Obstructive sleep apnoea in older people

Thesis submitted to Imperial College, London for the degree of Doctor of Philosophy in the Faculty of Science

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Declaration of originality

I, Alison McMillan, hereby declare that this thesis contains the results of my own work except where otherwise acknowledged.

The PREDICT trial was designed by my supervisor Professor Mary Morrell and the PREDICT investigators, with my input. Data was collected across 14 centres under my supervision. Mrs Marjorie Vennella, Department of Sleep Medicine, Royal Infirmary of Edinburgh analysed the respiratory polygraphy studies completed in the PREDICT trial. Statistical support was provided by Mr Daniel Bratton supervised by Professor Andrew Nunn, Medical Research Council Clinical Trials Unit (MRC CTU) at University College London. The health economics analysis was completed by Ms Rita Neves De Faria supervised by Dr Susan Griffin, Centre for Health Economics, University of York. Please note that since I did not carry out the cost effectiveness analysis only a summary of the main results will be reported in this thesis in the context of a clinical trial. I was responsible for all aspects of the PREDICT trial write-up.

I designed, collected the data, analysed and wrote-up the second study. Miss Lydia Paniccia, Research assistant, Royal Brompton Hospital assisted with data collection and Mr Vitor Roldao Clinical and Academic Unit of Sleep and Breathing Royal Brompton Hospital analysed the polysomnography studies under my supervision.

Information derived from the work of others and discussed in this thesis is referenced in the text and listed in the bibliography. No part of this thesis has previously been submitted for application for a higher degree. Publications in the form of abstract presentations arising from this work are listed.

Abstract

Obstructive sleep apnoea (OSA) is common and the prevalence increases with age. When OSA leads to sleep disruption and excessive daytime sleepiness, it is referred to as obstructive sleep apnoea syndrome (OSAS). The aim of this thesis was to investigate the consequences of OSAS in older people (> 65 years) and the effect of continuous positive airway pressure (CPAP) therapy. CPAP is the treatment of choice in moderate to severe OSAS in middle aged people. However, there is a paucity of evidence on the therapeutic and economic benefits of CPAP in older people with OSAS. The two studies in this thesis aimed to address this by comparing outcomes in older people with OSAS before and after treatment with CPAP.

The first study presented is the thesis is the PREDICT trial; a multicentre randomised controlled trial of CPAP in older people with OSAS. The trial studied the clinical efficacy of CPAP after 3 months, while determining the cost effectiveness of treatment over 12 months. The results of the trial showed that CPAP was an effective treatment for reducing excessive daytime sleepiness by -2.1 (95%CI -3.0 to -1.3); $p<0.001$ points as measured by the Epworth sleepiness scale. CPAP also improved quality of life, with a statistically significant increase in the quality adjusted life years calculated with the SF-6D, equating to one week. The CPAP group also accrued marginally lower health care costs over 12 months compared to the group treated with best supportive care alone. Overall the economic benefit of CPAP was linked to the reduced healthcare usage offsetting the cost of the equipment.

The second study presented in the thesis was a single centre randomised controlled trial to investigate the impact of CPAP on cognitive function and brain morphology in older people with minimally symptomatic OSAS after 6 months of treatment. In this study I tested the hypothesis that older patients with OSAS have cognitive impairment and corresponding brain changes which would be modifiable with treatment. The results of this study suggested older people with minimally symptomatic OSAS had normal cognitive function but impaired attention and executive function. CPAP treatment improved one aspect of attention, although memory and overall cognitive function were unchanged. The results of the brain MRI scans are not presented, and are in the process of being analysed.

In conclusion the data presented in this thesis support the use of CPAP therapy in older people with excessive daytime sleepiness due to OSAS.

Publications arising from this thesis

Published papers

A 12 month multicentre, randomised trial of Continuous Positive Airway Pressure in older people with Obstructive Sleep Apnoea Syndrome. McMillan A, Bratton D, Faria R, Laskawiec-Szkonter M, Griffin S, Davies R, Nunn AJ, Stradling JR, Riha RL, Morrell MJ, on behalf of the PREDICT Investigators. In review.

A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: The PREDICT trial. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, Nunn AJ, Stradling JR, Riha RL, Morrell MJ on behalf of the PREDICT Investigators. In review Health technologies Assessment Report.

Published abstracts

The impact of continuous positive airway pressure (CPAP) therapy on cognitive function in older people with sleep disordered breathing (SDB) and co-morbidity. McMillan A, Paniccia L, Martin Glasser M, Edison P, Simonds AK, Morrell MJ. Spoken presentation British Thoracic Society December 2013.

A 12 month multicenter, parallel, randomized trial of Continuous Positive Airway Pressure in older people with Obstructive Sleep Apnea Syndrome. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, Nunn AJ, Stradling JR, Riha RL, Morrell MJ on behalf of the PREDICT Investigators. Spoken presentation, American Thoracic Society May 2014 (awarded 2014 Best Scientific Abstract Award for Sleep and Neurobiology).

Publications associated or arising from this work but not directly presented in this thesis

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Upper airway factors that protect against obstructive sleep apnoea in healthy older males. Carlisle T, Carthy ER, Glasser M, Drivas P, McMillan A, Cowie MR, Simonds AK, Morrell, MJ. European Respiratory Journal 2014 May 15. pii: erj01772-2013. [Epub ahead of print].

Sleep Apnoea in Older People. Glasser M, Bailey N, McMillan A, Goff E and Morrell MJ. Breathe 2011, volume 7, no. 3

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Abbreviations

AI	Apnoea Index
AHI	Apnoea Hypopnoea Index
AD	Alzheimer's disease
APOE	Apolipoprotein
BMI	Body Mass Index
BP	Blood Pressure
BSC	Best Supportive Care
CPAP	Continuous Positive Airway Pressure
CHD	Coronary Heart Disease
CVD	Cardiovascular disease
CRF	Case Report Form
CSA	Central Sleep Apnoea
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
EQ-5D	European Quality of Life – 5 Dimensions
ESS	Epworth Sleepiness Scale
FEV_1	Forced Expiratory Volume in One Second
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HGV	Heavy Goods Vehicle

HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
MMSE	Mini Mental State Examination
MRC CTU	Medical Research Council Clinical Trial Unit
MRI	Magnetic Resonance Imaging
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NREM	Non rapid eye movement sleep
ODI	Oxygen Desaturation Index
OSA	Obstructive sleep apnoea
OSAHS	Obstructive Sleep Apnoea Hypopnoea Syndrome
OSAS	Obstructive Sleep Apnoea Syndrome
OSLER	Oxford Sleep Resistance Test
PLMS	Periodic Limb Movements during Sleep
PSG	Polysomnogram
QALY	Quality Adjusted Life Year
RBD	REM Behaviour Disorder
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REM	Rapid Eye Movement
RLS	Restless Legs Syndrome

RT	Reaction Time
RTA	Road Traffic Accident
SAQLI	Sleep apnoea quality of life index
SAR	Serious Adverse Reaction
SD	Standard deviation
SDB	Sleep disordered breathing
SE	Standard error
SF-36	Medical Outcomes Study 36-item Short Form Health Survey
SIGN	Scottish Intercollegiate Guidelines Network
$Sa0_2$	Arterial Oxygen Saturation
SUSARs	Suspected Unexpected Serious Adverse Reactions
TDS	Townsend Disability Scale
TMG	Trial Management Group
TMT	Trail Making Task
TUG	Timed Up and Go
VBM	Voxel based morphometry
WAIS	Wechsler Adult Intelligence Scale

Chapter 1: Introduction

1.1 Definition of Obstructive sleep apnoea

1.1.1 Overview

Obstructive sleep apnoea (OSA) occurs when the neural control to the upper airway muscles is reduced at sleep-onset, and the patency of the upper airway is compromised in susceptible individuals. The mechanisms associated with upper airway collapse will be discussed below in section 1.2. Airway collapse can be complete, with total obstruction of the lumen and no airflow (apnoea) or partial narrowing with reduced airflow (hypopnoea), both types of event are associated with hypoxia and hypercapnia. The drive to breath is on-going during these events, and increasing inspiratory effort often leads to a brief transient cortical arousal from sleep which restores the muscular tone and upper airway patency (Berry and Gleeson 1997). These events are also associated with an acute surge in blood pressure (O'Driscoll, Meadows et al. 2004, Jordan, McSharry et al. 2013). At sleep-onset the cycle repeats and can occur many hundreds of time throughout the night. This leads to fragmentation of the normal sleep architecture.

The daytime symptom of OSA is excessive daytime sleepiness that occurs in some but not all patients (Bixler, Vgontzas et al. 2005). When OSA is associated with symptoms (Stradling 1995) it is often referred to as obstructive sleep apnoea syndrome (OSAS), this is also synonymous with the term obstructive sleep apnoea / hypopnoea syndrome (OSAHS). In this thesis the terms OSA and OSAS are used, as opposed to OSAHS.

1.1.2 Classification of Obstructive sleep apnoea

OSA as classified by the International classification of sleep disorders American Academy of Sleep Medicine (Iber, Ancoli-Isreal et al. 2007) falls into the broad category of a dyssomnia, which are disorders that produce either difficulty initiating or maintaining sleep or excessive sleepiness. Dyssomnia's are broadly divided into three groups of disorders: intrinsic sleep disorders, extrinsic sleep disorders, and circadian rhythm sleep disorders. OSAS is an intrinsic sleep disorder. Intrinsic sleep disorders either originate or develop within the body or arise from causes within the body. OSA is also commonly associated with the term Sleep disordered breathing (SDB). This is an umbrella term used to describe a group of disorders which are characterized by abnormalities of respiratory pattern or quantity of ventilation that occur periodically during sleep such as primary or secondary central sleep apnoea (CSA), cheyne stokes respiration, high-altitude periodic breathing, or non-obstructive hypoventilation or hypoxemia disorders secondary to pulmonary parenchymal, vascular, neuromuscular or chest wall disorders.

1.1.3 Diagnosis of Obstructive sleep apnoea

OSA is diagnosed using a combination of clinical history, examination and a diagnostic test that measures physiological variables before and during sleep. The most comprehensive test is nocturnal polysomnography (NPSG) which simultaneously records the electroencephalogram, electrooculogram, electromyogram, oronasal airflow and oxyhaemoglobin saturations. This test was used in the study presented in chapter 4 and will be discussed in more detail in chapter 2, section 2.5.3. In addition various combinations of physiological signals can also be used dependant on the pre-test probability of the patient having the condition. Other related diagnostic tests are cardio-respiratory studies e.g. respiratory polygraphy or continuous single or dual bioparameter recording

e.g. overnight pulse oximetry. respiratory polygraphy and oximetry were used in the trial described in chapter 3, and discussed in more detail in chapter 2, section 2.5.

The above diagnostic tests allow identification and classification of sleep related apnoeas and hypopnoeas. An apnoea is defined as a complete cessation of airflow lasting for at least 10 seconds. Apnoeas are further classified as obstructive, central or mixed based on whether there is respiratory effort during the event. A hypopnoea is defined as a reduction in airflow. The criteria used for scoring apnoeas and hypopnoeas will be discussed in greater detail in chapter 2, section 2.5.2. The average number of apnoeas and hypopnoea per hour of sleep is defined as the apnoea hypopnoea index (AHI). The amount of nocturnal intermittent hypoxia can be expressed as the oxygen desaturation index (ODI) and the extent of the sleep fragmentation can be expressed as the arousal frequency or index. These variables will be used throughout this thesis to describe disease severity in combination with self-reported symptoms, and also used to monitor response to treatment.

