8300/QALY and at year 5 was £3200/QALY Small differences in clinical effectiveness and cost were found when comparing CPAP with dental devices but these were not explicitly quantified
Assessment of uncertainty	Univariate sensitivity analysis for impact of: time horizon, costs of investigation for CPAP, long term costs of maintenance, follow-up and other health-care costs, improved mortality, improved morbidity and discount rate
Conclusions	Treatment with CPAP was found to be as cost-effective as other commonly funded treatments. The results for CPAP over dental devices were likely to be highly uncertain
Key cost-effectiveness drivers	–
Uncertainties	ICER was sensitive to time horizon
Conflicts of interest	–

TABLE 58 Tousignant *et al.* data extraction table

Study details	Tousignant *et al.* (1994)[119]
Economic evaluation type	Cost–utility analysis
Intervention	Nasal CPAP
Comparator(s)	No treatment
Outcomes	Incremental costs per QALY
Currency (year)	Canadian dollars (1989?)
Study design	Cross-sectional study
Perspective	Third-party payer
Setting	UK
Patient population	Patients attending a hospital sleep clinic ($n = 19$, mean age 57 years, SE = 10 years) and who had been receiving CPAP treatment for an average of 9 months
Time horizon	Lifetime
Model structure	Not applicable
Treatment effectiveness and sources	CPAP improves HRQoL. Improvement in HRQoL expressed in utility, measured with standard gamble, and QALYs
Resources used and costs and sources	Third-party perspective: • Cost of supplies, maintenance and rental of CPAP • Costs of overnight sleep study at initiation of treatment
HRQoL and sources.	Health benefits expressed in terms of QALYs HRQoL weights obtained directly from patients via standard gamble The mean utility score for the pre-treatment state was 0.63 (± 0.29) and for the CPAP-treated state was 0.87 (± 0.17)
Compliance	Not considered
Mortality	Patient life expectancy estimated using Canadian lifetables
Adverse events	Not considered
Subgroup analysis	None
Discounting	5% costs and health benefits
Results	High estimate: ICER = CAN$279/QALY Low estimate: ICER = CAN$3523/QALY Analysis without three outliers: ICER +CAN$18,637/QALY
Assessment of uncertainty	Scenario analysis: alternative estimate of CPAP costs and excluding three outliers with high treatment effects
Conclusions	CPAP is likely to be a cost-effective intervention in the Canadian context
Key cost-effectiveness drivers	Not considered
Uncertainties	Costs of CPAP; impact of outliers in the estimate of the improvement in HRQoL
Conflicts of interest	None

Strategy to handle missing data

The strategy to handle missing data for the within-trial cost-effectiveness analysis followed three stages as proposed by Faria *et al.*:[208] (1) descriptive analysis of the missing data to inform the assumption on the missing data mechanism, (2) choice of strategy to handle missing data in accordance with the assumption made for the missing data mechanism and (3) sensitivity analysis.

Descriptive analysis of the missing data

Amount of missing data by trial group at each follow-up period

The percentage of patients with missing data on costs or health utility values was 62.2% ($n = 173$); that is only 37.8% ($n = 105$) of patients have complete data on costs or health utility values. The percentage of patients who answered the EQ-5D questionnaire at each month varied between 100% (CPAP group at baseline) and 65.71% (CPAP group at months 10 and 11). The percentage of returned questionnaires on resource use is similar across treatment groups and varied between 100% and 66%.

Missing data patterns

Figures 22–24 show the missing data pattern for EQ-5D, SF-6D and costs at each month. The pattern of missing data is non-monotonic; that is patients with missing data on one month may have complete data on a subsequent month. The pattern of missing data is different across the different months. Given that costs and QALYs are cumulative quantities, missing data at one time point has an impact in the quantities estimated for the entire trial duration.

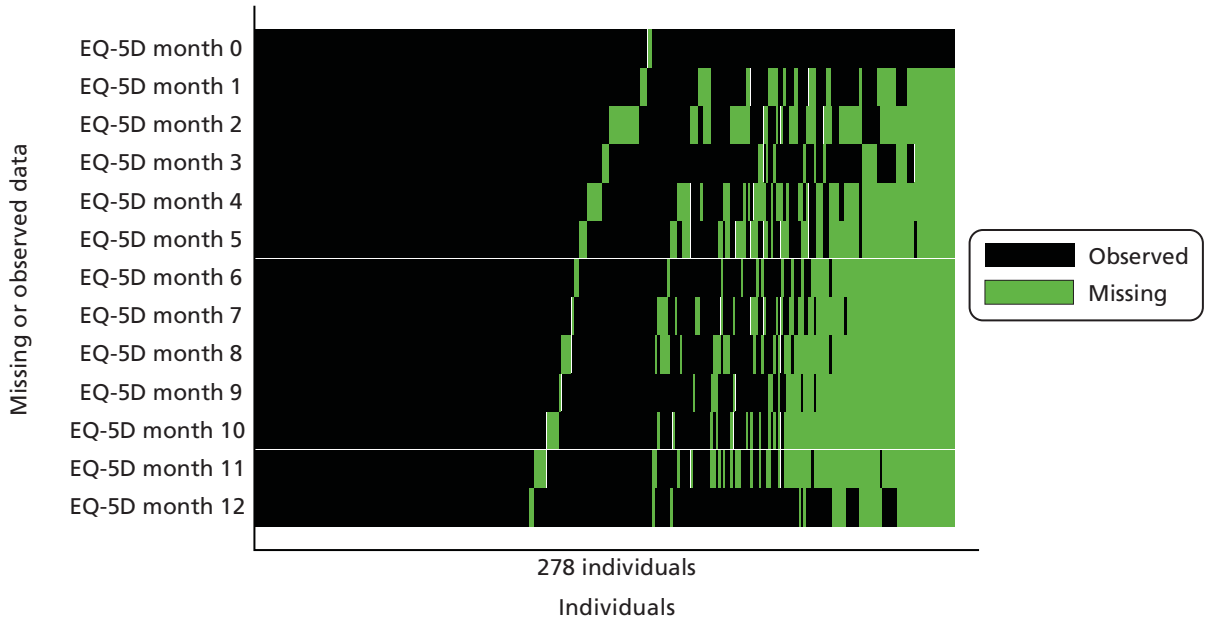

FIGURE 22 Missing EQ-5D data.

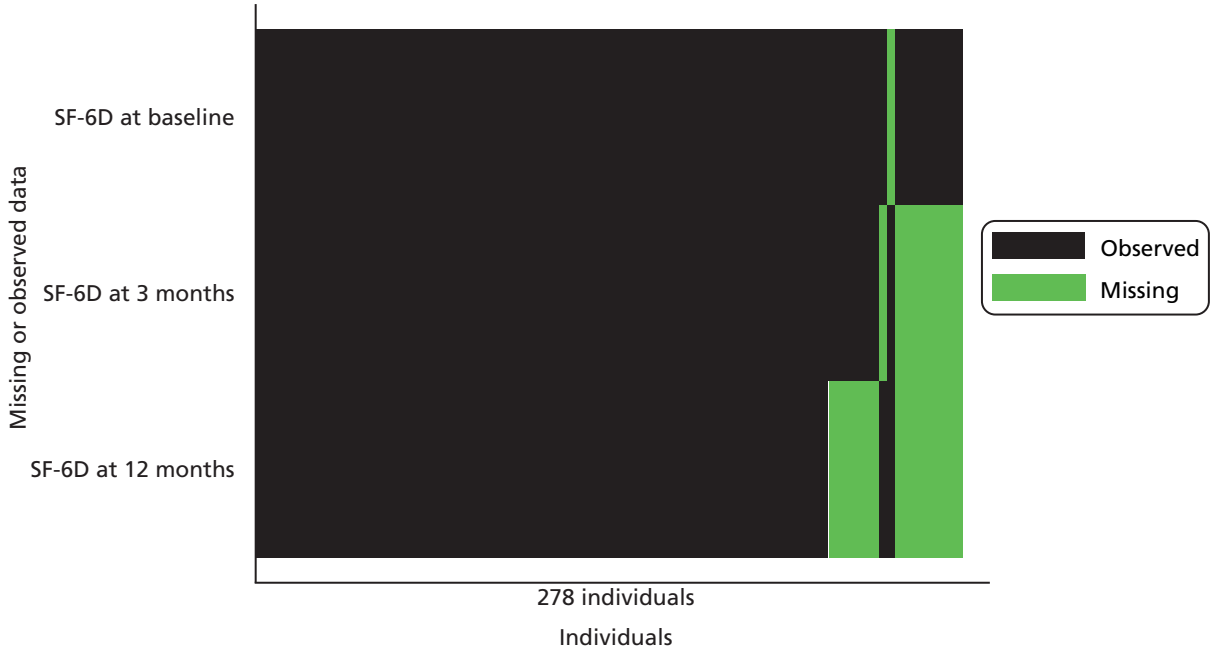

FIGURE 23 Missing SF-6D data before.

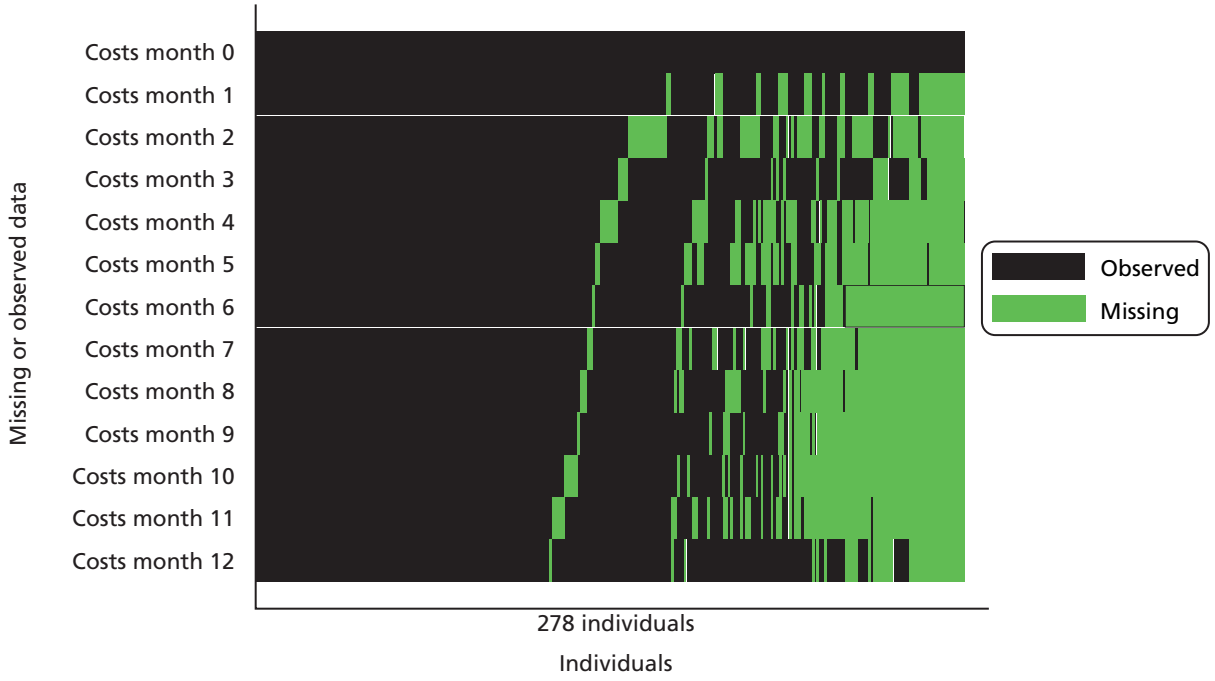

FIGURE 24 Missing data on costs.

Association between missingness and baseline variables

Association between missingness and baseline variables

Logistic regressions were conducted to establish whether or not baseline variables were predictors of missingness at 1%, 5% and 10% of statistical significance. The statistically significant baseline variables for missing costs were HbA_{1c} ($p < 0.01$), heart rate ($p < 0.05$), SF-6D ($p < 0.1$), total cholesterol ($p < 0.1$) and triglycerides ($p < 0.1$). The statistically significant baseline variables for missing EQ-5D values were HbA_{1c} ($p < 0.01$), health rate ($p < 0.05$), sex ($p < 0.05$) and ESS score ($p < 0.1$).

Association between missingness and observed outcomes

Logistic regressions were conducted to establish whether or not missing costs or health utility values at month 3 (which were collected in a clinic visit rather than by postal questionnaire) were predictors of missingness in subsequent months. Costs and health utility values at month 3 were statistically significant predictors of subsequent missingness of costs at month 4 ($p < 0.1$), month 8 ($p < 0.05$) and month 11 ($p < 0.05$) and predictors of missingness of EQ-5D at month 4 ($p < 0.1$), month 8 ($p < 0.1$) and month 11 ($p < 0.1$).

These analyses suggest that some baseline variables and some observed costs and EQ-5D values may be predictors of missingness of unobserved costs and health utility values. Therefore, data are unlikely to be missing completely at random. The base-case assumption is that data are missing at random and depend on baseline variables as well as observed costs and EQ-5D values. Given that it is impossible to know whether or not data are missing not at random from the observed data, sensitivity analysis tests the impact of departures from the missing at random assumption.

Choice of method to handle missing data

There are two broad types of methods that fit with the assumption that data are missing at random: multiple imputation and likelihood-based methods. Multiple imputation with chained equations was chosen because it is straightforward to implement and can deal with the non-normal distributions of costs and health utility values.

A number of imputation models were tested and their performance assessed by comparing the distribution of imputed with observed values. The model that produced the most similar distribution used linear regression to impute missing health utilities and log-transformed costs at each month over 63 imputations with predictive mean matching. The explanatory variables were the observed log-transformed costs and health utilities at each month, cardiovascular variables at baseline (angina, hypertension, previous heart attack, diabetes, atrial fibrillation, health rate), prognostic factors at baseline (smoking status, age, sex, blood glucose, HbA_{1c}, total cholesterol, triglycerides) and ESS score at each month.

Figures 25 and *26* compare the distribution of QALYs and total costs before (_mj = 0) and in the imputed data sets (_mj = 1 to 10). Only the first 10 multiple-imputed data sets are shown here. The distribution of QALYs and total costs is similar between the original and multiple-imputed data sets.

Table 59 compares the average costs per patient for each month between the original and multiple-imputed data sets. The average costs are similar between the data sets.

Table 60 compares the average EQ-5D and SF-6D per patient for each follow-up questionnaire between the original and multiple-imputed data sets. The point estimates and SDs are similar between original and imputed data sets.

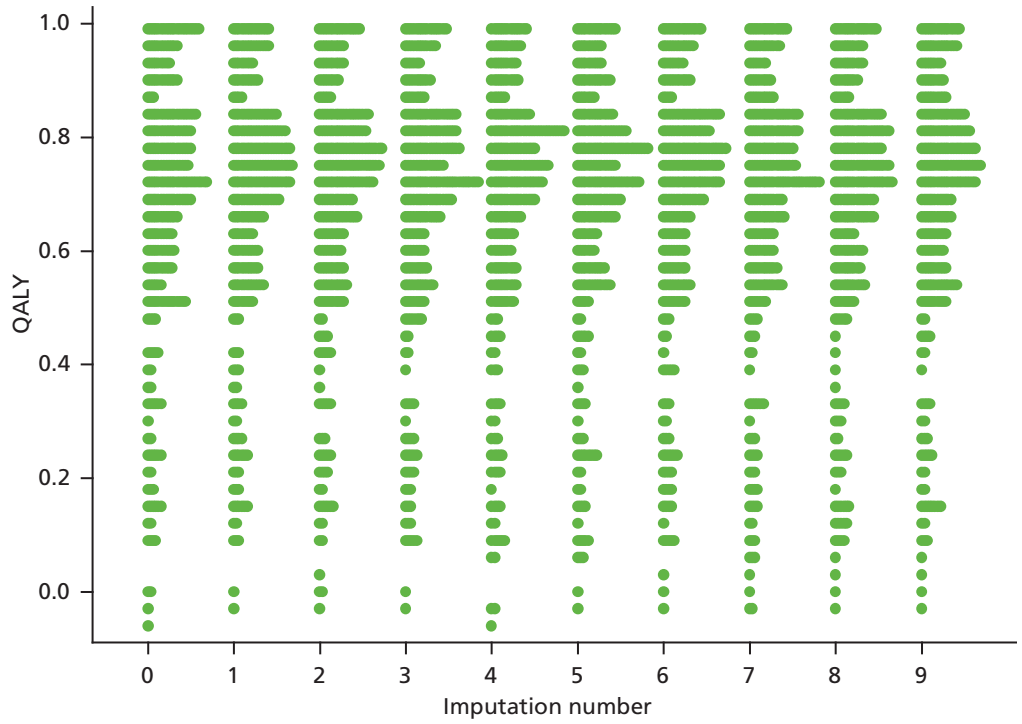

FIGURE 25 Distribution of QALYs post imputation.

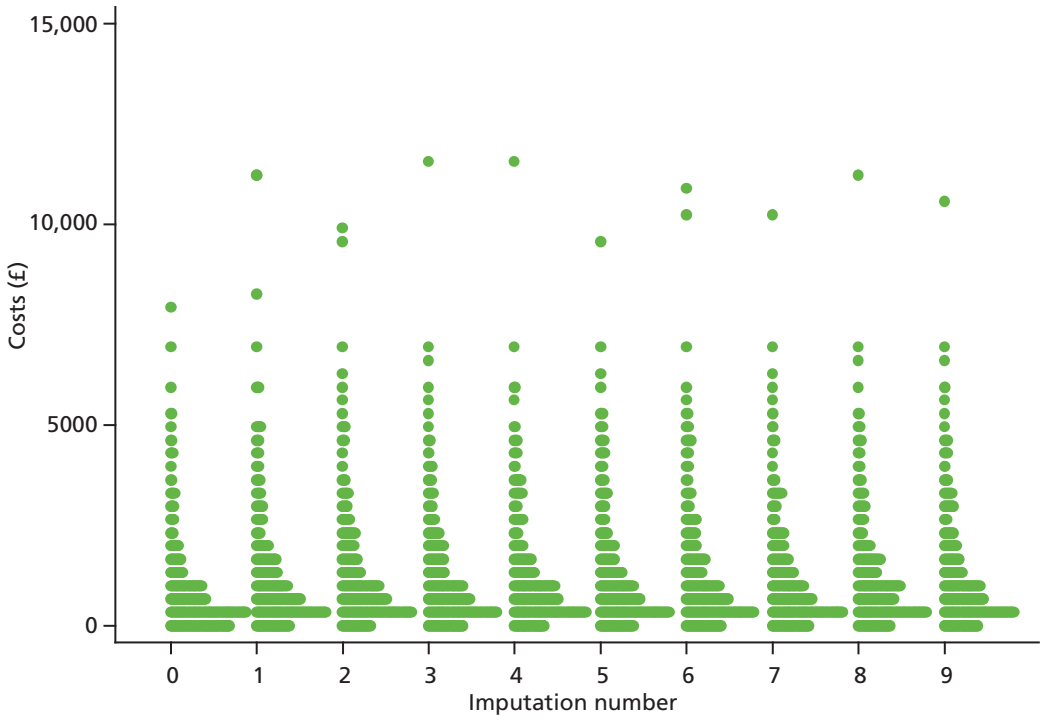

FIGURE 26 Distribution of total costs post imputation.

TABLE 59 Average costs per patient

	CPAP with BSC				BSC alone			
	Original		Imputed		Original		Imputed	
Time period	Mean (£)	SD (£)	Mean (£)	SD (£)	Mean (£)	SD (£)	Mean (£)	SD (£)
Month 1	79	159	84	166	116	218	125	231
Month 2	94	323	100	319	88	157	107	234
Month 3	90	223	97	239	111	253	120	269
Month 4	66	153	80	213	130	423	134	393
Month 5	71	135	74	150	95	216	100	213
Month 6	85	168	94	190	97	217	105	223
Month 7	82	159	90	173	84	187	88	188
Month 8	71	170	84	212	117	292	122	296
Month 9	82	137	95	169	96	182	101	188
Month 10	94	223	107	273	118	401	118	375
Month 11	80	143	93	175	109	221	115	226
Month 12	156	545	165	571	150	498	153	506
Total	1050		1163		1311		1389	

TABLE 60 Average EQ-5D and SF-6D per patient

	CPAP with BSC				BSC alone			
Item	Original		Imputed		Original		Imputed	
EQ-5D	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
Month 1	0.684	0.280	0.688	0.270	0.687	0.246	0.676	0.255
Month 2	0.700	0.292	0.699	0.289	0.685	0.258	0.680	0.257
Month 3	0.672	0.301	0.667	0.300	0.704	0.251	0.699	0.255
Month 4	0.692	0.284	0.691	0.279	0.679	0.259	0.677	0.257
Month 5	0.671	0.328	0.674	0.314	0.660	0.267	0.659	0.270
Month 6	0.677	0.295	0.662	0.295	0.663	0.255	0.644	0.272
Month 7	0.687	0.276	0.698	0.266	0.652	0.271	0.638	0.272
Month 8	0.668	0.311	0.655	0.300	0.683	0.268	0.660	0.284
Month 9	0.682	0.287	0.693	0.274	0.650	0.275	0.647	0.277
Month 10	0.647	0.318	0.660	0.295	0.694	0.254	0.672	0.273
Month 11	0.656	0.310	0.673	0.293	0.647	0.286	0.639	0.299
Month 12	0.689	0.301	0.693	0.291	0.680	0.264	0.684	0.260
SF-6D								
Month 3	0.681	0.087	0.679	0.087	0.661	0.088	0.662	0.087
Month 12	0.679	0.111	0.681	0.107	0.653	0.113	0.654	0.115

Sensitivity analysis to departures from missing at random assumption

Sensitivity analysis was conducted to the missing at random assumption (see next section for more details) by analysing the data as (1) complete-case analysis (assuming missing completely at random), (2) imputing data with mean interpolation and (3) assuming that individuals with missing data have 25% greater costs or 25% lower health utility values than what is predicted by the multiple imputation procedure (assuming missing not at random). The results are presented in the next section.

Detailed results for the sensitivity analysis

Scenario 1: frequent replacement of continuous positive airway pressure device and consumables

The base case makes a number of assumptions on the lifetime of the devices and the frequency that consumables, such as filters and masks, need replacing. However, there is some uncertainty around these parameters. The device or the consumables may need replacing earlier, which will drive up the costs. Therefore, the sensitivity analysis explores the impact of a worst-case scenario for costs, in which the lifetime of the CPAP device and humidifier is assumed to be 3 years, the masks are replaced every 3 months and the filters replaced monthly. This assumption corresponds to the maximum yearly CPAP supplies reimbursed by Medicare, a large US health insurer.[136] *Table 61* presents the costs of CPAP treatment for the worst-case scenario. The costs of CPAP treatment increased from £201.14 in the base-case scenario to £608.94 in the worst-case scenario, mostly as a result of the increased number of masks.

Table 62 presents the cost-effectiveness results for scenario 1. Increasing the costs of CPAP from £201.14 to £608.94 per patient reverses the difference in costs from –£35 (95% CI –£390 to £321) to £373 (95% CI £17 to £729). The ICER is £74,600 per EQ-5D QALY and £20,722 per SF-6D QALY.

Figure 27 presents the cost-effectiveness acceptability curve for the scenario 1. The probability that the CPAP is cost-effective is considerably lower than in the base-case analysis; it reduced from 0.61 to 0.25 for the base case with EQ-5D QALYs and from 0.96 to 0.46 for the base case with SF-6D QALYs. These results suggest that the greater costs associated with the CPAP treatment itself may deem the intervention not cost-effective.

TABLE 61 Costs of CPAP treatment for scenario 1

Item	Cost element	Number	Average cost per patient (£)
A	Annual equivalent cost of CPAP device	–	153.48
B	Annual equivalent cost of humidifier	–	58.89
C	Number (and proportion) of patients who received a humidifier	82 (59%)	–
D	Average annual equivalent cost of humidifier per patient (= B × C)	–	34.50
E	Average annual equivalent cost per patient (= A + D)	–	197.98
F	Average cost of masks	–	104
G	Average cost of masks assuming (patients received four masks) (= 4 × F)	–	414
H	Average cost per filter	–	0.58
I	Average cost of filters per patient per year (12 filters per year) (= 12 × H)	–	6.96
	Average cost of CPAP treatment per patient (= E + G + I)	–	608.94

TABLE 62 Cost-effectiveness results for scenario 1

	Costs		EQ-5D QALYs		SF-6D QALYs	
Intervention	Average	SE	Average	SE	Average	SE
CPAP with BSC	£1771	£123	0.680	0.021	0.678	0.007
BSC alone	£1389	£139	0.666	0.020	0.658	0.008
Incremental costs and QALYs						
CPAP with BSC – BSC alone	£373	£180	0.005	0.020	0.018	0.008

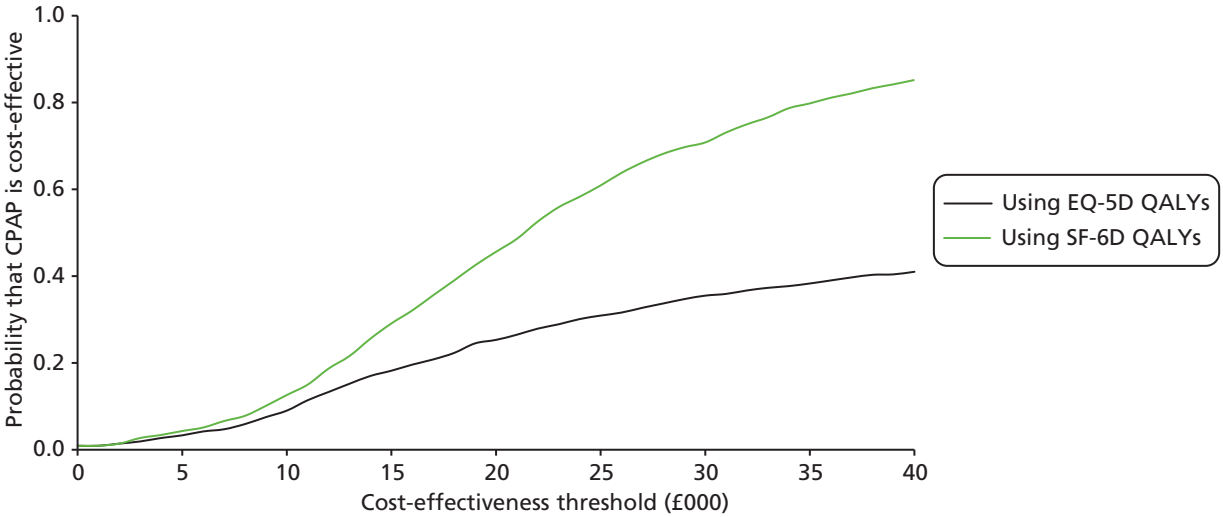

FIGURE 27 Cost-effectiveness acceptability curve for scenario 1.

Scenario 2: continuous positive airway pressure is used for 1 year

The base case assumes that the CPAP and humidifier devices have a lifetime of 7 years and can be reused across patients. Scenario 2 assumes that the CPAP and humidifier devices are used for 1 year only. Therefore, their costs are not annuitised and all the costs of CPAP treatment are incurred in the 1 year. *Table 63* shows the costs of CPAP treatment for this scenario. The cost of CPAP treatment increased from £201.14 in the base case to £710.16 in scenario 2.

Table 64 presents a summary of the cost-effectiveness results for scenario 2 (see *Appendix 3* for detailed results). As with scenario 1, the difference in costs between treatment groups is reduced because of the increase in the costs of CPAP to £474 (95% CI £119 to £830). The ICER is £94,800 per EQ-5D QALYs and £26,333 per SF-6D QALY gained.

Figure 28 presents the cost-effectiveness acceptability curve for the scenario 2, 1-year time horizon. The probability that the intervention is cost-effective is 0.20 for the base case (EQ-5D QALYs) and 0.30 for the scenario with SF-6D QALYs.