1.2 The pathophysiology of Obstructive sleep apnoea

In young healthy individuals sleep onset is associated with a 10-15% reduction in ventilation (Stradling, Chadwick et al. 1985) due in part to a removal of the wakefulness drive to breath and a reduction in chemosensitivity (Morrell, Harty et al. 1996). This sleep-related reduction in ventilation enables $PaC0_2$ to rise above the hypocapnic apnoeic threshold which stabilise breathing during sleep (Berssenbrugge, Dempsey et al. 1983). The reduction in ventilation during sleep is augmented in some people by increasing pharyngeal narrowing.

The patency of pharyngeal airway is maintained by dilator muscles that are activated during inspiration, (Jordan, McSharry et al. 2014). During sleep all muscle tone decreases including the muscle tone in the dilator muscles, this contributes to airway narrowing. The collapsibility of the pharyngeal airway in selected individuals is determined by the transmural pressure across the airway lumen, which in turn is influenced by the extra-luminal pressure. Many factors can increase extra-luminal pressure by increasing the surrounding soft tissues (Schwab, Pasirstein et al. 2003) such as obesity, tonsillar hypertrophy, endocrine disorders such as hypothyroidism, acromegaly, polycytic ovary syndrome, mucopolysaccharidoses or normal physiological changes that occur in pregnancy or menopause. The impact of obesity is discussed in more detail in the next section.

1.2.1 The impact of obesity on the aetiology of Obstructive sleep apnoea

Obesity is the most established risk factor for the development of OSA. Community based observational cohort studies have shown that excess body weight is uniformly associated with a graded increase in OSA prevalence (Bearpark, Elliott et al. 1995, Duran 2001, Ip 2001, Kim, In et al. 2004, Udwadia, Doshi et al. 2004). Additionally longitudinal studies have shown weight gain and loss influenced the severity of OSA (Young 1993) and studies on weight loss treatment also supports these findings (Fritscher, Canani et al. 2007, Grunstein, Stenlof et al. 2007). Other inter-related markers of obesity such as neck or waist circumference have also been shown to be independently associated with OSA severity (Davies, Ali et al. 1992, Young, Shahar et al. 2002).

Mechanisms by which increased body weight contributes to the pathogenesis of OSA include (Dempsey 2010):-

1) Increased phayngeal fat deposits and subsequent narrowing of the pharyngeal airway
2) Reduced lung volumes by a combination of increased abdominal fat and recumbent posture
3) Impairment of the Leptin signalling pathway
4) The possibility of pro-inflammatory cytokines derived from visceral adipose impacting on sleep or inflammatory responses in upper airway tissues

However, the association with obesity is less clear in older people (Young, Shahar et al. 2002). Older OSA patients typically have a lower body mass index and neck circumference, compared to younger patients with similar disease severity (Chung, Yoon et al. 2009) as described in the next section. The impact of obesity on the prevalence of OSA is discussed in section 1.4.1.

1.2.2 The impact of age on the aetiology of Obstructive sleep apnoea

The prevalence of OSA increases with age, which will be discussed later in (section 1.4.2. The mechanisms proposed for this age-related increase in prevalence include:-

1) **A reduction in pharyngeal muscle function**. Functionally, the response of the genioglossus muscle to negative pressure applied during wakefulness (Horner, Innes et al. 1991) and sleep (Horner, Innes et al. 1994, Eikermann, Jordan et al. 2007) is reduced in older people. Additional the upper airway reflex sensitivity (Erskine, Murphy et al. 1993) and the genioglossus response to hypoxia (Klawe and Tafil-Klawe 2003) but not hypercapnia (Browne, Adams et al. 2003) are also reduced in older people. Overall these changes result in reduced upper airway muscle function at sleep onset (Worsnop, Kay et al. 2000) and a more collapsible upper airway (Kirkness, Schwartz et al. 2008) with the critical closing pressure being -8.3 (2.3) cmH20 in older people, compared to -16.0 (6.9) cmH20 in younger people, independent of body mass index (Eikermann, Jordan et al. 2007). In healthy elderly people pharyngeal resistance during sleep is increased compared to that in younger people indicating a possible age-related predisposition to airway collapse (Worsnop, Kay et al. 2000, Browne, Adams et al. 2001, Eikermann, Jordan et al. 2007).
2) **Age-related differences in pharyngeal morphology**. A decrease in the size of the upper airway lumen in older people (Martin, Mathur et al. 1997, Carlisle, Carthy et al. 2014), associated with an age-related lengthening of the pharyngeal airway in both men (Shigeta, Ogawa et al. 2008) and women (Malhotra, Huang et al. 2006) and a descent of the hyoid bone (Pae, Quas et al. 2008) particularly in individual with long faces (Kollias and Krogstad 1999) which leads to increased airway resistance and a predisposition to airway collapse.
3) **The central control of breathing** is relatively stable in older people (Wellman, Malhotra et al. 2007), although arousal frequency increases with age (Mathur and Douglas 1995, Boselli, Parrino et al. 1998, Browne, Adams et al. 2003). Arousal from sleep leads to hyperventilation and relative hypocapnia, which can promote respiratory instability and periodic breathing during the subsequent period of sleep onset. A

tight correlation between fluctuation in the electroencephalogram frequency and breathing patterns in older people appears to support this notion (Pack and Millman 1986).

4) **The prevalence of co-morbidities** increases with age. . It is estimated that up to 50% of patients with mild symptomatic chronic heart failure will have sleep-related breathing disorders (Vazir, Hastings et al. 2007).

Taken together these factors suggest an anatomical and physiological predisposition for developing OSA with increasing age.

1.3 Symptoms of Obstructive sleep apnoea syndrome

The most common symptoms OSAS is excessive day time sleepiness. Patients awake in the morning feeling tired and unrefreshed regardless of their sleep duration. Other symptoms commonly reported include loud snoring, also reported by bed partners, witnessed episodes of gasping or choking, shortness of breath sensations during sleep and frequent movements that disrupt sleep. Less common symptoms include morning headaches, enuresis, reduced libido, nocturnal sweating and partner worried by apnoeic episodes. Rare symptoms such as recurrent arousals, insomnia and nocturnal cough are also reported. All the above symptoms will adversely affect quality of life and may also disrupt the bed partner's sleep. The most recent systematic review of the literature examining the accuracy of diagnosing obstructive sleep apnoea found that the most useful symptom for identifying patients with obstructive sleep apnoea was nocturnal choking or gasping. Snoring although common in OSA patients was not useful for establishing the diagnosis as it is not specific for OSA (Myers, Mrkobrada et al. 2013).

Several clinical prediction models have been used in the diagnosis of OSAS most based on BMI and male gender. In a study by Rowley the sensitivity, specificity and positive predict value of each model was tested on 370 patients (191 men 179 women). The sensitivities ranged from 33%-39%, specificities from 87%-93%, and positive predictive values from 72%-85%. The authors concluded none of the clinical prediction models tested were sufficiently accurate to discriminate between patients with or without OSAS, and there were disparities in groups such as women, non-obese and elderly.(Rowley, Aboussouan et al. 2000). Hence a diagnostic test is also required to confirm the diagnosis and inform treatment choices. The diagnostic tests will be described and discussed in the general methods chapter 2, section 2.5.

1.3.1 Symptoms of Obstructive sleep apnoea in older people

In the early 1990s there was an emerging expert opinion that OSA was a distinct condition in the elderly (Levy, Pepin et al. 1996). This was fuelled by the increased prevalence of objectively measured OSA in this population but with an apparent mismatch in symptomology. The view has largely been superseded (Launois, Pepin et al. 2007), although it is recognised the disease phenotype may be more variable in older people. Older people report different levels of sleepiness (Chung, Yoon et al. 2009) and rate their health differently for the same level of OSA severity compared to younger populations (Morrell, Finn et al. 2012). This may be because older people have become habituated to the reduction in sleep quality that occurs as part of the normal aging process which will be discussed in more detail in section 1.5, subsequently older people may not experience the same degree of excessive 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. Additionally with increasing age the prevalence of sleep disturbing co-morbidities (Gagnon, Bedard et al. 2002) and subsequent polypharmacy contributing to excessive daytime sleepiness (Willcox, Himmelstein et al. 1994) increase. Specifically nocturia may disturb sleep, and there is some suggestion that OSA exacerbates nocturia (Bloom, Ahmed et al. 2009, Bing, Jennum et al. 2012). Taken together these factors could modify daytime sleepiness and obscure the interpretation of possible symptoms related to OSA. Therefore, although excessive sleepiness, regardless of its cause is associated with increased all-cause mortality in older people (Empana, Dauvilliers et al. 2009) the proportion of sleepiness that is due to OSA in older people, and hence could be modified by treatment, is unknown. Equally it cannot be assumed that older people with OSA suffer from the same functional consequences as those in younger populations.

1.4 Prevalence and Incident of Obstructive sleep apnoea

1.4.1 The prevalence of Obstructive sleep apnoea in the general population

In the early 1990s one of first methodologically robust study of the prevalence of OSA in the general population was published (Young 1993). The Wisconsin Sleep Cohort, found an apnoea hypopnoea index (AHI) >5 events/hr of sleep to be present in 24% for men and 9% for women. When the symptom of excessive daytime sleepiness was included 4% of men and 2% of women met the diagnostic criteria for OSAS. Around the same time in the UK a similar study of middle aged men suggested a more conservative figure of 0.03% (Stradling 1996). The author proposed this difference could be explained by the higher prevalence of obesity in the USA. As discussed earlier (section 1.2.1) obesity is the largest risk factor for OSA. Subsequently there have been numerous prevalence studies in general populations throughout the world which have been summarised in Table 1. The most recent estimates from the Wisconsin sleep cohort predict that up to 14% of males and 5% of females have OSAS (Jennum and Riha 2009, Peppard, Young et al. 2013) This represents a substantial increase in the last two decades, in part due to the increasing prevalence of obesity (Flegal, Carroll et al. 2010) (the incidence of OSA is discussed in section 1.4.3).

The prevalence studies in Table 1 were performed in different geographical regions and reflect ethnic diversity; however, despite this we see that studies of similar design and methodology produce comparable prevalence rates of OSA. Furthermore when the Asian studies are compared against the Western countries the prevalence is similar despite the lower BMI in Asian studies. This is thought to be due to non-obesity related risk factors such as the variation in craniofacial morphology between different ethnic groups.

In summary, although the prevalence of OSA is influenced by the population studied, the diagnostic criteria applied and methodology used, similarly designed studies report the prevalence of OSAS in predominately white general populations as 3-7% for middle aged men and 2-3% for middle aged women. Furthermore as the prevalence of obesity continues to increase in both developed and non-developed nations this will be intrinsically linked to the increasing prevalence of OSA.

Table 1.1 Prevalence studies of obstructive sleep apnoea based in the general population

Study region (Author, Year)	Subjects	Age (Years)	AHI ≥ 5	AHI ≥15	OSAS	Methodology
Wisconsin, USA (Young 1993)	M: 352 W: 250	30-60	M: 24% W: 9%	M: 9% W: 4%	M: 4% W: 2%	Supervised NPSG
Australia (Bearpark, Elliott et al. 1995)	M: 294	40-65	NA	M: 10%	M: 3.1%	Home nasal flow and oximetry
Pennsylvania, USA (Bixler 1998, Bixler 2001)	M: 741 W: 1000	20-100	M: 17% W: 5%	M: 7% W: 2%	M: 3.3% W: 1.2%	Supervised NPSG
Spain (Duran, Esnaola et al. 2001)	M: 325 W: 235	30-70	M: 26% W: 28%	M: 14% W: 7%	M: 3.4% W: 3%	Supervised NPSG
Hong Kong, China (Ip 2001, Ip 2004)	M: 154 W: 106	30-60	M: 8.8% W: 3.7%	M: 5.3% W: 1.2%	M: 4.1% W: 2.1%	Supervised NPSG
Korea (Kim, In et al. 2004)	M: 309 W: 148	40-69	M: 27% W: 16%	M: 10.1% W: 4.7%	M: 4.5% W: 3.2%	Supervised or Home NPSG
India (Udwadia, Doshi et al. 2004)	M: 250	30-60	M: 19.5%	M: 8.4%	M: 7.5%	Home NPSG
India (Sharma 2006)	M:88 W:63	30-60	M: 19.7% W: 7.4%	NA	M: 4.9% W: 2.1%	Supervised NPSG
Brazil (Tufik, Santos-Silva et al. 2010)	M:466 W:576	20-80	M: 21.7% W: 20.9%	M: 24.8% W: 9.6%	M: 40.6% W:26.1%	Supervised NPSG
Australia (Simpson, Hillman et al. 2012)	M:381 W: 412	38-70	NA	M: 12.4% W :5.7%	NA	Nasal flow and Oximetry

AHI: Apnoea-hypopnea index; M: men; W: women; NA: Not applicable; NPSG: Nocturnal polysomnography, OSAS: Obstructive sleep apnoea syndrome defined as: AHI ≥5 and excessive daytime sleepiness.

1.4.2 The prevalence of Obstructive sleep apnoea in older people

Currently the quoted prevalence of OSA in older people in the general population over the age of 65 can vary from 20 to 40%, as this is a large variation in prevalence a more conservative estimate would suggest that the prevalence is at least double that seen in younger age groups (Ancoli-Israel, Klauber et al. 1995, Young, Peppard et al. 2002). Studies also demonstrate the prevalence steadily increased with advancing age with a plateau between 60 and 65 years of age (Ancoli-Israel, Gehrman et al. 2001). In a study that used similar criteria to define OSAS (AHI>10 events/hr with the symptom of excessive daytime sleepiness) OSAS was present at 3.2%, 11.3% and 18.1% in the 20 - 44, 45 - 64, 61 - 100 year age groups respectively (Bixler 1998). This trend was also seen in women although the gender difference was less apparent after menopause. These finding were also mirrored in the more recent study by (Duran 2001). Table 1.2 summarise the prevalence studies in older people.

Although there is a clear consensus in the literature that the prevalence is significantly increased in older people the estimates vary considerably. As discussed earlier some of this wide variation can be explained by the differences in the definition of the disease, the diagnostic threshold being used and the heterogeneity of the population studied e.g. healthy community dwelling individuals vs. nursing home residents with co-morbidity. This higher prevalence of OSA in older people has led to debate regarding the potential mechanisms, clinical significance and consequences in the older population. (Levy, Pepin et al. 1996).

Table 1.2 Prevalence of obstructive sleep apnoea in older people

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

OSA: obstructive sleep apnoea, AHI: apnoea-hypopnoea index. Table adapted from Glasser *et al.* 2011.

1.4.3 The incidence of Obstructive sleep apnoea in the general population

In contrast to the large number of cross-sectional studies examining the prevalence of OSA, there are only three longitudinal observational cohort studies that can evaluate the incidence of OSA namely the Wisconsin Sleep Cohort Study (Peppard, Young et al. 2000), the Sleep Heart Health Study (Newman, Foster et al. 2005) and the Cleveland Family study.(Tishler, Larkin et al. 2003) One of the difficulties of cross sectional observational studies is they cannot quantify incidence; these longitudinal observational cohort studies have addressed this.

In the Sleep Heart Health Study, the incidence rate for those with an AHI <5 events/hr developing an AHI ≥15 events/hr) in a community sample of middle aged men and women over a 5 year period was 11.1% and 4.9% respectively. The authors went on to demonstrate there is a direct relationship between OSA and obesity. . The Cleveland Family study also confirmed the incidence of OSA was independently determined by body weight, age and sex and the influence of body weight and sex diminished with increasing age with men and women being at equal risk after the age of 50. It is also worth noting longitudinal changes in AHI were nonlinear in respect to age and body weight, with older overweight and obese men experiencing the greatest rise in disease severity. This is also summarised in the review by (Lee, Nagubadi et al. 2008).

1.5 Sleep in healthy older people

Sleep patterns vary greatly with age. Older people report that they experience difficulty falling asleep and maintaining sleep, with frequent nocturnal awakenings, as well as early morning awakening (Cajochen, Munch et al. 2006) Sleep becomes more fragmented with age, independent of OSA (Mathur and Douglas 1995, Browne, Adams et al. 2003). (Boselli, Parrino et al. 1998) has shown the number of arousals per hour of sleep in older people (60 years and older) can be almost double that which occurs in younger people (see Figure 1.1). This may be a consequence of disruption to neural systems regulating sleep, and or lower thresholds to arousal inducing external stimuli. Interestingly, although older adults experience more awakening during the sleep period, they do not seem to have any more problems returning to sleep once awake, compared to younger adults (Klerman *et al* 2004). Age also influences diurnal preference as amorning preference appears to increase with age (Taillard, Philip et al. 2004), this may be due to changing work schedules or variation in social activities, as well as changes in the circadian and physiological requirements for sleep (Dijk, Duffy et al. 1999).

Sleep architecture also deteriorates with age with a loss of deep sleep which may be a consequence of cortical degeneration, disrupting synchronisation of neuronal activation and reducing the amplitude of delta waves detected on the EEG recordings (Dijk, Beersma et al. 1989). An increase in the lighter sleep partially compensates for the loss of deep sleep (Van Cauter, Leproult et al. 2000), although there is a reduction in the number of sleep spindles and K complexes within the EEG. In contrast, the duration of REM sleep tends to remain constant throughout adulthood (Landolt, Dijk et al. 1996), although a reduction in the proportion of REM sleep has been reported by

others (Van Cauter, Leproult et al. 2000). These contrasting results may reflect the increased inter-individual variability in sleep characteristics in older adults.

Many factors may contribute to poor sleep in older people. The predominant causes of sleep loss seem to change with age. The most common primary sleep disorders in the elderly are insomnia, Sleep Disordered Breathing, REM sleep behaviour disorder; Restless Legs Syndrome and Periodic Limb Movements. In addition the prevalence of other causes of sleepiness such as co-morbidity subsequent polypharmacy, loss of physical activity and iatrogenic sleep disruption increase with age.

Figure 1.1

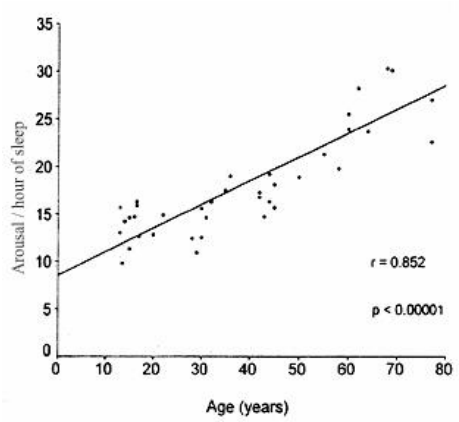


Figure 1.1: The influence of age on the number of arousals (awakenings ≥ 3 seconds) per hour of sleep. Taken from (Boselli, Parrino et al. 1998)

1.6 Consequences of Obstructive sleep apnoea

1.6.1 Cardiovascular disease

In the 1980s an association between cardiovascular diseases, severe OSA and increased mortality was recognized. Both animal and human physiological studies identified biologically plausible mechanisms whereby OSA could cause cardiovascular injury including increased sympathetic nervous system activity, hypoxic and oxidative stress, systemic inflammation, and mechanical factors secondary to intrathoracic pressure oscillations such as reduced left ventricular stroke volume, systemic arterial pressure, cardiac output and heart rate (Somers, White et al. 2008, Drager, Polotsky et al. 2011).

Early studies in people with severe OSA have shown a 3-fold increased likelihood of developing hypertension over 4 years, independent of other risk factors (Nieto, Young et al. 2000, Peppard, Young et al. 2000). Additionally randomised CPAP treatment trials in patients with severe OSAS produced a 2-3 mmHg reduction in blood pressure (Haentjens, Van Meerhaeghe et al. 2007, McDaid, Griffin et al. 2009, Montesi, Edwards et al. 2012) sufficient to

reduce vascular risk by about 20% (Faccenda, Mackay et al. 2001, Pepperell, Maskell et al. 2003, McDaid, Griffin et al. 2008).

Subsequently the cardiovascular impact of OSAS has been established, predominantly using community based epidemiological studies to show that people with untreated severe OSAS have an increased incidence of coronary heart disease (Punjabi, Caffo et al. 2009), myocardial infarction, heart failure (Gottlieb, Yenokyan et al. 2010), stroke (Yaggi, Concato et al. 2005, Redline 2010) and mortality after adjusting for established cardiovascular disease risk factors (Marshall, Wong et al. 2008, Young, Finn et al. 2008). In addition evidence from other smaller, single-centre randomized clinical trials which studied intermediate or cardiovascular risk factors such as blood pressure (Nieto, Young et al. 2000), glucose tolerance, insulin resistance, measures of atherosclerosis and left ventricular ejection fraction were also supportive.

Observational studies comparing OSAS patients treated with CPAP versus those not treated with CPAP found elevated cardiovascular risk in those with untreated OSAS (Peker, Hedner et al. 2002, Milleron, Pilliere et al. 2004, Marin, Agusti et al. 2012) and mortality (Marin, Carrizo et al. 2005). Although those who did not use treatment were self-selected as they had refused or were non-compliant with CPAP therapy, raising the possibility that the increased cardiovascular risk was related to other factors which are associated with non-compliance such as or adverse risk behaviour. Observational cohort data has also shown in patients with congestive heart failure, untreated OSA was associated with an increased mortality independent of confounding factors (Wang, Parker et al. 2007).

Whether or not to target treatment of OSA in patients who do not report excessive daytimes sleepiness is controversial, with some arguing that OSA should be treated even in subjects without daytime symptoms due to elevated cardiovascular risks (Levy, Pepin et al. 2002). In a long term observational cohort study (Young, Finn et al. 2008) OSA with and without sleepiness was equally predictive of cardiovascular mortality. The most recent multi-centre RCT of CPAP on cardiovascular risk (Craig, Kohler et al. 2012) demonstrated no reduction in cardiovascular risk in minimally symptomatic OSA patients although improvements in sleepiness.

In summary, the data supporting the association of OSAS with cardiovascular risk are sufficiently compelling, more importantly the magnitude of the potential public health risk is sufficiently great, although to date there remains uncertainty in the value of treating minimally or non-sleepy patients as the field has not effectively demonstrated that treatment in the form of CPAP therapy has reduced or prevented cardiovascular morbidity or mortality. In addition cardiovascular clinical trials would require large numbers of patients treated for a period of years to accrue a sufficient number of disease end points for meaningful analysis. There is currently an on going trial - SAVE - Sleep Apnea Cardiovascular End-points Study, which has been designed to address some of these questions.