TABLE 63 Costs of CPAP treatment for scenario 2

Item	Cost element	Number	Average cost per patient (£)
A	Cost of CPAP device	–	430
B	Cost of humidifier	–	165
C	Number (and proportion) of patients who received a humidifier	82 (59%)	–
D	Average cost of humidifier per patient (= B × C)	–	96.64
E	Average cost per patient (= A + D)	–	595
F	Average cost of masks	–	104
G	Average cost of masks assuming (10% received 2 masks) (= 1.1 × H)	–	114
H	Average cost per filter	–	0.58
I	Average cost of filters per patient per year (2 filters per year) (= 2 × H)	–	1.16
	Average cost of CPAP treatment per patient (= E + G + I)	–	710.16

TABLE 64 Cost-effectiveness results for scenario 2

	Costs (£)		EQ-5D QALYs		SF-6D QALYs	
Intervention	Average	SE	Average	SE	Average	SE
CPAP with BSC	1873	124	0.680	0.021	0.678	0.007
BSC alone	1389	139	0.666	0.020	0.658	0.008
Incremental costs and QALYs						
CPAP with BSC – BSC alone	474	180	0.005	0.020	0.018	0.008

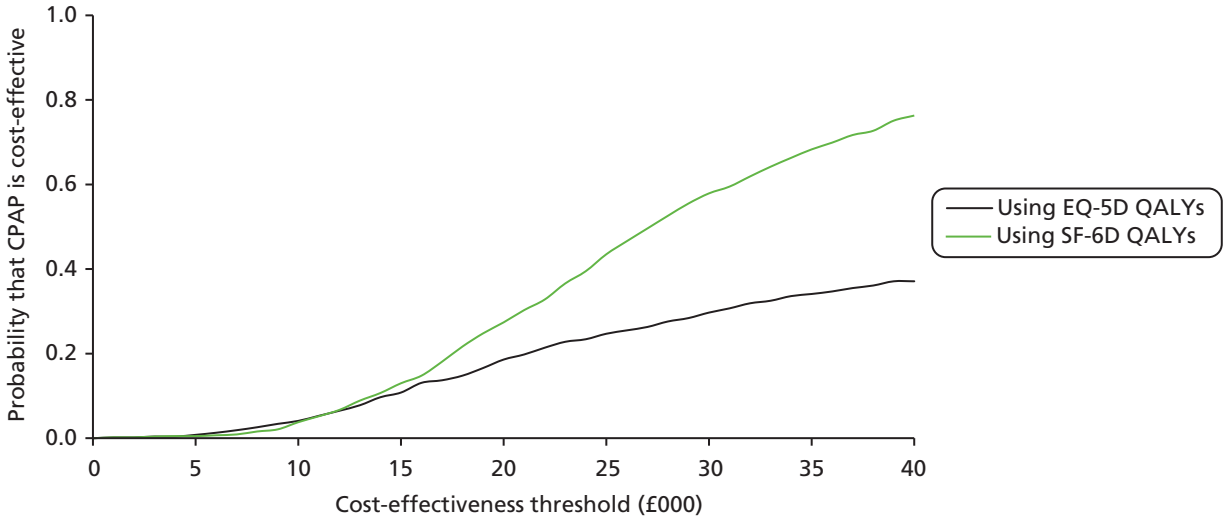

FIGURE 28 Cost-effectiveness acceptability curve for scenario 2.

Scenario 3: complete-case analysis

This scenario uses only the data from patients who completed all questionnaires on HRQoL and resource use (for costs). This assumes that data are missing completely at random, that is that the probability that data are missing is independent of both the observed and unobserved data. Therefore, the patients who completed all questionnaires are assumed to be representative of all patients. Complete-case analysis will result in biased estimates of the effect of the intervention on costs and QALYs if data are not missing completely at random. In addition, the estimates will be inefficient because not all data are used, as patients who returned some of the questionnaires are removed from the analysis. The complete-case sample for the scenario with EQ-5D QALYs consists of 59 patients (43%) allocated to BSC alone and 48 (34%) allocated to CPAP with BSC. The complete-case sample for the scenario with SF-6D QALYs consists of 61 patients (44%) allocated to BSC alone and 52 patients (37%) allocated to CPAP with BSC.

Table 65 presents the cost-effectiveness results for the complete-case scenario. The cost-effectiveness results are broadly similar to the base case. CPAP appears to be cost-saving but the difference is not statistically significant (complete-case scenario with EQ-5D QALYs, 95% CI –£769 to £252; SF-6D QALYs, 95% CI –£690 to £288). The group allocated to CPAP experienced more QALYs but the difference is not statistically significant (complete-case scenario with EQ-5D QALYs, 95% CI –0.048 to 0.067; SF-6D QALYs, –0.010 to 0.040). As a result, CPAP with BSC dominates BSC alone.

Figure 29 shows the cost-effectiveness acceptability curve for the complete-case scenario. CPAP appears highly likely to be cost-effective over a range of cost-effectiveness thresholds. The probability that the intervention is cost-effective at a threshold of £20,000 per QALY gained is 0.75 for the scenario with EQ-5D QALYs and 0.91 for the scenario with SF-6D QALYs.

TABLE 65 Cost-effectiveness results for scenario 3 complete-case analysis

	Costs (£)		QALYs	
Intervention	Average	SD	Average	SD
Complete case for EQ-5D				
CPAP with BSC	1146	1170	0.686	0.278
BSC alone	1382	1499	0.698	0.233
Incremental costs and QALYs				
CPAP with BSC – BSC alone	–258	258	0.010	0.029
Complete case for SF-6D				
CPAP with BSC	1169	1151	0.673	0.097
BSC alone	1354	1481	0.670	0.093
Incremental costs and QALYs				
CPAP with BSC – BSC alone	–201.04	247	0.015	0.013

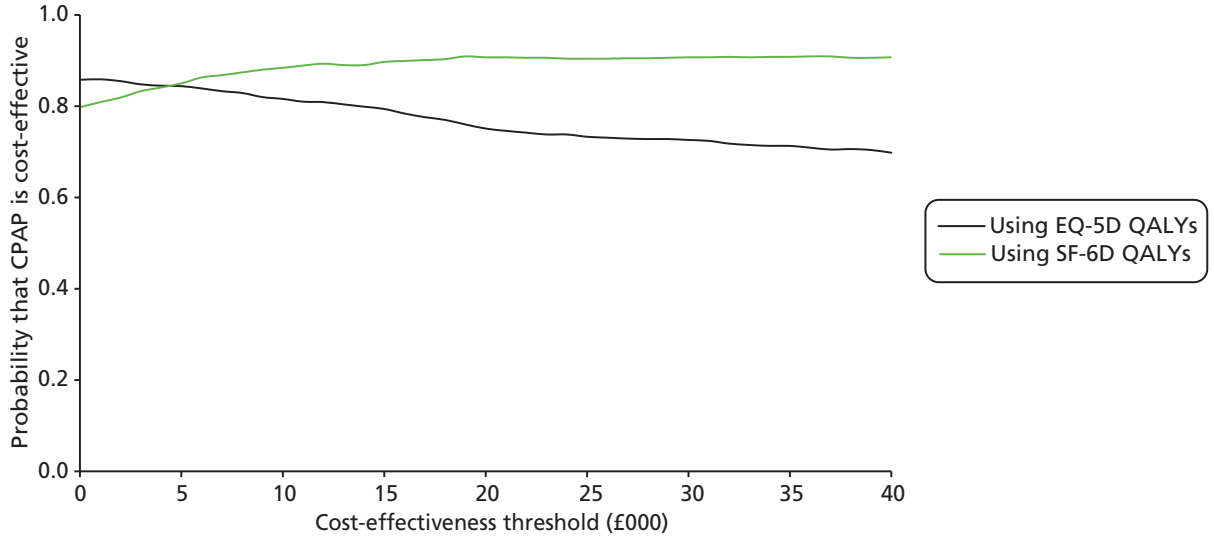

FIGURE 29 Cost-effectiveness acceptability curve for complete-case scenario.

Scenario 4: missing data imputed with interpolation

In this scenario, missing data on HRQoL and on costs are imputed with mean interpolation, that is missing data are imputed with the average observed data for each patient. This assumes that the probability that data are missing depends on the observed data but not on the unobserved values (missing at random assumption). This method has two major limitations that support its use only as a sensitivity analysis: first, it artificially reduces uncertainty by treating unobserved values as observed data, and second, it assumes the observed costs and HRQoL are representative of the unobserved data without taking into consideration other covariates, such as age or comorbidities. In addition, this method requires additional assumptions if only the baseline data were observed for some patients. Last value carried forward was conducted when no other data were observed in addition to baseline.

Table 66 shows the cost-effectiveness results for scenario 3. The results are generally similar to the base case. CPAP is associated with a small increase in costs but the difference is not statistically significant. The 95% CI is similar to that obtained for the base case (base case, 95% CI –£390 to £321; scenario 4, 95% CI –£353 to £440). In terms of QALYs, CPAP appears to increase QALYs by a small amount for both the EQ-5D and the SF-6D valuations; this difference is statistically significant for SF-6D QALYs (95% CI 0.001 to 0.028) but not for EQ-5D QALYs (95% CI –0.029 to 0.041). As a result, CPAP is associated with an ICER of £7167 per EQ-5D QALY gained and £3071 per SF-6D QALY gained.

Figure 30 presents the cost-effectiveness acceptability curve for scenario 4. The probability that the intervention is cost-effective at £20,000 per QALY gained is 0.55 for the base case with EQ-5D QALYs and 0.81 for the scenario with SF-6D QALYs.

TABLE 66 Cost-effectiveness results for scenario 4

	Costs (£)		EQ-5D QALYs		SF-6D QALYs	
Intervention	Average	SD	Average	SD	Average	SD
CPAP with BSC	1421	1806	0.678	0.253	0.675	0.081
BSC alone	1366	1697	0.662	0.229	0.659	0.087
Incremental costs and QALYs						
CPAP with BSC – BSC alone	43	201	0.006	0.018	0.014	0.007

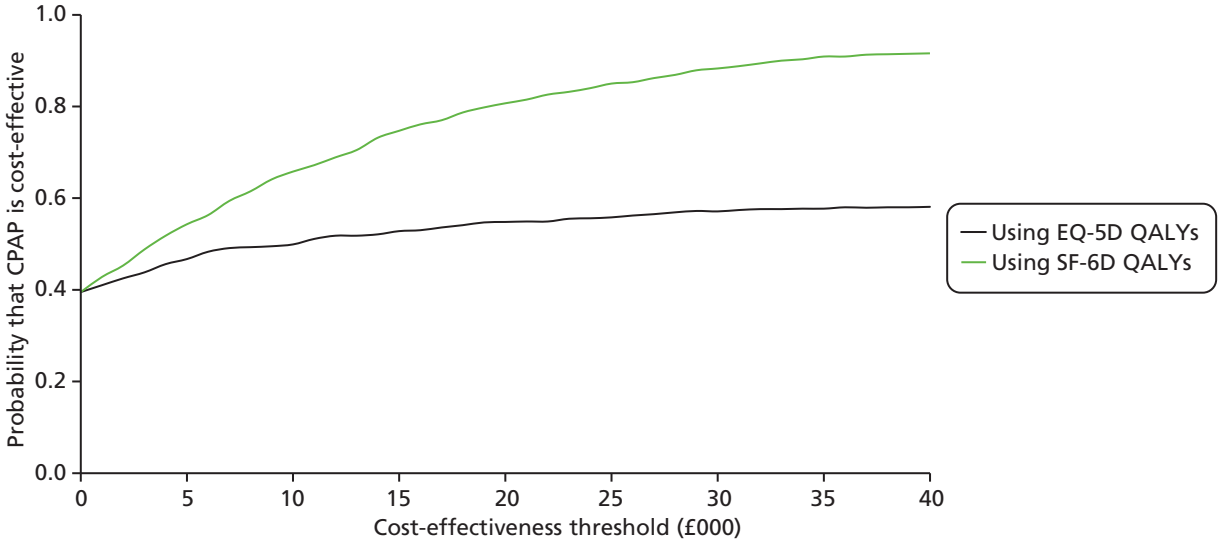

FIGURE 30 Cost-effectiveness acceptability curve for scenario 4.

Scenario 5: testing the missing at random assumption

This scenario explores the robustness of the results to the assumption underpinning multiple imputation that the data are missing at random. The multiple-imputation procedure predicts the unobserved data from the data which were observed, assuming that the observed are representative of the unobserved data conditional on covariates. However, the costs or the HRQoL of individuals with missing data may systematically differ from that of individuals without missing data. For example, individuals lost to follow-up may have experienced fewer health benefits than those who remained in the study. It is impossible to know for certain whether or not the costs and QALYs individuals with missing data are similar to those of individuals with complete data. However, sensitivity analysis can explore the impact on the cost-effectiveness results of assuming that individuals with missing data have greater costs or lower HRQoL than that predicted by the multiple-imputation model.

Table 67 shows the results for scenario 5. The results are consistent with those of the base case. Increasing the predicted costs of the individuals with missing data by 25% results in a similar difference in costs between treatment groups as in the base case [–£26 (95% CI –£422 to £369) vs. base case –£35 (95% CI –£390 to £321)]. Therefore, CPAP dominates. Reducing the predicted HRQoL of the individuals with missing data by 25% changes the direction of effect for EQ-5D QALYs [–0.006 (95% CI –0.044 to 0.031 QALYs)] but not for SF-6D QALYs [0.012 (95% CI –0.006 to 0.030 QALYs)]. Nonetheless, these differences, as in the base case, are not statistically significant. The ICER for the EQ-5D analysis is £5833 per QALY gained. CPAP dominates BSC in the analysis with SF-6D QALYs.

Figure 31 shows the cost-effectiveness acceptability curves for scenario 5. In the scenario in which costs are increased, the probability that CPAP is cost-effective at £20,000 per QALY gained is 0.62 for the analysis with EQ-5D QALYs and 0.96 for the analysis with SF-6D QALYs. This is similar to the base case at 0.61 for EQ-5D QALYs and 0.96 for SF-6D QALYs. In the scenario in which HRQoL is decreased, the probability that CPAP is cost-effective at £20,000 per QALY gained is 0.42 for the analysis with EQ-5D QALYs and 0.85 for the analysis with SF-6D QALYs.

TABLE 67 Cost-effectiveness results for scenario 5

	Costs (£)		EQ-5D QALYs		SF-6D QALYs	
Assumption	Average	SE	Average	SE	Average	SE
Patients with missing data have 25% greater costs						
CPAP with BSC	1462	140	0.680	0.021	0.678	0.007
BSC alone	1479	150	0.666	0.020	0.658	0.008
Incremental costs and QALYs						
CPAP with BSC – BSC alone	–27	201	0.005	0.020	0.018	0.008
Patients with missing data have 25% less HRQoL						
CPAP with BSC	1462	140	0.636	0.021	0.655	0.008
BSC alone	1479	150	0.633	0.019	0.642	0.008
Incremental costs and QALYs						
CPAP with BSC – BSC alone	–35	180	–0.006	0.019	0.012	0.009

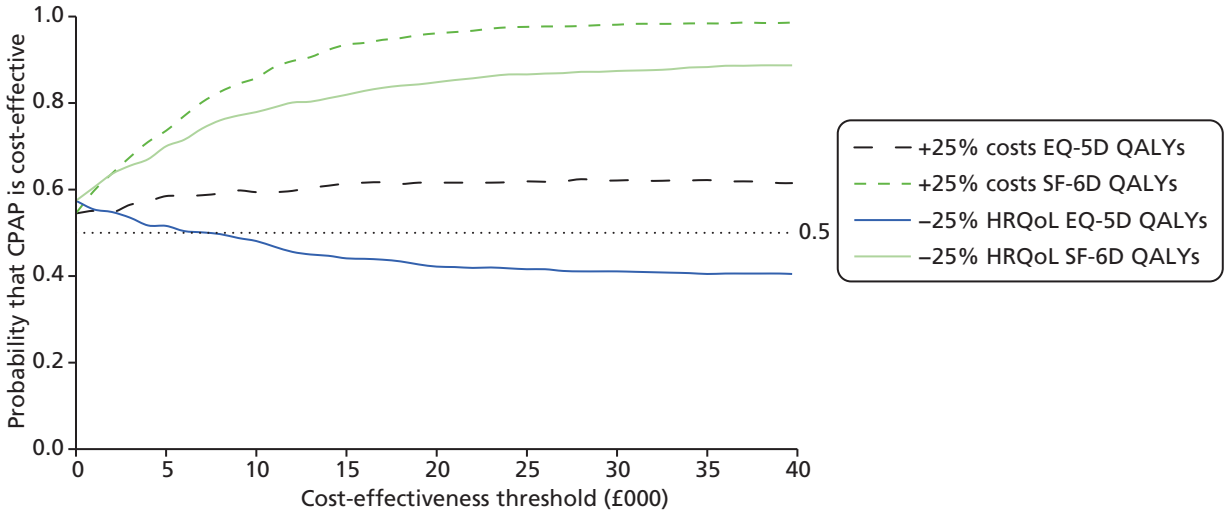

FIGURE 31 Cost-effectiveness acceptability curves for scenario 5.

Appendix 4 Search strategies

Searches for systematic reviews and guidelines

Cochrane Database of Systematic Reviews

Searched 28 March 2012.

URL: http://onlinelibrary.wiley.com

Search strategy

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

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

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

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

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

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

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

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

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

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

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

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

Database of Abstracts of Reviews of Effects

Searched 28 March 2012.

URL: http://onlinelibrary.wiley.com

Search strategy

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

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

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

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

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

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

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

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

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

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

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

Of 448 total results in Cochrane Library, 12 were from DARE.

Health Technology Assessment Database

Searched 28 March 2012.

URL: http://onlinelibrary.wiley.com

Search strategy

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

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

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

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

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

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

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

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

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

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

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

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

Scottish Intercollegiate Guidelines
Searched 28 March 2012.

URL: www.sign.ac.uk

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

National Guideline Clearinghouse
Searched 28 March 2012.

URL: www.guideline.gov/search/advanced-search.aspx

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

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

There were 67 results online which needed to be screened manually, as they could not be downloaded.

Health Services/Technology Assessment Text
Searched 28 March 2012.

URL: www.ncbi.nlm.nih.gov/books/advanced

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

Results screened and details of one 2011 AHRQ guideline added to Endnote library.

Turning Research into Practice Database
Searched 28 March 2012.

URL: www.tripdatabase.com

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

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

Clinical Evidence
Searched 28 March 2012.

URL: http://clinicalevidence.bmj.com

There were 12 post 2006 guidelines on sleep apnea identified. These could not be downloaded; therefore, a list with links was copied to word document 'Guidelines from Clinical Evidence search.docx'.

Searches for trials

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Searched 19 March 2012 via Ovid.

Search strategy

1. exp Sleep Apnea Syndromes/ (19,930)
2. (apnea or apnoea).ti,ab. (25,874)
3. (hypopnea or hypopnoea).ti,ab. (4789)
4. (hypoapnea or hypoapnoea).ti,ab. (36)
5. sleep disordered breathing.ti,ab. (2989)
6. (sleep adj2 respirat$ disorder$).ti,ab. (201)
7. sahs.ti,ab. (338)
8. shs.ti,ab. (971)
9. osa.ti,ab. (4692)
10. osas.ti,ab. (2314)
11. osahs.ti,ab. (651)
12. or/1-11 (32,846)
13. exp positive-pressure respiration/ (18,367)
14. (positive adj3 airway adj3 pressure).ti,ab. (5712)
15. (cpap or ncpap or apap or bipap).ti,ab. (5975)
16. (c pap or bi pap or nc pap).ti,ab. (50)
17. autocpap.ti,ab. (19)
18. or/13-17 (21,531)
19. 12 and 18 (5267)
20. limit 19 to yr="2006 - 2012" (2333)
21. randomized controlled trial.pt. (322,037)
22. controlled clinical trial.pt. (83,702)
23. randomized.ab. (237,867)
24. placebo.ab. (133,799)
25. drug therapy.fs. (1,509,972)
26. randomly.ab. (174,912)
27. trial.ab. (245,654)
28. groups.ab. (1,145,620)
29. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (2,887,984)
30. 20 and 29 (680)
31. limit 30 to english language (620)

EMBASE <1996 to 2012 Week 11>

Searched 19 March 2012 via Ovid.

Search strategy

1. Sleep Apnea Syndrome/ (23,594)
2. (apnea or apnoea).ti,ab. (24,479)
3. (hypopnea or hypopnoea).ti,ab. (5727)
4. (hypoapnea or hypoapnoea).ti,ab. (42)
5. Sleep Disordered Breathing/ (2654)
6. sleep disordered breathing.ti,ab. (3732)
7. (sleep adj2 respirat$ disorder$).ti,ab. (176)
8. sahs.ti,ab. (355)

9. shs.ti,ab. (1025)
10. osa.ti,ab. (6190)
11. osas.ti,ab. (2811)
12. osahs.ti,ab. (783)
13. or/1–12 (33,560)
14. positive end expiratory pressure/ (19,580)
15. (positive adj3 airway adj3 pressure).ti,ab. (5606)
16. (cpap or ncpap or apap or bipap).ti,ab. (6559)
17. (c pap or bi pap or nc pap).ti,ab. (56)
18. autocpap.ti,ab. (34)
19. or/14–18 (21,932)
20. 13 and 19 (7358)
21. controlled study/ (3,116,507)
22. exp clinical trial/ (719,714)
23. outcomes research/ (65,036)
24. randomized controlled trial/ (250,869)
25. (randomized or randomised or placebo or randomly).ab. (483,327)
26. trial.ti. (89,510)
27. or/21–26 (3,706,892)
28. 20 and 27 (2494)
29. limit 28 to (english language and yr="2006 – 2012") (1381).

Cochrane Central Register of Controlled Trials

Searched 28 March 2012.

URL: http://onlinelibrary.wiley.com

Search strategy

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

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

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

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

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

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

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

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

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

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

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

Of 448 total results in Cochrane Library, 395 were from CENTRAL.

Cumulative Index to Nursing and Allied Health Literature 1981 to present

Searched 19 March 2012 via EBSCO*host*.

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

S12. (S9 or S10 or S11) (4355)

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

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

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

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

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

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

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

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

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

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

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

In total there were 614 results.

Science Citation Index

1900 to 21 March 2012.

Searched 22 March 2012 via Web of Science.

Lemmatization off, 2006–12.

#14. #12 and #13

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

#12. #6 and #11

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

#10. TS = autocpap

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

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

#7. TS = (positive same airway same pressure)

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

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

#4. TS = "sleep disordered breathing"

#3. TS = (hypoapnea or hypoapnoea)

#2. TS = (hypopnea or hypopnoea)

#1. TS = (apnea or apnoea)

In total there were 1228 results.

Conference Proceedings Citation Index – Science

1990 to 21 March 2012.

Searched 22 March 2012 via Web of Science.

Lemmatization off, 2006–12.

#12. #6 and #11

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

#10. TS = autocpap

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

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

#7. TS = (positive same airway same pressure)

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

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

#4. TS = "sleep disordered breathing"

#3. TS = (hypoapnea or hypoapnoea)

#2. TS = (hypopnea or hypopnoea)

#1. TS = (apnea or apnoea)

388 results.

Zetoc Conferences

1993 to 22 March 2012.

Searched 22 March 2012.

URL: www.theses.com/default.asp

Search strategy

conference: autocpap

conference: bi pap

conference: c pap

conference: nc pap

conference: bipap

conference: apap

conference: ncpap

conference: cpap

conference: positive airway pressure

Search results from 2006 onwards were downloaded for each search – a total of 103 results were retrieved.

Index to THESES

1716 to 22 March 2012.

Searched 22 March 2012.

URL: www.theses.com/default.asp

Search strategy

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

In total, 22 total results were retrieved – there was no facility to save search, search by year restriction or view records without inputting search string each time, and no download facility. Results reviewed, and seven 2006-onwards results were printed off as hard copies and sent to Rita.

Cost-effectiveness searches

Economic evaluations of sleep apnoea and continuous positive airway pressure

NHS Economic Evaluation Database
Searched 28 March 2012.

URL: http://onlinelibrary.wiley.com

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

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

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

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

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

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

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

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

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

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

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

Of 448 total results in Cochrane Library, 14 were from NHSEED.

EconLit
1961 to February 2012.

Searched 23 March 2012 via Ovid.

Search strategy

1. (apnea or apnoea).ti,ab.
2. (hypopnea or hypopnoea).ti,ab.
3. (hypoapnea or hypoapnoea).ti,ab.
4. sleep disordered breathing.ti,ab.
5. (sleep adj2 respirat$ disorder$).ti,ab.
6. sahs.ti,ab.
7. shs.ti,ab.
8. osa.ti,ab.
9. osas.ti,ab.
10. osahs.ti,ab.
11. or/1–10

12. (positive adj3 airway adj3 pressure).ti,ab.
13. (cpap or ncpap or apap or bipap).ti,ab.
14. (c pap or bi pap or nc pap).ti,ab.
15. autocpap.ti,ab.
16. or/12–15
17. 11 and 16
18. limit 17 to yr="2006 – 2012"

Nil results found.

Economic evaluations of sleep apnoea (any intervention)

EconPapers
Searched 28 March 2012.

URL: http://econpapers.repec.org/

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

Limited to working papers.

Seven results were scanned – none was relevant.

NHS Economic Evaluation Database
Searched 30 March 2012.

URL: http://onlinelibrary.wiley.com

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

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

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

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

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

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

Of 1073 total results in Cochrane Library, 25 were from NHSEED.

Health Technology Assessment Database

Searched 30 March 2012.

URL: http://onlinelibrary.wiley.com

Search strategy

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

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

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

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

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

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

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

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1946 to present.

Searched 30 March 2012 via Ovid.

Search strategy

1. exp Sleep Apnea Syndromes/ (19,973)
2. (apnea or apnoea).ti,ab. (25,964)
3. (hypopnea or hypopnoea).ti,ab. (4820)
4. (hypoapnea or hypoapnoea).ti,ab. (36)
5. sleep disordered breathing.ti,ab. (3003)
6. (sleep adj2 respirat$ disorder$).ti,ab. (201)
7. sahs.ti,ab. (340)
8. shs.ti,ab. (977)
9. osa.ti,ab. (4726)
10. osas.ti,ab. (2328)
11. osahs.ti,ab. (655)
12. or/1-11 (32,955)
13. economics/ (26,193)
14. exp "costs and cost analysis"/ (162,116)
15. economics, dental/ (1836)
16. exp "economics, hospital"/ (17,730)
17. economics, medical/ (8429)
18. economics, nursing/ (3855)
19. economics, pharmaceutical/ (2307)
20. (econom$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab. (380,943)
21. (value adj1 money).ti,ab. (20)
22. budget$.ti,ab. (16,542)
23. or/13-22 (494,267)
24. ((energy or oxygen) adj cost).ti,ab. (2543)
25. (metabolic adj cost).ti,ab. (671)

26. ((energy or oxygen) adj expenditure).ti,ab. (14,406)
27. or/24-26 (16,967)
28. 23 not 27 (490,330)
29. letter.pt. (752,630)
30. editorial.pt. (302,459)
31. historical-article.pt. (280,726)
32. or/29-31 (1,322,522)
33. 28 not 32 (464,959)
34. animals/ (4,889,109)
35. human/ (12,139,643)
36. 34 not (34 and 35) (3,594,930)
37. 33 not 36 (439,079)
38. 12 and 37 (811)
39. limit 38 to (english language and yr="2006 – 2012") (319)

EMBASE

1996 to 2012 Week 12.

Searched 30 March 2012 via Ovid.