With respect to the cardiovascular impact of OSA in older people the data is less clear. There are limited studies on the long term consequences and epidemiologic studies have shown inconsistent associations of OSA with cardiovascular risk factors across age and gender groups. The Sleep Heart Health Study (SHHS) (Newman, Nieto et al. 2001) observational cohort showed that cardiovascular risk factors were more likely to be elevated in the younger (aged <65 years) than older participants.. Although a recent prospective cohort by the Spanish group (Martinez-Garcia, Campos-Rodriguez et al. 2012) followed 939 older patients ≥ 65 years of age for 69 months.

They found patients with untreated severe OSA had increased all cause and cardiovascular mortality. The cohort was further divided into group's dependent on upon OSA severity and whether they did or did not use CPAP. Patient with severe OSA AHI >30/hr who were not treated with CPAP had the highest risk of mortality, while patients with severe OSA who were treated with CPAP had a risk of mortality similar to the group with an AHI <15/hr.

There are major differences between the SHHS and the Spanish cohort study that could explain the different findings. In particular, the SHHS did not classify whether patients were receiving treatment and followed a large cohort of patients throughout the age range. The Spanish study, only included older patients and in addition those who did not use treatment were self-selected as they had refused or were non-compliant with CPAP therapy. This highlights the inherent bias of observational cohort studies as the increased cardiovascular risk may be related to other factors which are associated with non-compliance such as non-compliance with medication, advice or adverse risk behaviour. Likewise observational cohorts will always have a survival bias; older people with OSAS who have survived into older age may be different in some way to younger people with OSAS. Alternately, studies in older people with OSA may be selecting those that have developed OSA later in life and hence a different pathophysiological mechanism.

In addition a further study by (Haas, Foster et al. 2005) in older people with OSA showed the risk of having hypertension is no greater than for older people without the disorder, this may be in part explained by the finding that older people have a reduced acute cardiovascular response to arousal from sleep compared to young people (Goff, O'Driscoll et al. 2008). Thus the poorer cardiovascular reactivity of older adults may paradoxically reduce the impact of arousal from sleep which may be a protective response.

In summary: although the vascular risk benefits from treating OSA may be larger in older people, since the higher cardiovascular event rate in the older people implies that more events could be prevented per unit change in risk, the actual magnitude risk reduction may be less, furthermore some sources propose that OSA in older people may actually be an adaptive response to possible future fatal or sub-fatal cardiac events.

1.6.2 Cerebral vascular disease

Observational cohort studies within the general population as discussed above in section 1.6.1 have also shown an increased risk of stroke (Redline 2010). Although it has been difficult to determine whether OSA preceded the stroke or was independent of the confounding risk factors of age, sex, smoking, body mass index, diabetes mellitus and cardiovascular disease.

(Arzt, Young et al. 2005) performed a longitudinal analysis of OSA and stroke risk and found moderate to severe OSA (AHI ≥20) was associated with increased risk of stroke, whereas no increased risk was observed in patients with mild SDB. In this study the increased risk of stroke appeared to be partially independent of hypertension but confounded by obesity. (Yaggi, Concato et al. 2005) also reported an increased incidence of stroke, including transient ischemic attacks or death from any cause in patients with pre-existing OSA and showed a relationship between OSA severity and risk independent of confounding factors although reported the combined outcome measure of stroke or death and so difficult to ascertain the contribution of each.

There is one population based cohort study in older patients mean age 77 years (Munoz, Duran-Cantolla et al. 2006) this study suggested that severe OSA (AHI ≥30) increased the risk of ischaemic stroke independent of known co-founding factors.

Another interesting study by (Minoguchi, Yokoe et al. 2007) who used brain MRI to compare the percentage of silent brain infarcts in subjects with and without OSA showed, 25% of the individuals with severe OSA had silent infarcts in contrast to 7% of the obese matched normal controls. In support of a direct relationship, the group measured two serum markers for cerebrovascular disease, sCD40L and P-selectin. Both of these markers were higher in OSA group and declined upon effective treatment with nasal CPAP.

In summary, the data supports an association of OSAS with cerebral vascular disease, although to date the field has not effectively demonstrated that treatment in the form of CPAP has reduced or prevented cerebral vascular disease morbidity or mortality. There is currently an on going trial Sleep Tight: Sleep Apnea in TIA/Stroke: Reducing Cardiovascular Risk with Positive Airway Pressure which has been designed to evaluate the impact on CPAP on cerebral vascular disease in high risk vascular patients with OSA.

1.6.3 Metabolic

OSA is associated with obesity as discussed previously in section 1.2.1. Observational cohort studies have found that OSA is associated with insulin resistance, which is correlated with the severity of OSA but independent of general obesity (Ip, Lam et al. 2002, Punjabi, Sorkin et al. 2002). It is postulated that insulin resistance in OSA is due to, not only to visceral or central obesity but also to increased sympathetic drive from frequent arousals, intermittent hypoxia and sleep fragmentation (Punjabi, Shahar et al. 2004, Spiegel, Tasali et al. 2009). The metabolic response to CPAP treatment has been more variable in a RCT by (West, Nicoll et al. 2007) 3 months of CPAP treatment in men with type 2 diabetes and newly diagnosed OSA did not show any significant improvements in glycaemic control or insulin resistance although showed improvements in subjective and objective sleepiness and sleep apnoea quality of life scores. Other metabolic parameter have also been studied by Sharma (Sharma, Agrawal et al. 2011) likewise in a RCT demonstrated that 3 months of CPAP treatment reduced blood pressure in line with other studies, blood lipid levels (triglycerides, low density lipoproteins, non-high density lipoproteins and total cholesterol) and the frequency of metabolic syndrome. The study was a cross-over design with 90 patients randomised to receive either 3 months of CPAP or sham-CPAP treatment, separated with a one month washout period. The duration of the washout period is of concern if the components of the metabolic syndrome did not return to baseline before the start of the subsequent intervention and the study has subsequently been retracted due to issues with data. The impact of OSA on Triglycerides as a marker of cardiovascular disease has also been evaluated in a RCT (Phillips, Yee et al. 2011) following 2 months of CPAP triglyceride and cholesterol levels were lower in OSA patients treated CPAP, which may in turn reduce cardiovascular risk.

In summary RCT trials do not support the use of CPAP treatment solely for the treatment of metabolic syndrome.

1.6.4 Quality of Life, mood and functionality including driving.

OSAS patients are more likely to experience mood changes (McCall, Harding et al. 2006, Douglas, Young et al. 2013) and reduced quality of life (Baldwin, Griffith et al. 2001, Moyer 2001) which is often attributed to reduced social functioning and vitality (Jenkinson, Stradling et al. 1997). Daytime sleepiness impairs function and increases accident risk (Teran-Santos, Jimenez-Gomez et al. 1999, Masa, Rubio et al. 2000), with OSAS patients being 2-4 times more likely to have road traffic accidents as a result of reduced alertness while driving (George 2001, George, Findley et al. 2002, George 2004).. There have been four systematic reviews of observational studies examining the risk of road traffic accidents in OSA patients and the impact of CPAP therapy (Ellen, Marshall et al. 2006, Tregear, Reston et al. 2009, Tregear, Reston et al. 2010, Antonopoulos, Sergentanis et al. 2011).. These meta-analyses demonstrated a sizeable protective effect of CPAP on road traffic accidents both in real life and virtual environments. Although all of the studies included in these reviews evaluated the risk of road traffic accidents in patients whose average age was below 60 years. Additionally it should be considered that RCTs are unlikely to capture reductions in the rate of road traffic accidents given their infrequency. For example, the number of road traffic accidents in drivers aged 60-69 years was 14,249 or 6.96% in 2012. (Department for Transport 2012)

1.6.5 Cognitive function

As already discussed earlier in section 1.1.1, OSAS is characterised by chronically fragmented sleep and daytime somnolence both factors of which are thought to contribute to cognitive dysfunction, although the relative contributions of each remains poorly understood. More recently chronic intermittent hypoxia (the hall mark of OSA) has been proposed as a third factor contributing to hypoxic-induced neural injury and increasingly the research in this field has concentrated on this area.

Cognitive dysfunction is frequently recognised in patients with OSAS (Engleman and Joffe 1999, Twigg, Papaioannou et al. 2010, Kushida, Nichols et al. 2012, Wallace and Bucks 2013) and has been studied since the 1980's although the pathogenesis, sequel and clinical presentation remain hotly debated. (Gozal 2013, Rosenzweig, Williams et al. 2013). Cognitive function will be discussed separately in chapter 4 section 3.

1.7 Overview of treatment in patients with OSAS

Treatments for OSAS include advice on modifying lifestyle (weight loss, stopping smoking, and increasing cardiovascular exercise), improving sleep opportunity and environment, optimising medical management of co-morbidities, positional measures, use of stimulants such as caffeine, oral mandibular advance devices, surgery and airway pressure (positive airway pressure, oral negative pressure and end-expiratory pressure).

The section will summarise the evidence for positive airway therapy as it is considered the mainstay treatment for patients with moderate to severe OSAS. The mechanism by how positive airway pressure is delivered and works will be discussed in the general methods chapter 2, section 2.2.1. Positive airway pressure has several variants including continuous positive airway pressure (CPAP), autotitrating CPAP (auto-CPAP), compensated pressure waveform, and expiratory pressure relief. Bilevel and adaptive seroventilation will not be discussed as although

may be used in the treatment of OSAS these modes are considered a form of ventilation and to date there is no evidence in the non hypercapnic patient (Gay, Herold et al. 2003). The majority of the literature is based around the use of CPAP and auto-CPAP. Multiple systematic reviews and meta-analyses of RCT have assessed the efficacy of CPAP therapy in OSAS and summarized in the following guidelines Australian NHMRC 2000 (publication rescinded) Cochrane database systematic review (Giles, Lasserson et al. 2006) and Scottish intercollegiate Guidelines Network (SIGN) 2003. The most recent and relevant to the NHS being The National Institute of Clinical Excellence (NICE) Health Technology assessment systematic review and economic analysis of continuous positive airway pressure devices for the treatment of OSAS (McDaid, Griffin et al. 2009). These reviews support the use of CPAP as the evidence-based treatment of choice for moderate to severe OSAS in middle-aged patients.

The therapeutic benefit of CPAP is typically measured as an improvement in sleepiness. Using the Epworth Sleepiness Scale (ESS) (see Section 2.3.2 for detailed description) as a measure of subjective sleepiness, the mean difference between patients treated with CPAP versus conservative (or placebo) treatment is a reduction of 2.7 points (95% CI interval -3.45 to -1.96), the magnitude of change is greater in patients with severe symptoms (mean difference in ESS -5.0, 95% CI -3.0 to -1.6) (McDaid, Griffin et al. 2009). These results are also in keeping with earlier meta-analysis by (Patel, White et al. 2003) which showed CPAP reduced the ESS an average of 2.9 points more than did placebo, additionally patient with moderate to severe OSAS had a greater fall in ESS than did those with mild OSAS.

Not only is CPAP efficacious it was also deemed to be cost effective treatment for moderate to severe OSA in well-defined middle aged populations. The cost of CPAP therapy is approximately £4,000 per quality adjusted life year (QALY) gained; allowing for changes in sleepiness, quality of life, vascular risk, driving performance and CPAP equipment costs (McDaid, Griffin et al. 2009, Weatherly, Griffin et al. 2009).

There are some caveats to this extensive review. It identified the majority of studies investigating the effect of CPAP treatment had enrolled patients between 44 and 58 year of age and 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 co-morbidity complicates assessment would be beneficial'* (McDaid, Griffin et al. 2009).