Search strategy

1. Sleep Apnea Syndrome/ (24,439)
2. (apnea or apnoea).ti,ab. (25,475)
3. (hypopnea or hypopnoea).ti,ab. (5996)
4. (hypoapnea or hypoapnoea).ti,ab. (43)
5. Sleep Disordered Breathing/ (2644)
6. sleep disordered breathing.ti,ab. (3906)
7. (sleep adj2 respirat$ disorder$).ti,ab. (187)
8. sahs.ti,ab. (365)
9. shs.ti,ab. (1067)
10. osa.ti,ab. (6367)
11. osas.ti,ab. (2902)
12. osahs.ti,ab. (820)
13. or/1-12 (34,818)
14. health-economics/ (13,562)
15. exp economic-evaluation/ (147,865)
16. exp health-care-cost/ (143,430)
17. 14 or 15 or 16 (253206)
18. (econom$ or cost or costs or costly or costing or pharmacoeconomic$).ti,ab. (356,198)
19. (value adj2 money).ti,ab. (872)
20. budget$.ti,ab. (13,757)
21. 18 or 19 or 20 (364,417)
22. 17 or 21 (487,556)
23. letter.pt. (477,438)
24. editorial.pt. (310,953)
25. note.pt. (397,942)
26. 23 or 24 or 25 (1,186,333)
27. 22 not 26 (434,638)
28. (metabolic adj cost).ti,ab. (510)
29. ((energy or oxygen) adj cost).ti,ab. (1653)
30. ((energy or oxygen) adj expenditure).ti,ab. (12,628)
31. 28 or 29 or 30 (14,363)

32. 27 not 31 (431,837)
33. exp animal/ (680,271)
34. exp animal-experiment/ (773,680)
35. nonhuman/ (2,423,637)
36. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (2,170,304)
37. 33 or 34 or 35 or 36 (3,344,387)
38. exp human/ (7,831,966)
39. exp human-experiment/ (168,040)
40. 38 or 39 (7,832,215)
41. 37 not (37 and 40) (2,390,216)
42. 32 not 41 (397,819)
43. 13 and 42 (1267)
44. limit 43 to (english language and yr="2006 - 2012") (700)

TABLE 68 Total search results

Source	Results	After de-duplication	Custom 4 field
CDSR	20	0	–
DARE	12	1	DARE 28/03/12
HTA	7	6	HTA 28/03/12
SIGN	0	–	–
National Guidelines Clearinghouse	67	Not downloadable	–
HSTAT	1	1	HSTAT 28/03/12
TRIP	3	0	–
Clinical Evidence	12	Not downloadable	–
MEDLINE	620	609	MEDLINE and MEDLINE In-Process 09/03/12
EMBASE	1381	896	EMBASE 19/03/12
CENTRAL	395	107	CENTRAL 28/03/12
CINAHL	614	376	CINAHL 19/03/12
Science Citation Index	1228	595	Science Citation Index 22/03/12
Conference Proceedings Citation Index	388	271	Conference Proceedings Citation Index 22/03/12
Zetoc conferences	103	65	Zetoc conference abstracts 22/03/12
Index to THESES	7	Not downloadable	–
NHSEED (sleep apnoea AND cpap)	14	1	NHSEED CPAP 28/03/12
EconLit	0	–	–
EconPapers	0	–	–
NHSEED (all sleep apnoea)	25	6	NHSEED ALL SLEEP APNEA 30/03/12
HTA (all sleep apnoea)	36	30	HTA ALL SLEEP APNEA 30/03/12
MEDLINE (sleep apnoea cost studies)	319	242	MEDLINE and MEDLINE In-Process ALL SLEEP APNEA costs 30/03/12
EMBASE (sleep apnoea cost studies)	700	354	EMBASE ALL SLEEP APNEA costs 30/03/12
Totals	–	3560	–

CDSR, Cochrane Database of Systematic Reviews; CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects; HSTAT, Health Services/Technology Assessment Text; NHSEED, NHS Economic Evaluation Database; TRIP, Turning Research Into Practice.

Appendix 5 Systematic review on the clinical effectiveness of continuous positive airway pressure

Methods

A systematic review on the clinical effectiveness of CPAP was conducted to identify RCTs comparing CPAP with sham CPAP, BSC/usual care and dental devices in a patient population with an average age of 60 years or over with OSAS and capacity to give informed consent. Therefore, studies in patients with dementia were excluded. The literature searches updated the searches conducted for the McDaid *et al.*[20] report on CPAP and dental devices but focused on the period from January 2006 to March 2012. The studies identified in this review were checked for their relevance for our systematic review.

Results

The updated searches found 4872 titles, which were added to the library with the results of the cost-effectiveness searches and de-duplicated. In total, the searches identified 3560 unique titles. Of these, 67 studies appeared to be potentially relevant for the systematic review on clinical effectiveness. *Figure 32* presents the flow diagram of identification and selection of studies. The searches retrieved six potentially relevant reviews on the use of CPAP.[20,209–212] The studies included in these reviews were examined. Only one study met our inclusion criteria;[88] however, since it was a conference abstract referring to another title included in the review,[88] it was subsequently excluded. From the other 60 titles identified, three studies met our inclusion criteria.[88–90] The systematic review in the previous HTA report had identified 48 relevant studies out of 6325 potentially relevant titles.[20] Given that the average age across the 48 studies ranged from 44 years to 58 years, none met our inclusion criteria and therefore none was included in our review. In sum, the systematic review on clinical effectiveness of CPAP identified three relevant RCTs comparing CPAP with sham CPAP, BSC/usual care and dental devices in a patient population with an average age of 60 years or over with OSAS.

Table 69 summarises the characteristics of the studies included in the systematic review of clinical effectiveness. Full data extraction tables can be found in the section *Data extraction tables*.

The three studies included in the systematic review compared CPAP therapy with sham CPAP,[88] or no CPAP[89,90] for OSAS in the secondary care setting in patients with cardiovascular conditions. None of the studies was conducted in the UK. The studies varied in duration: 1 month in Ruttanaumpawan *et al.*,[89] 3 months in Egea *et al.*[88] and 24 months in Parra *et al.*[90] The primary outcome was different for each study: left ventricular ejection fraction,[88] baroreflex sensitivity[89] and a number of neurological, quality of life, sleep-related and mortality outcomes.[90] Common secondary outcomes examined by two or more studies were ESS score,[88–90] BP[88,89] and quality of life with SF-36.[88,90]

Egea *et al.*[88] and Ruttanaumpawan *et al.*[89] included patients with chronic heart failure referred to the sleep clinic whose AHI was greater than 10 events/hour[88] or equal or greater than 20 events/hour,[89] while Parra *et al.*[90] included patients admitted with first ever ischaemic stroke with Apnoea–Hypopnoea Index equal or greater than 20 events/hour.[90] Egea *et al.*[88] included patients with Cheyne–Stokes apnoea (17% of the study population) but presented results for the subgroup of patients with confirmed OSAS. Participants were mostly male and overweight or obese, as indicated by an average BMI of at least 28 kg/m^2. The AHI and ESS measures at baseline suggest that patients across the three studies suffered from moderate to severe OSAS.

Egea *et al.*[88] observed a statistically significant improvement in left ventricular ejection fraction and in ESS score in the CPAP group but no statistically significant differences were recorded for BP and quality of life. Results were similar for the subgroup of patients with confirmed OSAS. Ruttanaumpawan *et al.*[89] also observed a statistically significant improvement in baroreflex sensitivity, Apnoea–Hypopnoea Index, heart rate and systolic BP. In Parra *et al.*,[90] the CPAP group experienced a statistically significantly higher improvement in the neurological outcomes at 1 month, which was not sustained throughout follow-up. There were no statistically significant differences in SF-36 scores at any of the data collection points (1, 3, 12 and 24 months).

Across the three studies, CPAP appears to improve sleep function, cardiovascular outcomes and quality of life in patients over 60 years of age. However, the limitations of the studies prevent definitive conclusions. First, all three studies included only patients with cardiac conditions, who are unlikely to represent all patients over 60 years of age with OSAS. Second, two studies had short follow-up and small samples sizes. Given that Parra *et al.*[90] found that statistically significant differences at 1 month were not sustained at longer follow-ups, there are doubts on whether or not the results observed at 1 month[89] and at 3 months[88] can be extrapolated over longer time horizons. Third, none of the studies collected measures of HRQoL, such as EQ-5D or SF-6D, that can be used for cost-effectiveness analysis.

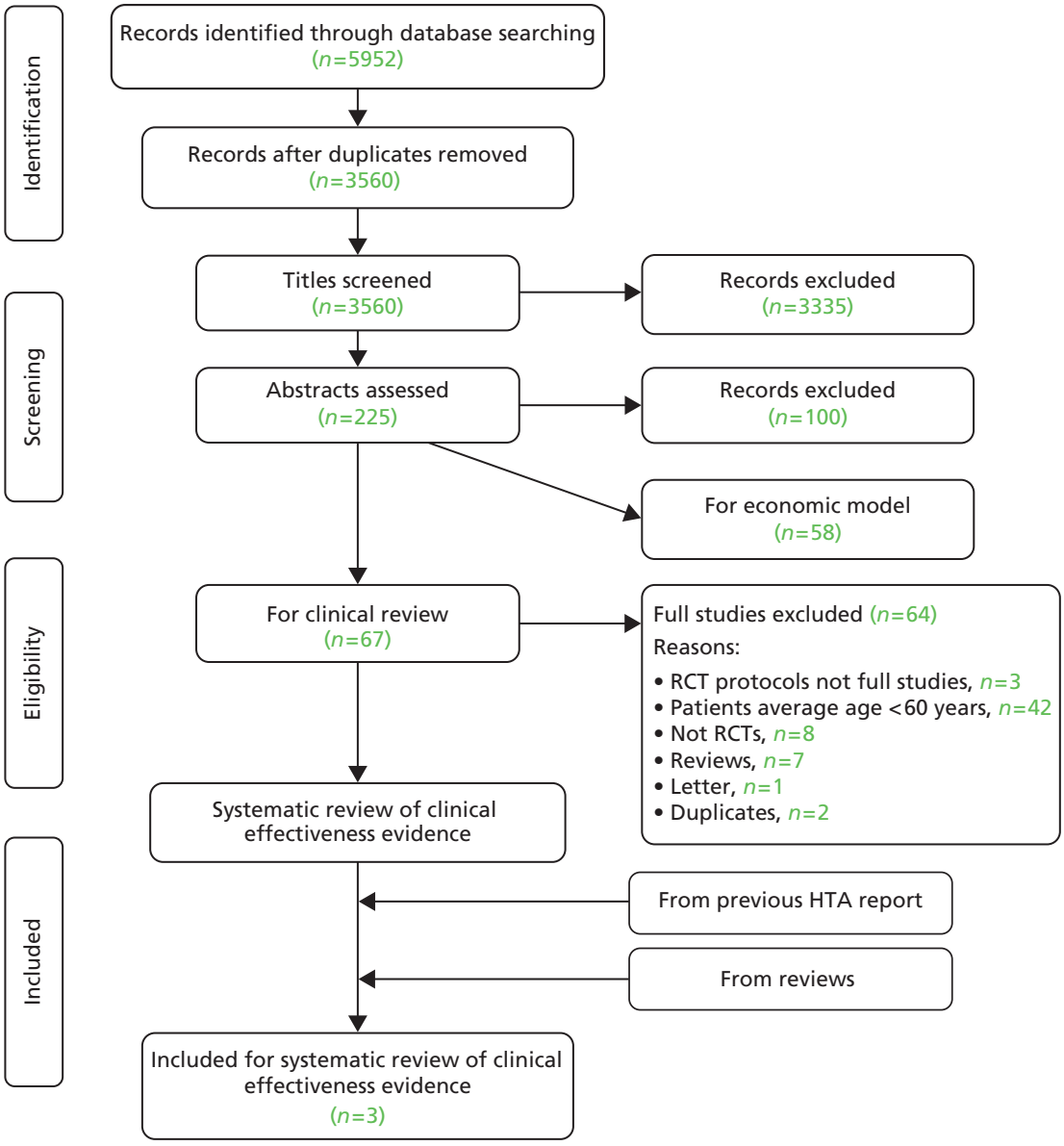

FIGURE 32 Flow diagram showing number of studies identified and included in the review of clinical effectiveness of CPAP.

TABLE 69 Characteristics of included studies

	Egea *et al.* (2008)[88]	Ruttanaumpawan *et al.* (2008)[89]	Parra *et al.* (2011)[90]
Methods			
Study design	Multicentre RCT	RCT	Multicentre RCT
Comparator	Sham CPAP	No CPAP	No CPAP
Number randomised, mean (SE)	I 35; C 38	I 19; C 14	I 71; C 69
Treatment duration	3 months	1 month	24 months
Primary outcomes	Left ventricular ejection fraction	Baroreflex sensitivity	Neurological, cardiovascular, quality of life and mortality outcomes
Patient characteristics			
Age (years), mean (SE)	I 64 (0.9); C 63 (1.6)	I 59.0 (7.8); C 60.5 (10.3)	I 63.7 (9.1); C 65.5 (9.1)
% male	I 96; C 91	I 94.7; C 85.7	I 71.9; C 69.6
BMI (kg/m^2), mean (SE)	I 31.7(2.4); C 30.5 (1.6)	I 30.3 (5.80); C 32.3 (8.6)	I 30.2 (4.6); C 28.8 (4.0)
BP (systolic/diastolic, mmHg), mean (SE)	I 123 (3.7)/76 (2.3); C 126 (2.9)/75 (2.1)	I 122 (15)/66 (12); C 131 (24)/64 (14)	–
Disease severity [AHI, mean (SE)]	I 43 (4.4); C 41 (5.6)	I 36.2 (18.1); C 51.3 (15.6)	I 38.4 (12.6); C 38.4 (14.6)
Severity of sleepiness [ESS score, mean (SE)]	I 8.0 (0.7); C 7.3 (0.8)	–	I 8.3 (3.3); C 7.3 (4.1)
Results			
Primary outcomes, mean (SE)	Baseline: **I mean 28.0 (SE 1.5)**; C mean 28.1 (SE 1.5)	Baseline: I median 5.4 (IQR 2.2–8.3); C median 4.9 (IQR 3.1–8.7)	–
	3 months: **I mean 30.5 (SE 0.8)**; C mean 28.1 (SE 1.7)	1-month I median 7.9 (IQR 4.4–9.4); C median 4.7 (IQR 2.9–7.4)	–
Other outcomes of relevance to economic evaluation			
BP (systolic/diastolic, mmHg), mean (SE)	Baseline: I 123.0 (3.7)/76.3 (2.3); C 124.2 (2.8)/74.8(2.1)	Baseline: I 122 (15)/67 (12); C 131 (24)/64 (14)	–
	3 months: I 123.0 (4.1)/75.3 (2.3); C 120.5 (2.6)/75.2 (3.1)	1 month: I 113(12)/61(9); C 136(28)/63(12)	–
ESS score, mean (SE)	Baseline: **I 8.0 (0.7)**; C 7.1 (0.8)	–	–
	3 months: **I 4.8 (0.6)**; C 5.3 (0.7)	–	–
AHI, mean (SE)	–	Baseline: **I 36.2 (18.1)**; **C 51.3 (15.6)**	–
	–	1-month: **I 9.3 (8.7)**; **C 47.4 (19.1)**	–

AHI, Apnoea–Hypopnoea Index; C, control; I, intervention.
Statistically significant results at $p = 0.05$ are shown in bold. (–) indicates not provided or not applicable.