A systematic literature review of the clinical effectiveness of CPAP therapy in older people was conducted in preparation for the studies presented in this thesis. Randomised controlled trials (RCTs) assessing the efficacy of CPAP treatment in OSAS, with an average age of 60 years or older and the capacity to give informed consent identified only three studied from a possible 3,560 titles from January 2006 to April 2012. The previous Health Technology assessment (HTA) report (McDaid, Griffin et al. 2009) included studies up to 2006.

These studies included patients with cardiovascular conditions and compared CPAP therapy with sham-CPAP (Egea, Aizpuru et al. 2008) or no CPAP (Ruttanaumpawan, Gilman et al. 2008, Parra, Sanchez-Armengol et al. 2011) for OSAS. None of the studies were conducted in the UK or in a secondary care setting. Furthermore they did not assess daytime sleepiness or collect generic measures of health care usage. The primary outcome was left ventricular ejection fraction in Egea et al, baroreflex sensitivity in Ruttanaumpawan et al and a number of neurological, quality of life, sleep-related, and mortality outcomes in Parra et al. Two studies reported blood

pressure at baseline and at follow-up (Egea et al; Ruttanaumpawan et al); 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, no statistically significant differences were found in blood pressure. In the Ruttanaumpawan et al study, the reduction in average systolic blood pressure at 1 month was statistically significant but not the reduction in average diastolic blood pressure.

Overall the results of these three studies are difficult to generalise given their focus in patients with concomitant cardiovascular disease. Egea et al and Ruttanaumpawan et al included only patients with chronic heart failure and Parra et al included only patients who had had an ischaemic stroke.

In summary, 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. Additionally, it cannot be assumed the benefits of CPAP treatment in younger populations will be replicated in older people by the same magnitude or even at all.

1.7.1 Adherence to CPAP

OSA can be treated effectively with CPAP, but it is often a lifelong condition. Current guidelines recommend that CPAP be used during the total time in bed, although the minimum threshold compliance level for improving outcomes has not been established. It is recognised there is a gap between actual and recommended use.

When adherence to CPAP treatment is defined as greater than 4 hours a night, studies report estimates of non-adherence between 29% to 83% (Weaver and Grunstein 2008). A summary of predictors of poor CPAP adherence include (Sawyer, Gooneratne et al. 2011):-

- Patient characteristics– increase nasal resistance, depression
- Disease characteristics - either severe of mild minimally symptomatic disease
- Psychological or social – less self-efficacy, poor social support, limited disease or treatment knowledge
- Technical - lack of heated humidification and flexible pressure

Studies addressing adherence should ideally assess the long-term compliance of CPAP as the cost-effectiveness of CPAP is largely dependent on adherence over years as opposed to months.

Four published studies were found which reported the percentage of patients with OSAS who continued using their fixed pressure CPAP device over various periods: 68% over 60 months, (McArdle, Devereux et al. 1999) 85% over 84 months (Krieger *et al* 1996) 80% over an unspecified period (Marquez-Baez et al 1998) 72% over 24 months (Findley et al 2000). The average of these four studies reported that the percentage of patients who continued using their CPAP device fell from 84% at the end of the first year to 68% after 4 years, remaining at this level for a further 3 years. This equates to a discontinuation rate of 5% per annum over 4 years. Similarly, Krieger et al reported that the percentage of patients who continued using their CPAP device fell from 90% after 3 years to 85% after 7 years, equivalent to a discontinuation rate of 1% per annum over 4 years.

However there is limited information on the adherence to CPAP treatment in older people. A recent systematic review on adherence to CPAP identified 3 studies in older people (Sawyer, Gooneratne et al. 2011). These three studies evaluated compliance with CPAP use in patients with an average age of 65 years and over; Russo-Magno et al 2001 in patients with an average age of 73 years. Bravata et al in patients with an average age of 66 years and Woehrle et al presented subgroup analysis in patients 60 to 70 years and patients 70 years of age and older (Russo-Magno, O'Brien et al. 2001, Bravata, Concato et al. 2010, Woehrle, Graml et al. 2011). However, none of the three studies reported the proportion of patients using CPAP at specified time points from treatment initiation but suggested that CPAP compliance is similar in older and younger OSA patients. Finally it is not unusual for patients to comply more under observation, both when in hospital or in a research study.

1.8 Aims of thesis

The aim of this thesis was to investigate the effectiveness of CPAP therapy in older people (greater than 65 years) with OSAS. In chapter 3 the clinical efficacy of CPAP was measured by assessing the impact of 3 and then 12 months of CPAP treatment on excessive daytime sleepiness in a symptomatic UK population referred for diagnosis and further management by primary care physicians. Various other clinical measurements and outcomes including the cost effectiveness of treatment were also assessed. The cost effectiveness analysis was completed by the Centre for health economics, University of York and hence only a summary of the main results will be reported in the context of a clinical trial.

In chapter 4, a group of older people with minimally symptomatic OSAS were investigated to determine the impact of CPAP on cognitive function and brain morphology. Cognitive function and Brain MRI imaging were measured before and after 6 months of CPAP therapy. The MRI imaging is currently being analysed and hence will not be reported in this thesis. The aim of this study was to test the hypothesis that older patients with OSA have cognitive impairment and corresponding brain changes independent of excessive daytime sleepiness which would be modifiable with treatment.

The overall aim of these studies presented in this thesis was to determine if CPAP therapy is as effective in older people as it is in middle aged people with OSAS.

Chapter 2: General methods

2.1 Study Design

The two studies presented in this thesis are randomised, parallel, and single blinded controlled trials. Recruitment to the PREDICT trial started on the 01/02/2010 and the Brain MRI study on the 01/01/2012. The design of the trials was similar but distinct, further details of specific trial design will be discussed in the relevant chapters. The PREDICT trial was a multicentre trial delivered by 14 centres in the UK (chapter 3). The Brain MRI study was a single centre trial based at the Royal Brompton Hospital (chapter 4).

2.1.1 Ethical consideration and consent

Both trials were given a favourable ethical opinion from the national NHS research ethics service via the Integrated Research Application System (IRAS). The PREDICT trial reference number is 09/H0708/33 and The Brain MRI study reference number is 10/H0711/101. The PREDICT trial was also approved by the local NHS Research and Development Office at each recruiting centre.

Patients were given patients information sheets in person or posted. They were given an adequate period of time to review the information and there was no upper time limit for consideration of trial entry. Contact details were included on the patient information sheet to give patients an opportunity to ask any questions they might have. Written consent was only sought after a full explanation had been given in person. The right of the patients to refuse to participate without giving reasons was respected. Consent was obtained by appropriately qualified investigators who had completed Good Clinical Practice training.

2.1.2 Selection of patients

All patients 65 years and older referred to the Royal Brompton and Harefield Hospital NHS trust with a potential diagnosis of OSA were identified from new patient's referrals and diagnostic studies between 01/01/2010 and 31/11/2012. Potentially eligible patients were then seen in person when they attended their appointments or contacted via telephone. Once their eligibility was confirmed i.e. fulfilled all of the inclusion criteria and none of the exclusion criteria they were given or posted the appropriate patient information sheet dependant on which trial they were eligible for. All eligible patients were offered trial entry. Approximately 1 week later or at a time specified by the patients they were called and if they agreed to participate a convenient date for their enrolment visit was agreed. Screening logs were kept, documenting reasons for non-inclusion; data from the screening logs are presented in chapter 3, section 3.13.1 and chapter 4, section 4.15.1. The individual inclusion and exclusion criteria for each trial are given in chapter 3, section 3.3.1 (The PREDICT trial) and chapter 4, section 4.7.4 (The Brain MRI study).

2.2 Intervention

All patients were randomised to either CPAP therapy with Best Supportive Care or Best Supportive Care (BSC) alone on completion of their enrolment visit.

2.2.1 Continuous positive airway pressure (CPAP)

CPAP is the main stay of medical treatment in middle-aged people with OSAS, as described earlier in Chapter 1, section 1.7. CPAP machines are small, electric pumps that deliver pressurised air to the upper airway via a hose and tightly fitting plastic mask which is worn over the nose and or mouth during sleep. The air pressure acts as a pneumatic splint, dilating the upper airway, increasing functional residual capacity and tracheal traction, and thus preventing the soft tissue at the pharyngeal level from collapsing (Sullivan, Issa et al. 1981). This is demonstrated schematically in Figure1.

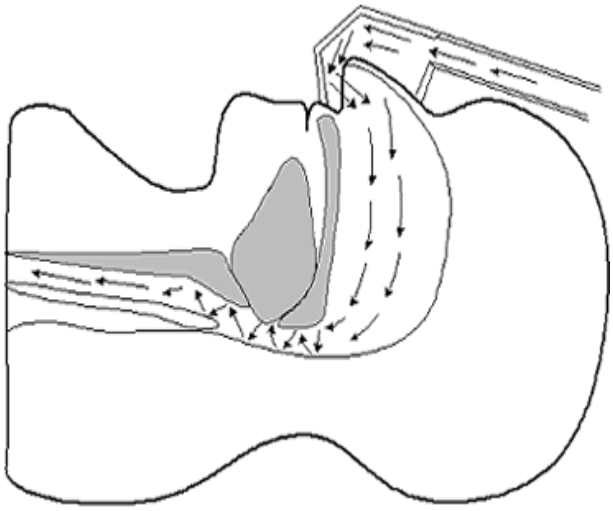


Figure 1: Schematic diaphragm the upper airway (sagittal view) with positive airway being delivered via the nose.

The positive airway pressure can be delivered as a fixed optimal pressure, which is usually manually set based on observation of the respiratory data during sleep or manual titration of the pressure during sleep. Alternatively the pressure can be automatically adjusted, which is referred to as autotitrating CPAP (auto-CPAP); these machines detect airflow limitation and automatically increase and decrease the air pressure needed to maintain airway patency over the night. Hence it was proposed that for the PREDICT study the auto-CPAP would optimise OSA control and reduce the need for titration studies. It was proposed that this would be a cost effective alternative to fixed level CPAP. Additional as the pressure delivered is adjusted by autotitrating machines, the mean pressure is often lower than that set on the fixed level CPAP machines and therefore thought to reduce both the pressure required and associated side effects (Hailey, Jacobs et al. 2005). However, it is important to note that many RCTs and meta-analysis comparing fixed level CPAP vs auto-CPAP (Ayas, Patel et al. 2004, Smith and Lasserson 2009, Ip, D'Ambrosio et al. 2012, Xu, Li et al. 2012) have not demonstrated any significant differences in sleep measures or clinically important changes such as adherence or patient preference. It has been proposed auto-CPAP may benefit certain subgroups although so far these have not yet been identified (Haniffa, Lasserson et al. 2004). Most recently there have been some studies that have suggested that auto-CPAP may affect haemodynamic and

possibly worsen autonomic function as measured by BP, augmentation index, Homeostasis Model Assessment (HOMA) and Heart rate variability. Auto-CPAP machines are also more expensive than fixed level CPAP which was taken into account when calculating the cost effectiveness of treatment in the PREDICT trial (Chapter 3).

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 (Martins De Araujo, Vieira et al. 2000) and various delivery interfaces (i.e. type of mask). A recent systematic review highlighted the lack of research on the impact of different masks on adherence to treatment. Likewise there is no evidence of increased adherence with humidified CPAP (McDaid, Griffin et al. 2009). Furthermore humidification will also increase the overall cost.

The recruitment centres in the PREDICT trial (Chapter 3, section 3.2.2) were provided with identical autotitrating CPAP machines and humidification (AutoSet™®, ResMed (UK) Ltd) and a range of standard 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 choice of interface were made according to individual patient preference. At each follow-up visit, the hours of CPAP use, delivered pressure and any leak were downloaded from a smart card in the CPAP machine. All recruiting centres had established clinical expertise in the diagnosis and treatment of OSAS.

The costs of the CPAP equipment including the machine, mask and tubing are shown in Table 2.1. The costs were the standard cost obtained from the manufacture. Costs may vary in different settings because of locally negotiated procurement discounts. The lifespan of a CPAP device has been reported to be approximately 7 years. The lifespan of a mask is 6-12 months.

Table 2.1: Costs of CPAP equipment

Item	Unit cost	Maximum duration of use
CPAP machine (S9 Autoset™)	£430	7 years
Humidifier (H5i™ and climate line)	£165	7 years
Consumables		
Mask (Mirage Quattro FFM)	£120	1 year
Mask (Mirage Liberty)	£125	1 year
Mask (Mirage Swift)	£89	1 year
Mask (Mirage Micro NM)	£80	1 year
Air filter (S9), pack of 50	£8	6 months
Air filter, hypoallergenic (S9), pack of 50	£50	6 months

2.2.2 Best supportive care (BSC)

The BSC was used as the comparative treatment in both studies presented in Chapter 3 and Chapter 4. It was defined as 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 (Shneerson and Wright 2001, Araghi, Chen et al. 2013). BSC was used as a comparator in the NICE HTA systematic review and economic analysis of CPAP machines for the treatment of OSAS (McDaid, Griffin et al. 2009). This report showed that trials using BSC as a comparator produced results essentially identical to those from trials using sub-therapeutic or sham CPAP as a comparator.

Sham devices are CPAP machines that have been modified to deliver sub-therapeutic pressure and have been validated as a placebo ; however, there is no consensus on the ideal comparator in sleep apnoea trials as it is argued that sham CPAP may have an adverse impact on sleep quality. Alternative comparators such as placebo pills or nasal dilator strips have also been used.. Two of the lead centres in the PREDICT trial 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. Additionally in a recent 6 month randomised controlled trial, using CPAP versus sham CPAP the trial retention was lower in those allocated to sham CPAP (Kushida, Nichols et al. 2012). BSC was therefore chosen as the trial comparator for both studies in this thesis, as it improved the simplicity of the trial delivery and was more appropriate for a multicentre trial. The greater simplicity of BSC was also thought to be more suitable for a trial with 12 months follow-up and in older people.

2.3 General measurements

For both studies standardised central record forms (CRF) were used throughout and standard operating procedures (SOP) were employed to maintain consistency between staff and centres; these are included in Appendix 2. In the PREDICT trial a training session for staff was completed at each centre prior to the centre being open for recruitment. Training, administration and clinical support was provided by myself via telephone and email; additional visits were completed if required.

2.3.1 Medical and sleep history

All patients had a structured medical history which included their co-morbidity, cardiovascular risk factors and medication. They also had a standardised sleep history which included direct questioning on specific symptoms related to OSAS, their bedtime, wake time, nocturia, daytime naps, bed partner and their alcohol and caffeine intake. Their daily exercise and years of education were also quantified. Additionally domestic accidents were recorded and driving accidents were confidentially self-reported at each assessment. The CRF for this information for the PREDICT trial (Chapter 3) is included in Appendix 2.

2.3.2 Clinical assessment

Patients completed bedside spironmetry, anthropometric measurements (height, weight, neck and waist measurements) office blood pressure, resting pulse and fasting bloods (Full blood count, renal and electrolyte function, liver function tests, glucose, lipids, HbA1c and thyroid function) at each assessment. Blood pressure measurements were carried out using a digital automatic monitor (M7, Omron Healthcare, Kyoto, Japan). Three readings were taken in the seated position, following five minutes rest (El Feghali et al 2007). The SOPs for these procedures are included in appendix 2. Patients recruited to the PREDICT trial also consent to a serum blood sample being stored in a biobank at Oxford Respiratory Trials Units (ORTU) for possible future use.

2.3.3 Subjective sleepiness

Daytime sleepiness was assessed by asking the patients to complete the Epworth Sleepiness Scale (ESS) (Johns 1991). The ESS is the most widely used subjective severity scale in clinical and research practice. It is a short, self-administered questionnaire with 8 questions that requires participants to rate the likelihood of dozing or falling asleep in recent times in 8 varying soporific everyday situations. Patients are asked to rate their chance of falling asleep as never, slight, moderate or high and this corresponds with a scale from 0 to 3. The sum of the responses is the score, which can range from the lowest possible score of 0 no symptoms to highest of 24 highly symptomatic. There is no universally agreed cut off score to distinguish between sleepy and non-sleepy but scores in the range from 9 to 11 would be considered symptomatic. When the ESS is used clinically or as a research tool the reported change in ESS is considered as opposed to the absolute score. A reduction in the score represents an improvement. Although the ESS is not disease specific for OSA it is has subsequently been validated in this patient population by its wide spread use within the international literature, guidelines and routine clinical practise.

The advantages of the ESS are that it is simple, self-administered and is currently among the most commonly used measures of sleepiness in clinical practice aiding diagnosis and quantifying the effect of treatment (Hardinge,

Pitson et al. 1995). The disadvantages are it relies on the individual's ability to differentiate tiredness from sleepiness and is open to bias whether that is unintentional or purposeful underreporting of sleepiness.. It has also been reported that up to a third of new users make errors or may have may have difficult completing the ESS (Ghiassi, Murphy et al. 2011). In the PREDICT trial this was minimised as research staff were trained in completing the ESS and a standardised SOP was employed. Research staff where available if the patient needed assistance to complete the questionnaire and once the questionnaire was completed it was checked for missing answers. The ESS and the SOP is included in Appendix 2.

2.3.4 Objective sleepiness

The most widely accepted objective measurements of sleepiness are the Multiple Sleep Latency Test (MSLT) (Carskadon, Dement et al. 1986) endorsed as the gold standard by the American Academy of Sleep Medicine (AASM) *(Iber et al.* 2007) and Maintenance of Wakefulness Test (MWT) (Mitler, Gujavarty et al. 1982) although they are time consuming and expensive, which makes them difficult to use for large studies or in clinical practise.

In the studies presented in this thesis daytime sleepiness was measured objectively using The Oxford Sleep Resistance Test (OSLER) (Bennett, Stradling et al. 1997), (Stowood Scientific Instruments, Oxford, UK)which is considered a simple alternative to the MWT. The OSLER test measures the patient's ability to resist sleep for up to 40 minutes. . The test requires standardised equipment which includes a display unit, handset and power supply. It is performed in a quiet, darkened room with the patient sitting comfortably in an upright position on a bed. The head is supported to prevent the neck jerking if the patient dropped off to sleep. Their dominant arm is rested on a pillow beside them on the bed with the handset. The display unit is placed approximately 1-2m in front of the patient and they are given the handset and shown how to hold it, resting their index finger of their dominant hand over a touch sensitive pad. They are told "This is a test to measure you reaction to a flashing light on the box by pressing the sensor on the hand box. The light will flash frequently and you should respond to each flash by touching the sensor each time the light flashes." It was re-alliterated not to keep their finger on the sensor but remove it immediately after contact. The display unit contains a small red LED light that flashes for 1 second every 3 seconds. When 7 consecutive flashes are missed it is assumed that the patient has fallen asleep and the test terminates, hence the occurrence of sleep is assessed behaviourally rather than by EEG monitoring. The test is run for the maximum time of 40 minutes and was performed at a set time in the same room. The results are recorded on the display unit which shows the time sleep occurred (the sleep latency) and the number of misses. The SOP is included in Appendix 2.

The OSLER test has been shown to discriminate normal subjects from those with excessive sleepiness secondary to OSA as well as the traditional MWT. In the original description of the test by (Bennett, Stradling et al. 1997) the test was performed on 4 occasions throughout the day, subsequently it has been shown by (Priest, Brichard et al. 2001) 3 tests either the first three or last three retained the same average results plus the same specificity and sensitivity as the 4 tests. When the profile of the errors were assessed by Pepin et al. (Mazza, Pepin et al. 2002) they concluded a single test at 9 am appeared as sensitive as 3 consecutive test in identifying patients with significant daytime sleepiness.

2.3.5 Quality of life and Mood

The following validated questionnaires were used to assess quality of life and mood. They are included in Appendix 2.

- **European Quality of Life – 5 Dimensions (EQ-5D)**. This is a generic questionnaire which covers the following 5 domains: mobility, self-care, usual activity, pain and discomfort, and anxiety and depression. It is consists of five questions on a 3 point Likert scale. 0 = No problems, 1 = some problems, 2 = inability or extreme problems. In addition, a single overall score can be generated from the EuroQol thermometer, on which respondents mark their overall perceived health from worse to best imaginable health state. It is has been validated in a variety of settings and countries, including the US and UK, including patients with arthritis, post-surgery and outpatient settings (Kind, Dolan et al. 1998). Patients with OSA have been found to have relatively high scores prior to treatment (indicating good health status) and hence little change with CPAP treatment (Jenkinson, Stradling et al. 1998). The lack of sensitivity of this questionnaire to OSA related quality of life may be due to the EQ-5D being a generic instrument which does not have any questions on symptoms such as insomnia, sleepiness or tiredness. The EQ-5D was used to calculate health outcomes expressed as quality adjusted life years (QALYs).

- **Quality adjusted life years (QALYs).** This is a measure of a value of health outcomes and is based on the number of years of life that would be added by the intervention. The cost-effectiveness thresholds conventionally used in the NHS is £20,000 per additional QALY gained.

- **Medical Outcomes Study Short Form-36 (SF-36).** This is one of the most frequently used generic quality of life questionnaires which consist of 36 quality of life related questions. Answers to questions are condensed into 8 summary scores which are further condensed in to a mental and physical component summary score (MCS and PCS). Each summary score was calculated using the formulae proposed by (Jenkinson, Layte et al. 1996). If any of the 36 questions were not answered, the MCS and PCS were set to missing along with any of the 8 summary scores which are dependent on the missing answers. Jenkinson et al. found that the SF-36 showed the significant adverse effects of OSAS on patients' subjective health assessments and that CPAP treatment produced improvements in SF-36 scores. The SF-36 was also used to calculate QALYs.

- **Calgary Sleep Apnoea Quality of Life Instrument (SAQLI).** This is one of the few disease specific quality of life questionnaires which also includes questions on CPAP side effects. The SAQLI is scored by averaging the answers to 14 obstructive sleep apnoea related questions and, if applicable, adjusting for side effects attributable to CPAP therapy. Should any of the answers to 14 questions be missing, the SAQLI was also set to missing.. The SAQLI has shown good internal consistency, face validity as judged by experts and patients and correlates with the SF-36, as well as demonstrating responsiveness to successful CPAP treatment, with the greatest change occurring in the symptom dimension (Flemons 1998).

- **Hospital Anxiety and Depression Scale (HADS).** This is a self-screening questionnaire for depression and anxiety (Zigmond and Snaith 1983). It consists of 14 questions, 7 on each aspect. Each question is scored on a 0 to 3 scale. The scored is the sum of all the questions. A score over 10 is indicative of mild depression, with scores great than 16 indicating severe depression. It was designed for hospital general medical outpatients and has also been used extensively in primary care (Wilkinson and Barczak 1988).

2.3.6 Functionality and Mobility

Functionality was assessed using the Townsend Disability Scale (TDS) (Townsend 1979). This is a 9 item questionnaire containing questions surrounding activities of daily living. Each items on the TDS 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 out of 18. If at least one of the components is missing the TDS was also set to missing.