Data extraction tables

TABLE 70 Egea *et al.* data extraction table

Study details	Egea *et al.* (2008)[88]
Intervention	CPAP therapy
Comparator(s)	Sham CPAP therapy
Study setting	Spain
Design	Randomised multicentre controlled trial
Duration	3 months
Inclusion criteria	• Patients with chronic heart failure referred to the sleep laboratory • Diagnosis of heart failure with at least one episode of cardiac failure • Left ventricular ejection fraction < 45% using radionucleotide ventriculography • Clinically stable for at least 1 month prior to inclusion • Optimum treatment with diuretics and/or beta-blockers and/or digoxin and/or angiotensin-converting enzyme inhibitors according to tolerance • No change in treatment for 1 month prior to inclusion • AHI (events/hour) > 10, measured by polysomnography
Exclusion criteria	• Patients who had a previous diagnosis of sleep apnoea or who had had CPAP therapy • Uncontrolled arterial hypertension • Valvular or congenital cardiopathy, unstable angina, acute MI or cardiac surgery in the 3 months prior to enrolment • Severe somnolence in situations of activity • Present or past medical history of clinically significant renal, liver or pulmonary disease • Untreated hypothyroidism • Clinically significant kyphoscoliosis • Morbid obesity with a BMI > 41 kg/m^2 • Concomitant use of morphine, hypnotics and sedatives, theophylline, acetazolamide (Diamoz®, AMCo) or home oxygen therapy
Outcomes	Primary outcome: left ventricular ejection fraction Secondary outcomes: • BP (systolic and diastolic) • Subjective daytime sleepiness as measured by ESS score • Quality of life as measured by SF-36 Dyspnoea using the Borg scale, New York Heart Association scale and the 6-minute walking test
Pre-defined subgroups	Patients with Cheyne–Stokes apnoea defined as: • Cheyne–Stokes apnoeas reported in over 50% of total sleep time Respiratory events were classified as: • Obstructive apnoea: airflow cessation with thoraco-abdominal motion lasting 10 seconds • Obstructive hypopnoea: discernible airflow reduction with thoracoabdominal motion lasting 10 seconds or more associated with arousal and/or a 3% cyclical SaO_2 dip Cheyne–Stoke apnoea: absence of flow without thoracoabdominal motion followed by a clear-cut crescendo–decrescendo pattern of breathing

TABLE 70 Egea *et al.* data extraction table (*continued*)

Study details	Egea *et al.* (2008)[88]			
Participants: number randomised	73 patients randomised: • 35 for CPAP • 38 for sham CPAP			
Participants: number of withdrawals with reasons	7 patients randomised for CPAP withdrawn: • 2 refused for personal reasons; • 5 CPAP intolerant 6 patients randomised for sham CPAP withdrawn: • 1 death • 1 angina 4 sham CPAP intolerant			
Baseline characteristics	Baseline characteristics (adapted from Table 1, p. 663)[88]			
		CPAP ($n = 28$)		Sham CPAP ($n = 32$)
	Age (years), mean (SE)	64 (0.9)		63 (1.6)
	Sex (% male)	96		91
	BMI (kg/m^2), mean (SE)	31.7 (2.4)		30.5 (1.6)
	Daily snoring (%)	83		69
	Snoring three or more times/week (%)	88		76
	ESS score, mean (SE)	8.0 (0.7)		7.3 (0.8)
	Minimum SaO_2 (%), mean (SE)	76.9 (2.0)		77.4 (2.1)
	AHI (events/hour), mean (SE)	43 (4.4)		41 (5.6)
	Systolic BP (mmHg), mean (SE)	123 (3.7)		126 (2.9)
	Diastolic BP (mmHg), mean (SE)	76 (2.3)		75 (2.1)
	Pretibial oedema (%)	19		13
	Jugular ingurgitation (%)	8		0
	Left ventricular ejection fraction (%), mean (SE)	28.0 (0.5)		28.1 (1.5)
	Statistically significant results at $p = 0.05$ in bold			
Results	Results at 3 month follow-up (adapted from Table 3, page 665)[88]			
		Baseline	3 months	Baseline	3 months
	Left ventricular ejection fraction (%), mean (SE)	**28.0 (1.5)**	**30.5 (0.8)**	28.1 (1.5)	28.1 (1.7)
	ESS score, mean (SE)	**8.0 (0.7)**	**4.8 (0.6)**	7.1 (0.8)	5.3 (0.7)
	Systolic BP (mmHg), mean (SE)	123.0 (3.7)	123.0 (4.1)	124.2 (2.8)	120.5 (2.6)
	Diastolic BP (mmHg), mean (SE)	76.3 (2.3)	75.3 (2.3)	74.8 (2.1)	75.2 (3.1)
	SF-36 physical, mean (SE)	41.8 (1.8)	45.1 (1.4)	42.1 (1.7)	41.3 (1.9)
	SF-36 mental, mean (SE)	47.8 (2.4)	49.9 (2.0)	47.0 (2.3)	49.8 (1.8)
	New York Heart Association (% class I–II)	75	82	65	74

continued

TABLE 70 Egea *et al.* data extraction table (*continued*)

Study details	Egea *et al.* (2008)[88]				
	New York Heart Association (% class II)	64	71	58	74
	6-minute walking test (m), mean (SE)	424 (20)	420 (19)	394 (20)	405 (22)
	Statistically significant results at $p = 0.05$ in bold				
Results for subgroups	Results at 3-months follow-up for the patients with obstructive apnoea or hypopnoea (adapted from Table 4, page 665)[88]				
		CPAP ($n = 20$)		Sham CPAP ($n = 25$)	
		Baseline	3 months	Baseline	3 months
	Left ventricular ejection fraction (%), mean (SE)	**28.8 (1.6)**	**31.0 (1.6)**	27.2 (1.6)	26.7 (1.7)
	ESS score, mean (SE)	**8.6 (0.8)**	**5.0 (0.8)**	**6.9 (5.2)**	**5.2 (0.8)**
	Systolic BP (mmHg), mean (SE)	124.3 (4.2)	124.3 (4.9)	125 (2.7)	123.4 (2.8)
	Diastolic BP (mmHg), mean (SE)	75.6 (2.3)	76.0 (2.8)	75.8 (2.4)	77.0 (3.7)
	SF-36 physical, mean (SE)	41.4 (2.0)	44.9 (1.8)	42.0 (2.1)	40.7 (2.1)
	SF-36 mental, mean (SE)	46.4 (3.0)	48.8 (2.3)	45.8 (2.7)	48.7 (2.2)
	New York Heart Association (% class I–II)	60	70	50	67
	6-minute walking test (m), mean (SE)	403 (21)	406 (21)	381 (23)	393 (24)
	Statistically significant results at $p = 0.05$ in bold				
Conclusions	CPAP therapy increases left ventricular ejection fraction in patients with associated sleep-related disordered breathing and severe chronic heart failure, however, this improvement was not translated into an improvement in quality of life or cardiac function				
Limitations	• Small sample size • Difficult to generalise given that patients were predominantly male and with moderate to severe OSA • Long-term outcomes, namely mortality, not evaluated				
Conflicts of interest	None				

AHI, Apnoea–Hypopnoea Index.

TABLE 71 Rutanaumpawan *et al.* data extraction table

Study details	Rutanaumpawan *et al.* (2008)[89]		
Intervention	CPAP		
Comparator(s)	Usual care for heart failure		
Study setting	Canada		
Design	RCT		
Duration	1 month		
Inclusion criteria	• Patients with heart failure due to ischaemic or non-ischaemic dilated cardiomyopathy of more than 6 months' duration • Left ventricular ejection fraction of ≤ 45% by nuclear angiography or echocardiography • Stable condition for at least 3 months prior to the study • Moderate to severe OSA, defined as AHI ≥ 20 events/hour, with more than 50% of events obstructive		
Exclusion criteria	• Primary valvular heart disease • Atrial fibrillation or a paced cardiac rhythm • Ventricular premature beats > 15 beats for 100 heart beats • Unstable angina, MI or cardiac surgery within the 3 months before to the study		
Outcomes	• Primary outcome: baroreflex sensitivity • Secondary outcomes: ○ Sleep-related: AHI, mean and lowest oxyhaemoglobin saturation, arousal index, total sleep time, stages I and II sleep, slow-wave sleep, rapid eye movement sleep • Cardiovascular outcomes: left ventricular ejection fraction; heart rate; systolic and diastolic BP		
Pre-defined subgroups	• None		
Participants: Number randomised	• 34 enrolled		
Participants: number of withdrawals with reasons	• 1 patient excluded because of technical problems in assessing baroreflex sensitivity • 33 patients: 14 randomised to control and 19 to CPAP		
Baseline characteristics	Baseline characteristics (adapted from table 1, page 1165)[89]		
	Selected variables	CPAP ($n = 19$)	Control ($n = 14$)
	Age (years), mean (SE)	59.0 (7.8)	60.5 (10.3)
	Sex (% male)	94.7	85.7
	Cause of heart failure		
	Ischaemic (%)	63	64
	Non-ischaemic (%)	37	36
	New York Heart Association functional class, mean (SE)	2.4 (0.6)	2.3 (0.4)
	BMI (kg/m^2), mean (SE)	30.3 (5.8)	32.3 (8.6)
	Left ventricular ejection fraction (%), mean (SE)	29.0 (11.4)	30.8 (8.9)
	SBP (mmHg), mean (SE)	122 (15)	131 (24)
	Diastolic BP (mmHg), mean (SE)	66 (12)	64 (14)
	Data expressed as means (SE). Statistically significant results at $p = 0.05$ in bold		

continued

TABLE 71 Rutanaumpawan *et al.* data extraction table (*continued*)

Study details	Rutanaumpawan *et al.* (2008)[89]			
Results	Results at 1-month follow-up (adapted from tables 2 and 3 pages 1165–6)[89]			
	Selected variables	CPAP ($n = 19$)		Control ($n = 14$)	
		Baseline	1 month	Baseline	1 month
	Sleep-related				
	AHI events per hour, mean (SE)	36.2 (18.1)	9.3 (8.7)	51.3 (15.6)	47.4 (19.1)
	Mean SaO_2 (%), mean (SE)	94.7 (1.6)	96.1 (1.6)	94.3 (2.1)	94.1 (2.0)
	Cardiovascular				
	Left ventricular ejection fraction (%), mean (SE)	29.0 (11.4)	36.1 (10.6)	30.8 (8.9)	29.4 (8.0)
	Heart rate (bpm), mean (SE)	66 (8)	62 (8)	66 (11)	66 (9)
	SBP (mmHg), mean (SE)	122 (15)	113 (12)	131 (24)	136 (28)
	Diastolic BP (mmHg), mean (SE)	67 (12)	61 (9)	64 (14)	63 (12)
	Baroreflex sensitivity				
	Slope (ms/mmHg), median (IQR)	5.4 (2.2; 8.3)	7.9 (4.4–9.4)	4.9 (3.1–8.7)	4.7 (2.9–7.4)
	Slope in +SBP/+R–R sequences, median (IQR)	4.7 (2.4; 8.5)	8.1 (4.5–12.6)	5.5 (3.3–10.0)	4.0 (3.2–6.9)
	Slope in SBP/–R–R sequences, median (IQR)	5.4 (2.2; 8.8)	5.6 (4.3–10.0)	5.5 (4.1–11.2)	5.0 (2.7–7.7)
	Between-groups statistically significant results at $p = 0.05$ in bold				
Results for subgroups	None				
Conclusions	Treatment of OSA in patients with heart failure improves baroreflex sensitivity and cardiovascular signs				
Limitations	• Small sample size • Short follow-up • No quality-of-life assessment				
Conflicts of interest	None				

AHI, Apnoea–Hypopnoea Index; SBP, systolic blood pressure.