Mobility was measured using the Timed Up and Go test (TUG). This is the time taken in seconds to stand up from an arm chair, walk 3 metres, turn, walk back to the chair and sit down (Podsiadlo and Richardson 1991).

2.4 Cognitive measures

A neuropsychological battery assessing principally attention, memory and executive function was designed for the studies in this thesis. The patients in the Brain MRI study, chapter 4 completed all the tests at baseline and at 6 months. A shorter panel of four tests (Mini Mental State Examination, Trail Making Test B, Digit Symbol Substitution Test and Simple and four-choice reaction time) were used in the Predict trial chapter 3 and completed at baseline, 3 months and 12 months. All tests are validated measures of cognitive function and. have been shown to distinguish patients from health volunteers and different patients groups from each other. All patients completed the tests at each assessment in the same order. The cognitive tests are described below and included in appendix 2

2.4.1 Mini Mental State Examination (MMSE)

This test is the most widely used screening tool for a global assessment of cognitive function and was developed by psychiatrists (Folstein, Robins et al. 1983). It is a verbal assessment of orientation, registration (immediate memory), short term memory (but not long-term memory) as well as language functioning and the ability to follow commands. It takes approximately 10 minutes to complete and is scored out of 30; scores of 25-30 are considered normal; 18-24 indicate mild-to-moderate impairment; scores of 17 or less indicate severe impairment. The MMSE is not suitable for making a diagnosis but can be used to indicate the presence of cognitive impairment (Crum, Anthony et al. 1993) although it is limited because it will not detect subtle memory losses, particularly in well-educated patients additionally people from different culture groups, or of low intelligence may score poorly in the absence of cognitive impairment (Brayne and Calloway 1990).

2.4.2 Addenbrooke's Cognitive Examination – Revised (ACE-R)

This more recent global assessment of cognitive function was developed by the MRC cognitive and brain sciences units, Cambridge, UK (Mioshi, Dawson et al. 2006). This is a brief and simple validated cognitive screening tool sensitive to detect early cognitive decline. It incorporates the MMSE, but extended to encompass important areas not covered by it. The ACE- R assesses a wider spectrum of cognitive domains – attention, orientation, memory, verbal fluency, language and visuospatial skills. The test consists of questions and simple tasks such as copying a drawing. It takes approximately 15 minutes to administer and consists of 26 tasks and is available in multiple languages. The total score is 100, higher scores indicate better cognitive functioning, each domain has individual scores and there are age and education dependent norms for the total score as well as for the individual domains. A cut of score of 82 has 100% accuracy in classifying normal controls as non-demented.

2.4.3 Trail Making Test (TMT)

This is one of the most widely used neuropsychological tests and is included in most neuropsychological panels. TMT provides information on visual conceptual and visuomotor tracking, motor speed, attention and executive functions. The TMT consists of two parts, A and B. Part A requires individuals to draw a line sequentially connecting 25 encircled numbers on a piece of paper. Part B requires the individual to draw a line alternating between numbers and letters (e.g. 1, A, 2, B, 3, C, 4, D etc.). It is a timed test and the score represents the amount

of time required to complete the task. Performance decreases with increasing age and lower levels of education although normative data is available (Tombaugh 2004). The majority of people complete the test in less than 300 seconds (Reitan 1979).

2.4.4 Digit Symbol Substitution Test (DSST)

This is a coding exercise assessing working memory. 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 requires 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.

2.4.5 Simple and four-choice reaction time

This is the time between presentation of a sensory stimulus and the subsequent behavioural response. The test screens for visual, movement and comprehension. It is a two-part computer based test. The first part measures the time to react to a symbol appearing in a white box on the screen by pressing any key on the keyboard in response. It acts as a simple introduction to the screen for the patient and if the patient is unable to comply with the simple reaction time it is unlikely that they will be able to complete the second part. The second part of the test requires the individual to respond to the symbol appearing in any one of four boxes at random. The patient has to respond using the allocated keys on the keyboard. The number of correct responses, errors, the mean reaction time, variability and SD corrected for the mean are recorded. Reaction time is quickest for young adults and gradually slows down with age. It can be improved with practice, up to a point, and it declines under conditions of fatigue and distraction (Deary, Liewald et al. 2011).

2.4.6 The Stroop Colour and Word test

The test measures the relative dominance of the verbal reading system and the ability to sort information from the environment and to selectively react to this information. The test consists of 3 pages. Each page has 100 items, presented in 5 columns of 20 items. The word page consists of the words “RED”, “GREEN”, and “BLUE” arranged randomly and printed in black ink on an A4 sheet of paper. No word is allowed to follow itself within a column. The colour page consists of 100 items, all written as XXXX, printed in red, green or blue. The patient has to ignore the meaning of the word and to name the ink colour as quickly as possible (Stroop 1935).

2.4.7 Wechsler Adult Intelligence Scale, third edition (WAIS-III)

This is a commonly used commercially available validated assessment of cognitive function. The following five tests were subtests of the (WAIS-III) and administered and scored as recommended by the WAIS-III instruction manual.

- **Logical Memory** tests the patient’s ability to remember two short stories presented orally. There is an immediate test and then a delayed recall test after 30 minutes. It is a measure of verbal memory.

- **Verbal paired associates** are also a measure of verbal memory and involve 10 word pairs presented verbally. Recall is tested immediately and after 30 minutes delay.

- **Letter number sequencing** is a working memory task but requires more than just immediate memory. In this task, the individual is presented with a series of numbers and letters in a random order. Patients are then asked to repeat back the numbers in order first followed by the letters in alphabetical order. There is no minimum academic skill prerequisite other than knowing the numbers one to nine and having a functional knowledge of the alphabet.

- **Faces** are a test of normal verbal memory and are a two part test. In part one patient's are shown 24 pictures of faces one at a time for two seconds. The patients are then shown 48 faces and are asked to identify the 24 faces they saw previously by responding either yes or no to each face. Patients are then prompted to remember the faces as they will be asked to remember the faces again later on. After a 30 minute delay part II is completed. Once again patients are shown 48 faces and asked to identify the faces they have seen before responding with yes and no answers. This test has been shown to be impaired in early cognitive impairment although not as sensitive as verbal memory tests (Seelye, Howieson et al. 2009).

- **Spatial Span Forward and Backwards** is a measure of visual-spatial processing and working memory. It uses a three-dimensional board with 10 blocks on it. The examiner points to a series of blocks at the rate of about one block per second in a predetermined pattern to create a series of spatial patterns. The patient is then immediately asked to duplicate the same pattern in the same order as shown by the examiner (forward span) or recall in the reverse order (backwards span). The test begin with a series of just 2 blocks, the maximum number of blocks in a series is 8. One point is scored for each correct series, maximum 32 (16 forward and 16 backwards). It is validated in older patients as cognitive impairment severity increases there is a reduction in the total score. The spatial span backwards is a more sensitive measure of early cognitive impairment as opposed to the spatial span forward which remains relatively stable regardless of the level of impairment (Wiechmann, Hall et al. 2011). Spatial Span forward is an attention task, whereas spatial span backward is considered a working memory task as it requires holding information in the memory.

2.5 Measurements of sleep and breathing

The diagnosis of OSA and other sleep-related disorders has been traditionally based on nocturnal polysomnography. This technique is expensive and requires the availability of specialised facilities and expertise which are often not available in the UK (Flemons, Douglas et al. 2004). I therefore took the view that this would hinder the conduct of a large multicentre randomised clinical trial, More importantly, limited channel home-based testing typically measuring airflow, respiratory effort and pulse oximetry, is now widely used in the diagnosis of OSA throughout the UK, therefore this form of monitoring was selected as the primary measurement in the PREDICT trial, chapter 3. The following investigations were also used in the screening and diagnosis of OSA.

2.5.1 Overnight pulse oximetry

This simple test is widely used in the domiciliary setting and is a useful screening tool or as part of a clinical decision pathway regarding the need for and type of further investigations required. Oximetry (Konica-Minolta Inc, Osaka, Japan) provides a measure of the arterial oxygen saturation of haemoglobin and heart rate. The technique relies on 2 basic principles:-

- The absorption of light at two different wavelengths by haemoglobin differs depending on the degree of oxygenation of Haemoglobin.
- The light signal following transmission through the tissues has a pulsatile component, resulting from the changing volume of arterial blood with each pulse beat and is distinguishable by the microprocessor from the non-pulsatile component resulting from venous, capillary and tissue light absorption.

An oximetry probe can be placed on the finger, ear lobe or nose. Within the probe there are 2 light emitting diodes one in the visible red spectrum (660nm) and the other in the infrared spectrum (940nm). The beams of light pass through the tissues to a photodetector. During passage, some light is absorbed depending on the concentration of haemoglobin. The amount absorbed at each frequency depends on the degree of oxygenation of haemoglobin. The microprocessor selectively analyses the pulsatile fraction of blood. Saturation values are averaged out over 5 to 20 seconds. Heart rate is also averaged out over a variable period depending on the particular monitor. The microprocessor calculates the ratio of absorbed light at each frequency and then compares them to standardised measurements within its memory (derived from previous human experiments) to arrive at a percentage oxygen saturation.

Pulse oximetry has the following limitations (Jubran 1999)

- It is not a monitor of ventilation
- It is less effective in critically ill patients
- Waveform presence is essential for accurate reading, inaccuracies can occur in the following situations, abnormal Hb (methaemoglobinaemia), carboxyhaemoglobin, nail varnish, vasoconstriction or hypothermia,

tricuspid regurgitation (can cause venous pulsations), values below 70% are inaccurate and cardiac arrythmias

- Lag monitor – the partial pressure of oxygen can have fallen considerable before the oxygen saturation starts to fall

- Response delay due to signal averaging

Oximetry can be used to report the average, and lowest heart rate and oxygen saturations. It also typically reported an oxygen desaturation index (ODI) this is the number of episodes of oxygen desaturation per hour of recording time during which blood oxygen fell by a set criteria usually 4%. Pulse oximeters also measure heart rate and brief increases are an indirect marker of transient arousal form sleep.

A series of studies looking at the clinical utility, reproducibility and adequacy of pulse oximetry for the diagnosis of OSA has shown that oximetry is reliable in the diagnosis of moderate to severe OSA but of less useful in mild OSA, (Ryan, Hilton et al. 1995).

In patients who have a negative or ambiguous study may require a more detailed investigation. Moreover, a normal result cannot eliminate the diagnosis of OSA in patients with a high pre-test probability of OSA.

2.5.2 Respiratory polygraphy

In the PREDICT trial presented in Chapter 3 a limited multichannel respiratory polygraphy (Embletta®GOLD™, Embla®) was carried out either in the participants home or within a sleep laboratory, according to the patients preference or ability. Heart rate (via electrocardiography), snoring, breathing effort (respiratory inductance plethysmography), airflow at the nostrils (cannula with a pressure transducer), arterial oxygen saturation (SaO_2) by pulse oximetry and body position were recorded.

Patients were asked to complete a sleep diary documenting time in bed (TiB) (lights off to awakening) and any periods of extended wakefulness. A software package was used for downloading and the studies were manually scored centrally by one person. A recording was considered acceptable if there was >4 hours of recording with at least one effort band either chest or abdomen and SaO2 was obtained. If for any reason the recording was unacceptable the patient was offered a second or rarely third night of monitoring.