TABLE 72 Parra *et al.* data extraction table

Study details	Parra *et al.* (2011)[90]
Intervention	Nasal CPAP in addition to usual stroke care
Comparator(s)	Usual stroke care, in accordance with the recommendations of the Spanish Cerebrovascular Study Group of the Spanish Society of Neurology
Study setting	Spain
Design	Randomised controlled multicentre study
Duration	24 months

Inclusion criteria	• Patients who were admitted to hospital with first-ever ischaemic stroke
	• Age < 75 years
	• AHI ≥ 20 events/hour
	• At least one of the following conditions:
	  ○ habitual snoring
	  ○ observed apnoeas
	  ○ history of hypertension or ischaemic heart disease

Exclusion criteria	• Patients with consciousness impairment • Patients previously diagnosed and treated for OSA
Outcomes	Assessments at baseline, 1, 3, 12 and 24 months after stroke • Barthel index for functional abilities • Canadian scale for neurological impairment • Modified Rankin scale for outcomes from stroke • SF-36 for quality of life • Questionnaire for sleep–wake habits and symptoms • ESS score for daytime sleepiness
Pre-defined subgroups	None
Participants: Number randomised	140 patients were randomised but only 126 were followed up: • 71 patients randomised to CPAP • 69 randomised to no treatment
Participants: Number of withdrawals with reasons	14 patients randomised to CPAP dropped-out because of machine discomfort
Baseline characteristics	Baseline characteristics (selected data from Table 1, page 1131)[90]

	CPAP ($n = 57$)	Control ($n = 69$)
Age (years), mean (SE)	63.7 (9.1)	65.5 (9.1)
Sex (% male)	71.9	69.6
BMI (kg/m^2), mean (SE)	30.2 (4.6)	28.8 (4.0)
Snoring, often or always (%)	94.7	85.5
Observed apnoea at night, often or always (%)	70.2	46.4
ESS score, mean (SE)	8.3 (3.3)	7.3 (4.1)
AHI (events/hour), mean (SE)	38.4 (12.6)	38.4 (14.6)
Physical component SF-36, mean (SE)	42.3 (11.1)	43.1 (7.8)
Mental component SF-36, mean (SE)	47.1 (13.3)	48.2 (12.9)

Statistically significant results at $p = 0.05$ in bold.

continued

TABLE 72 Parra *et al.* data extraction table (*continued*)

Study details	Parra *et al.* (2011)[90]		
Results	Mean CPAP use was 5.3 hours (SE = 1.9 hours) per night during an average of 6.8 (SE = 0.6) nights a week		
	Results (adapted from table 3 page 1133)[90]		
		CPAP ($n = 57$), mean (SE)	Control ($n = 69$), mean (SE)
	Barthel index		
	Baseline	75.9 (27.9)	73.6 (27.0)
	3 months	95.0 (13.4)	92.8 (17.8)
	12 months	95.3 (10.0)	91.4 (17.8)
	24 months	94.3 (10.9)	93.1 (15.8)
	Canadian scale		
	Baseline	8.3 (1.6)	8.0 (1.9)
	3 months	9.3 (1.0)	9.3 (1.3)
	12 months	9.4 (1.2)	9.4 (1.3)
	24 months	9.3 (1.3)	9.5 (1.0)
	Rankin scale		
	Baseline	2.3 (1.3)	2.8 (1.3)
	3 months	1.6 (0.9)	2.0 (1.1)
	12 months	1.6 (0.9)	2.1 (1.2)
	24 months	1.8 (1.1)	2.2 (1.1)
	SF-36 physical		
	Baseline	42.6 (10.2)	42.3 (11.8)
	3 months	44.9 (9.2)	44.8 (11.8)
	12 months	46.7 (8.8)	46.5 (11.7)
	24 months	45.8 (10.0)	46.0 (9.8)
	SF-36 mental		
	Baseline	43.3 (13.2)	43.7 (14.1)
	3 months	46.9 (10.9)	46.3 (14.4)
	12 months	49.1 (14.0)	44.6 (12.8)
	24 months	47.6 (13.8)	47.8 (12.1)
	Statistically significant results at $p = 0.05$ in bold. The overall cardiovascular event-free survival rate after 24 months was 87.7% (50 out of 57 subjects) in the CPAP group and 88.4% (61 out of 69) in the control group ($p = 0.911$)		
Results for subgroups	None		
Conclusions	Early use of CPAP in patients with a first-ever ischaemic stroke and moderate to severe OSA is associated with a significant improvement in neurological function, but this improvement is not sustained at follow-up		

TABLE 72 Parra *et al.* data extraction table (*continued*)

Study details	Parra *et al.* (2011)[90]
Limitations	• Limited generalisability owing to exclusion criteria (patients with altered consciousness or age > 75 years of age were excluded) • Non-placebo controlled • Per protocol analysis • Neurological measures may not be sensitive enough to detect changes in patients with minor stroke
Conflicts of interest	None

AHI, Apnoea–Hypopnoea Index.

Appendix 6 Detailed results of the model-based sensitivity analysis

Scenario 1: continuous positive airway pressure is used for 1 year (costs = £710.016)

The base case assumes that the CPAP and humidifier devices have a lifetime of 7 years and can be reused across patients. Scenario 2 assumes that the CPAP and humidifier devices are used for 1 year only. Therefore, their costs are not annuitised and all the costs of CPAP treatment are incurred in the 1 year. CPAP therapy costs £710.16 per patient and the difference in costs estimated from the within-trial analysis (see *Appendix 3*, *Table 64*) was £474 (95% CI £119 to £830). The model extrapolates this difference over the patient's lifetime.

Table 73 shows the cost-effectiveness results for scenario 1. The average difference in costs is £4785 over the patient's lifetime. The difference in EQ-5D QALYs was 0.051 and in SF-6D QALYs was 0.182; the ICERs, respectively, are £94,404 and £26,599 per QALY gained.

Figure 33 presents the cost-effectiveness acceptability curve for the scenario 1. The curve has a similar shape to the curves for scenarios 1 and 2 of the within-trial sensitivity analysis (see *Appendix 3, Figures 27* and *28*). The probability that CPAP is cost-effective at £20,000 is 0.20 for the analysis with EQ-5D QALYs and 0.31 for SF-6D QALYs. The reduction in the probability that the intervention is cost-effective reflects the trade-off between small and uncertain gains in health and the increase in costs.

TABLE 73 Cost-effectiveness results for scenario 1 of model-based analysis (CPAP is used for 1 year at an average cost per patient of £710.16)

Treatment	Average costs (£)	Average EQ-5D QALYs	Average SF-6D QALYs
CPAP with BSC	21,002	8.041	7.859
BSC alone	16,216	7.990	7.678
Incremental costs and QALYs			
CPAP with BSC – BSC alone	4785	0.051	0.182

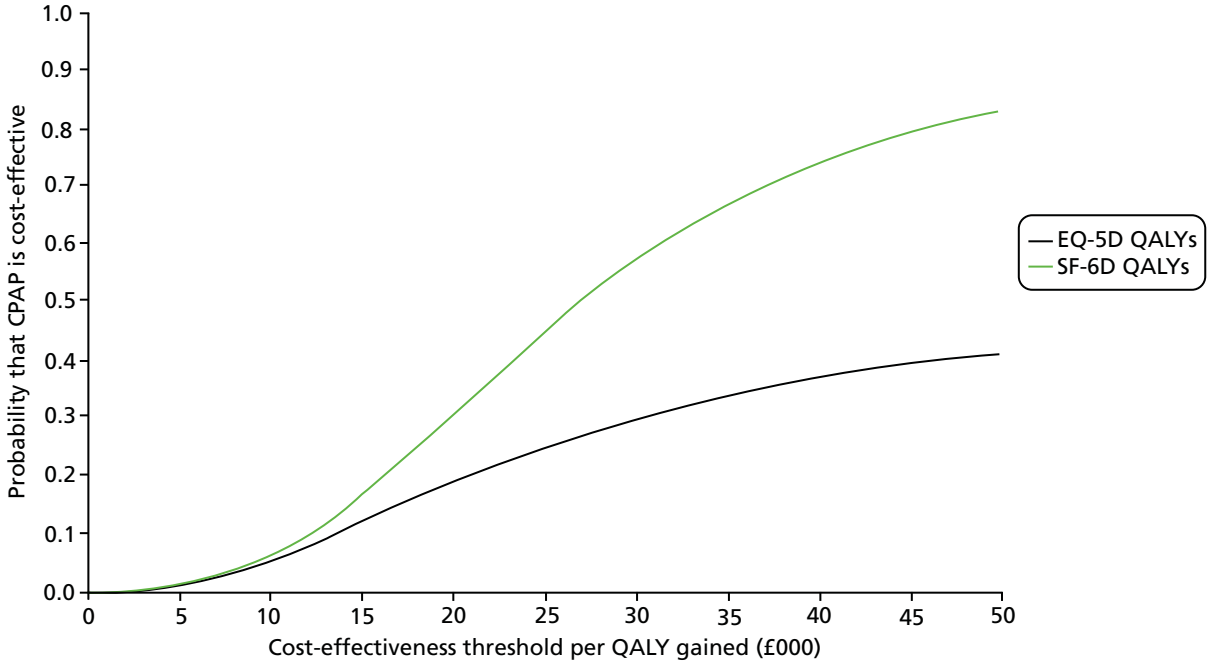

FIGURE 33 Cost-effectiveness acceptability curve for scenario 1 (CPAP is used for 1 year at an average cost per patient of £710.16).

Scenario 2: cardiovascular effects with effect of continuous positive airway pressure on costs and quality-adjusted life-years

In scenario 2, the model includes two additional health states (post stroke and post CHD) and two additional events (stroke and CHD). The model is run for six patient subgroups defined according to their sex, smoking status and diabetes status. The final results are a weighted average of the results for each subgroup weighted by their relative proportion in the patient population participating in PREDICT. *Table 74* presents the percentage of each subgroup in the overall population. Note that this calculation uses only the patients with complete data in these variables.

TABLE 74 Population subgroups for cardiovascular scenario

Population	1	2	3	4	5	6
Sex (=0 male)	0	0	0	0	1	1
Smoking status (=0 no smoker)	1	1	0	0	0	0
Diabetes (=0 not diabetic)	1	0	0	1	0	1
Number of patients	5	8	102	56	15	5
Percentage	2.6	4.2	53.4	29.3	7.9	2.6

Tables 75 and *76* show the cost-effectiveness results for each subgroup and for the overall population. The differences in costs and QALYs are similar to those in the base-case analysis. Overall, the cost savings are approximately £300 (vs. £329 in the base case). The difference in the results for EQ-5D and SF-6D QALYs is a result of the intrinsic variation from the probabilistic analysis. The increase in EQ-5D QALYs is 0.022 (vs. 0.051 in the base case) and the increase in SF-6D QALYs is 0.139 (vs. 0.182 in the base case). Therefore, including cardiovascular effects appears to reduce the health benefits obtained with CPAP therapy but has little impact on costs.

Figure 34 shows the cost-effectiveness plane for the most common subgroup, patients who are male, non-smokers and non-diabetic. The distribution of the simulations across the quadrants is similar to that of the base case. In the analysis with EQ-5D QALYs, the simulations are scattered evenly across the four quadrants. In the analysis with SF-6D QALYs, the simulations are concentrated in the eastern quadrants (better health outcomes).

TABLE 75 Cost-effectiveness results for scenario 2 of model-based analysis (cardiovascular effects with effect of CPAP on costs and QALYs; EQ-5D analysis)

	Population					
	1	2	3	4	5	6
Costs without CPAP (£)	15,776	15,946	16,442	16,310	16,988	16,323
Costs with CPAP (£)	15,535	15,610	16,089	16,019	16,652	16,075
Outcomes without CPAP	6.130	6.604	7.224	6.839	7.877	7.244
Outcomes with CPAP	6.135	6.611	7.248	6.858	7.920	7.268
Weights (%)	2.62	4.19	53.40	29.32	7.85	2.62
Difference in costs (£)	–241	–336	–353	–291	–337	–248
Difference in QALYs	0.005	0.007	0.023	0.018	0.043	0.023
Weighted average						
Difference in costs (£)	–327					
Difference in QALYs	0.022					

TABLE 76 Cost-effectiveness results for scenario 2 of model-based analysis (cardiovascular effects with effect of CPAP on costs and QALYs; SF-6D analysis)

	Population					
	1	2	3	4	5	6
Costs without CPAP (£)	15,779	15,948	16,440	16,309	16,987	16,320
Costs with CPAP (£)	15,502	15,593	16,106	16,036	16,679	16,061
Outcomes without CPAP	5.886	6.343	6.939	6.570	7.566	6.959
Outcomes with CPAP	5.994	6.461	7.082	6.700	7.735	7.100
Weights (%)	2.62	4.19	53.40	29.32	7.85	2.62
Difference in costs (£)	–277	–354	–334	–273	–308	–258
Difference in QALYs	0.108	0.119	0.143	0.131	0.168	0.141
Weighted average						
Difference in costs (£)	–311					
Difference in QALYs	0.139					

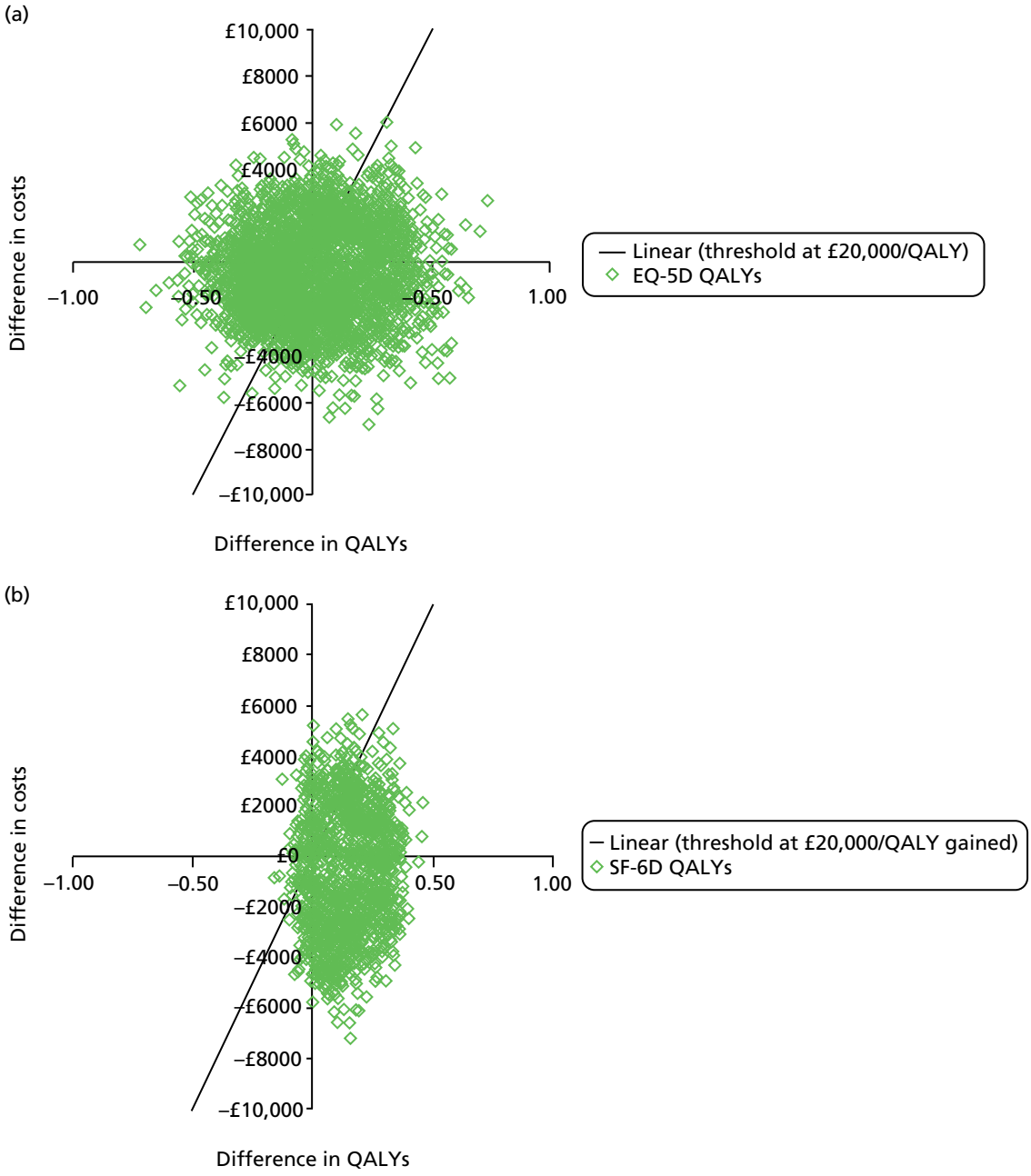

FIGURE 34 Cost-effectiveness plane for scenario 3 (subgroup population 3). (a) EQ-5D; and (b) SF-6D.

Figure 35 shows the cost-effectiveness acceptability curve for subgroup 3. The curve is similar to the base-case analysis. The probability that CPAP is cost-effective is 0.58 for EQ-5D QALYs and 0.92 for SF-6D QALYs. These results suggest that including cardiovascular effects has little impact on the results.

Scenario 3: cardiovascular effects without effect of continuous positive airway pressure on costs and quality-adjusted life-years

Scenario 3 uses the model with cardiovascular effects but does not consider the impact of CPAP therapy on costs and QALYs. In other words, it assumes that there is no improvement in QALYs or cost savings from CPAP therapy over 1 year. Therefore, the QALY improvement and cost saving from CPAP is set to zero. The purpose of this scenario is to test the impact of including cardiovascular effects of CPAP on costs and QALYs independent to the direct effect of CPAP. This will indicate whether or not the cardiovascular effects are a key driver of the cost-effectiveness results.

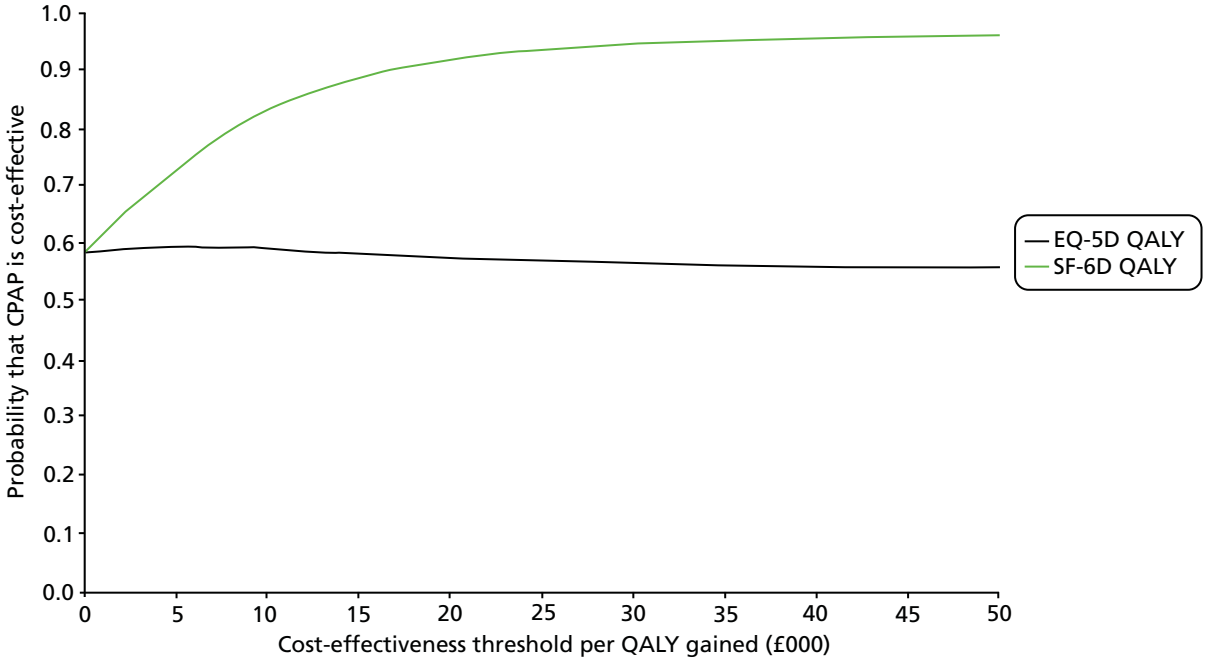

FIGURE 35 Cost-effectiveness acceptability curve for scenario 2 (subgroup population 3).

Table 77 and *78* present the cost-effectiveness results for this scenario. The difference in costs and QALYs is very small; cost savings of £10 and QALY decrement of approximately 0.023. The results are similar for EQ-5D and SF-6D QALYs because the same HRQoL parameters are used for these analyses except HRQoL at baseline (0.687 for EQ-5D and 0.660 for SF-6D).

TABLE 77 Cost-effectiveness results for scenario 3 of model-based analysis (cardiovascular effects with effect of CPAP on costs and QALYs; EQ-5D analysis)

	Population					
	1	2	3	4	5	6
Costs without CPAP (£)	15,776	15,944	16,445	16,310	16,986	16,322
Costs w/ CPAP (£)	15,802	15,909	16,421	16,309	17,018	16,380
Outcomes without CPAP	6.128	6.605	7.223	6.839	7.876	7.246
Outcomes with CPAP	6.095	6.571	7.200	6.813	7.864	7.222
Weights (%)	2.62	4.19	53.40	29.32	7.85	2.62
Difference in costs (£)	26	–35	–24	0	32	59
Difference in QALYs	–0.033	–0.034	–0.023	–0.027	–0.012	–0.024
Weighted average						
Difference in costs	–10					
Difference in QALYs	–0.024					

TABLE 78 Cost-effectiveness results for Scenario 3 of model-based analysis (cardiovascular effects with effect of CPAP on costs and QALYs; SF-6D analysis)

	Population					
	1	2	3	4	5	6
Costs without CPAP (£)	15,777	15,944	16,441	16,308	16,989	16,321
Costs with CPAP (£)	15,802	15,910	16,417	16,307	17,021	16,379
Outcomes without CPAP	5.887	6.343	6.939	6.570	7.567	6.960
Outcomes with CPAP	5.854	6.311	6.917	6.544	7.555	6.937
Weights (%)	2.62%	4.19	53.40	29.32	7.85	2.62
Difference in costs (£)	25	–34	–24	–1	32	58
Difference in QALYs	–0.033	–0.032	–0.022	–0.026	–0.011	–0.023
Weighted average						
Difference in costs (£)	–10					
Difference in QALYs	–0.023					

Figure 36 shows the cost-effectiveness planes for subgroup 3. The differences in costs and QALYs are very small; most of the simulations are between –£100 and £100 and –0.10 QALYs and 0.10 QALYs. In addition, the differences are also uncertain. Approximately one-quarter of the simulations are located in the north-east quadrant, indicating better QALYs but also increased costs; the remaining 75% of the simulations are located in the south-west quadrant, indicating worse health outcomes and lower costs.

Figure 37 shows the cost-effectiveness acceptability curve for subgroup 3. At low thresholds (< £1000/QALY gained), the cost savings compensate the losses in QALYs. As the threshold increases, potential losses in health are valued more highly and the probability that CPAP is cost-effective drops to below 0.30.

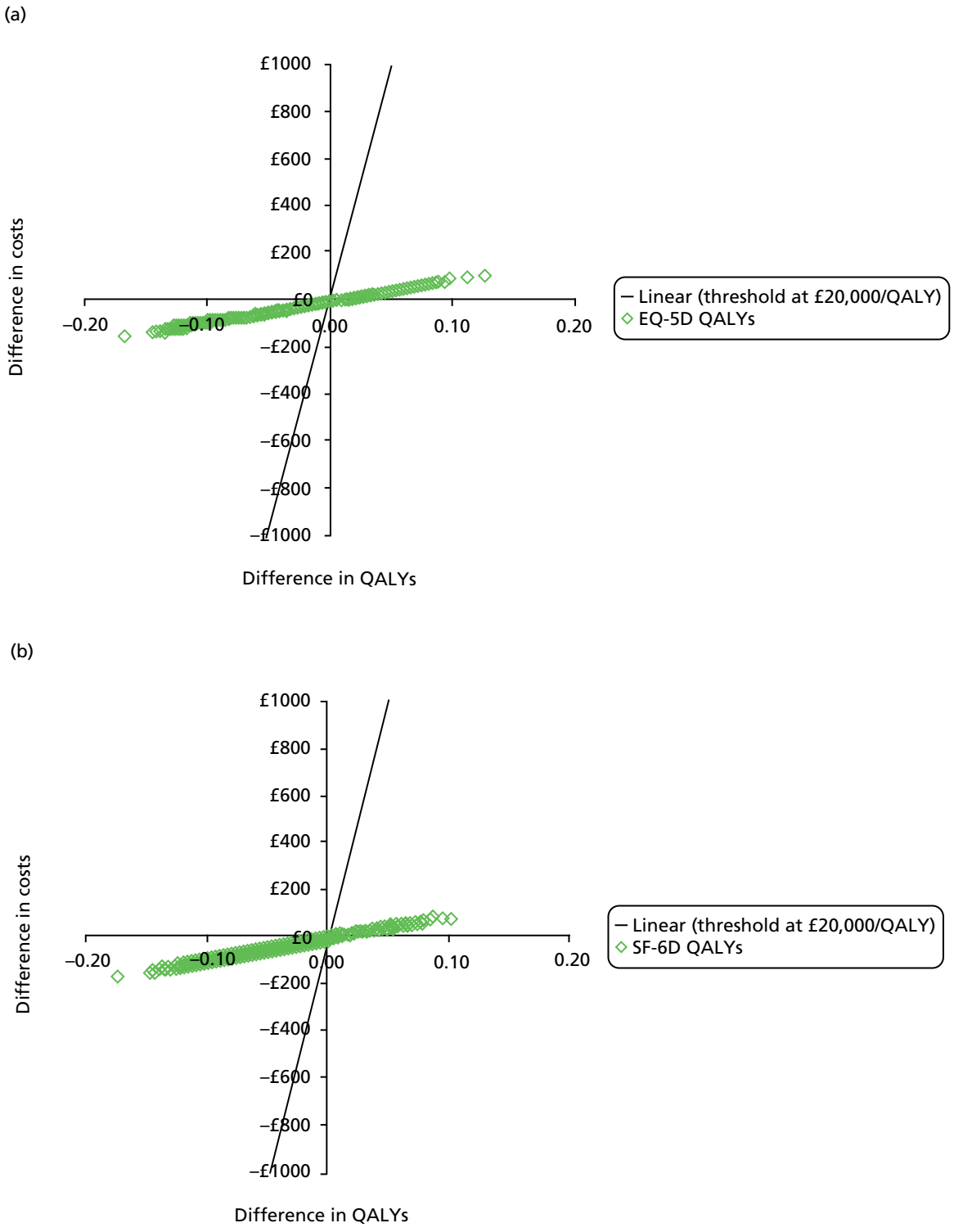

FIGURE 36 Cost-effectiveness plane for scenario 3 (subgroup 3). (a) EQ-5D; and (b) SF-6D.

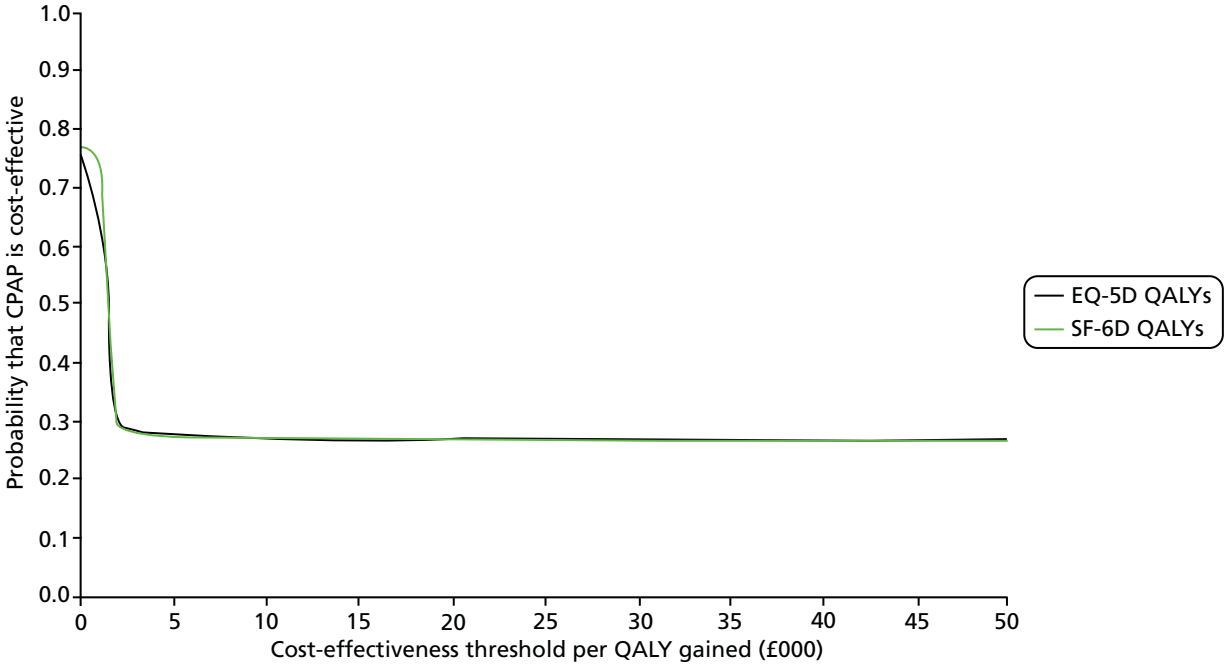

FIGURE 37 Cost-effectiveness acceptability curve for scenario 3 (subgroup 3).

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