Data were analysed using the AASM (Iber *et al* 2007) recommended scoring criteria. Apnoeas were defined as the absence of airflow lasting for >10seconds or a decrease in airflow of ≥90% lasting for ≥10 seconds accompanied by either on going respiratory efforts (obstructive); cessation of respiratory efforts (central); or cessation of respiratory effort in the first half of the apnoea with resumption of respiratory efforts before resumption of airflow (mixed). Hypopnoeas were defined as a ≥30% reduction in airflow lasting for ≥10 seconds accompanied by a ≥4% decrease in oxygen saturation. No distinction was made between obstructive and central hypopnoeas. The apnoea and hypopnoea index (AHI) was established as the number of events per hour of recording. The following indices of nocturnal hypoxemia; mean Sa02; percentage of recording time below 90%; minimal Sp02 during sleep and the

oxygen desaturation index (ODI) were also recorded. An AHI ≥ 7.5 events/hour was used to define the presence of OSA.

Several groups have validated the utility of domiciliary respiratory polygraphy against nocturnal polysomnography in the diagnosis of OSA (Kuna, Gurubhagavatula et al. 2011, Masa, Corral et al. 2011). The level of agreement was moderate 79% rising to >90% in patients with AHI > 30 and overall these studies support the use of domiciliary respiratory polygraphy for the diagnosing OSA.

2.5.3 Nocturnal polysomnography

The patients included in the study presented in Chapter 4 completed laboratory based monitoring overnight using standard polsomnography equipment (SOMNOscreen, Somnomedics GmBH, Germany) to determine their sleep patterns. Patients had their neural activity monitored using electroencephalogram (EEG), derivations (C3, C4, O1, 02). Eye movements were measured by bilateral electroocculogram (LOC and ROC) which monitors the resting potential of the retina. Chin muscle activity was also monitored using submental and anterior tibialis electromyogram (EMG). Heart rate was monitored using electrocardiogram (ECG). Breathing was assessed using nasal/oral airflow via a thermistor and nasal cannula, respiratory effort using chest and abdominal inductance plethysmography and finger pulse oximetry (SaO2) monitored using an infra-red finger probe.

Sleep architecture, including total sleep time, sleep efficiency and sleep stages were scored in according to the rules of the AASM *(Iber et al* 2007). Sleep data were scored using standard visual rules to differentiate wake and different stages of sleep. Data were divided into 30 second epocs and classified as wake, rapid eye movement (REM) sleep or non-REM sleep (further divided into stages N1, N2 and N3). In addition the apnoea hypopnoea index (AHI) was defined as the number of apnoea plus hypopnea per hour of sleep. The total arousal index (ARI) was defined as the number of arousals per hour of sleep. An AHI of 5 or less is deemed to be within normal limits.

2.6 Measurement of CPAP therapy use

CPAP use was measured objectively in both the studies presented in this thesis by downloading a smart card in the CPAP machine at each visits. The output was in a standardised commercially available format provided by the manufactures of the CPAP machines. It contained data on hours and days used, pressure provided and estimated leak. 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 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 visit. The hours of usage was set to zero hours per night in those with missing data and those who had subsequently stopped treatment.

2.7 Statistical analysis

2.7.1 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, standard deviation (SD) or median, 25th and 75th percentiles as appropriate.

In the PREDICT trial patients were randomised to two groups CPAP treatment plus BSC *versus* BSC only. Statistical significance was tested at the 5% level for all analyses. Differences between groups were assessed using t-tests.

The statistical analysis for the PREDICT trial will be discussed in chapter 3, section 3.10 and for the Brain MRI study in chapter 4, section 4.14.

Chapter 3: Positive Airway Pressure in Older People: A Randomised Controlled Trial (PREDICT)

3.1 Introduction

Overview

The recent National Institute of Clinical Excellence (NICE) Health Technology appraisal of the use of CPAP treatment in OSAS concluded that CPAP was an effective treatment for moderate to severe OSAS in middle-aged people. However it identified evidence gaps with a need for trials in other patients groups such as older patients (see chapter 1, section 1.7 for a summary of CPAP trials in older people).

NICE also concluded that CPAP treatment was also a cost efficient treatment in middle-aged moderate to severe OSAS patients, as the therapeutic improvements included lower risk of road traffic accidents (Mar, Rueda et al. 2003, Ayas, FitzGerald et al. 2006, Guest, Helter et al. 2008, Tan, Ayas et al. 2008, McDaid, Griffin et al. 2009, Sadatsafavi, Marra et al. 2009, Gander, Scott et al. 2010, Pietzsch, Garner et al. 2011), work accidents (Gander, Scott et al. 2010), cardiovascular events (Mar, Rueda et al. 2003, Guest, Helter et al. 2008, McDaid, Griffin et al. 2009, Sadatsafavi, Marra et al. 2009, Gander, Scott et al. 2010, Pietzsch, Garner et al. 2011) and diabetes (Gander, Scott et al. 2010) and direct improvements in health-related quality of life from reduced sleepiness. The improvement in health-related quality of life was estimated by converting other measures of quality of life (Chilcott, Clayton et al. 2000) or daytime sleepiness (McDaid, Griffin et al. 2009, Sadatsafavi, Marra et al. 2009) into health utilities, obtained directly from patients in before-and-after studies (Tousignant, Cosio et al. 1994, Mar, Rueda et al. 2003, Ayas, FitzGerald et al. 2006, Guest, Helter et al. 2008, Tan, Ayas et al. 2008) or from assumptions (Gander, Scott et al. 2010, Pietzsch, Garner et al. 2011).

Unfortunately, these therapeutic and economic benefits cannot be presumed to be replicated in older people without appropriate data. Firstly, none of trial in the NICE appraisal examined the cost-effectiveness of CPAP in patients aged 65 years and over and secondly, all relied on indirect evidence to estimate the health utility benefit from treatment. Both OSAS and ageing reduce independence and cognitive function, as well as potentially increasing cardiovascular morbidity. In older people co-morbidities and other causes of excessive daytime sleepiness may obscure the diagnosis of possible OSAS symptoms (Bixler et al. 2005). The magnitude of benefits seen in younger populations cannot be assumed to be replicated in older people. In addition the cost efficiency of CPAP therapy in older OSAS patients may also be different from that in younger patients. Different perceptions of health related quality of life, changes in vascular risk, life expectancy and driving profile will also influence the health economic analysis by changing the cost analysis over a shorter lifetime horizon. This complex situation requires randomised data to identify whether CPAP treatment for OSAS is of value in this age group.

Therefore, despite the high prevalence of OSA in older people as discussed earlier in section 1.4.2 there is a paucity of evidence on the relative benefits or risks of CPAP treatment in older people. Additionally, it cannot be assumed the benefits of CPAP treatment in younger populations will be replicated in older people by the same magnitude or even at all. The PREDICT trial (Positive airway pressure in older people: a randomized controlled trial) was an investigator initiated project, funded by the Health Technology Assessment (HTA) programme of the

UK National Institute for Health Research (NIHR) and was designed to address the evidence gap, and enable the formulation of good-quality guidance on care for older people with OSAS.

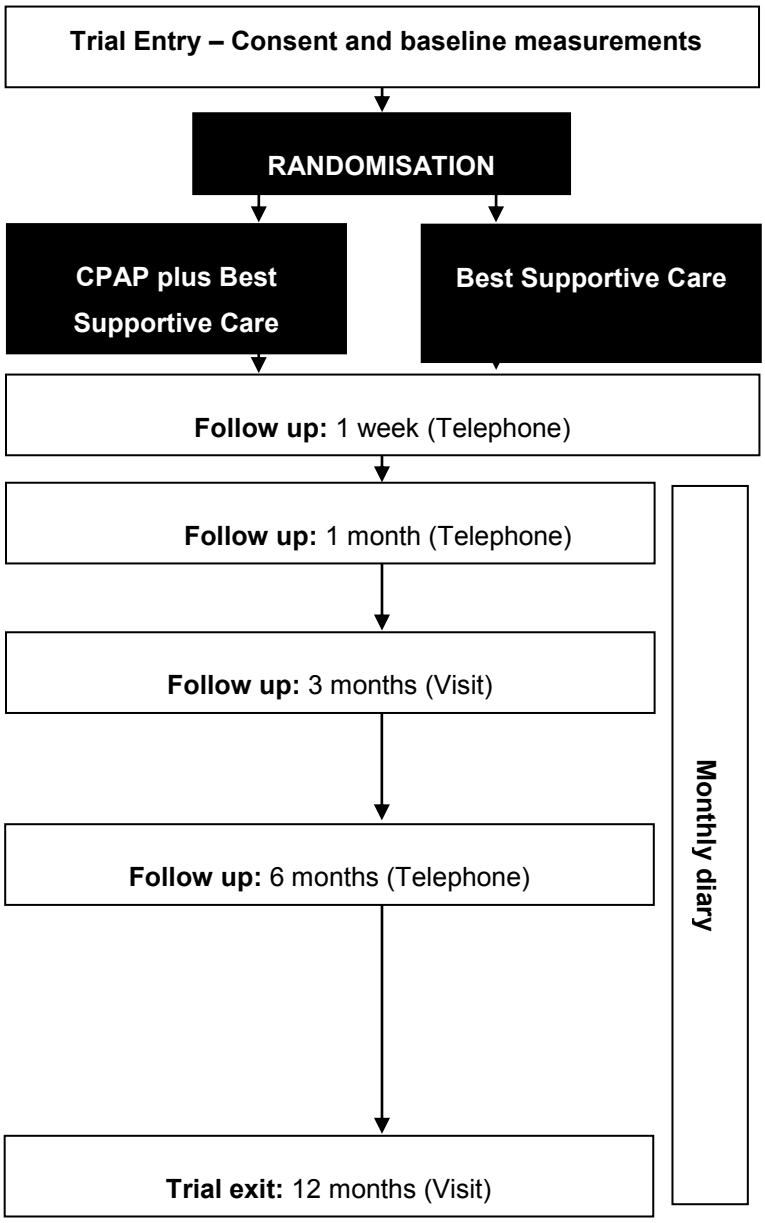
3.2 Methods

3.2.1 Trial design

The PREDICT trial (ISRCTN90464927) was a pragmatic, single-blinded (investigator blinded), parallel group, multi centre, randomised controlled trial (RCT) of 12 months duration (Figure 3.1).

All patients were randomised to receive CPAP, plus best supportive care (BSC), or BSC only (see chapter 2, section 2.2 for a full description of each treatment modality. The co-primary 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.

Figure 3.1: Trial design



3.2.2 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 referral centres: Churchill Hospital (Oxford), Musgrove Park Hospital (Taunton), Royal Brompton Hospital (London), Royal Infirmary Edinburgh, St James' 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 due to recruitment difficulties, leaving eight additional secondary care referral centres: Aintree Hospital (Liverpool), Blackpool Victoria Hospital, City General Hospital (Stoke-on-Trent), Freeman Hospital (Newcastle), Great Western Hospital (Swindon), Heartlands Hospital (Birmingham), New Cross Hospital (Wolverhampton), Royal Berkshire Hospital (Reading). All centres had established sleep services where patients with OSAS are diagnosed and treated with CPAP therapy.

3.2.3 Ethical consideration

The trial was approved via the Integrated Research Application System (IRAS) (National Research Ethics Service / NHS / Health and Social Care Committees) (Reference number 09/H0708/33). A copy of the approval is provided in appendix 3. The trial was also approved by the local NHS Research and Development Office at each site and registered on the internal standardised randomised controlled trial register (ISRCTN no. 90464927).

3.3 Patients

3.3.1 Eligibility criteria

Patients were invited to participate if they were aged 65 years or older at the enrolment visit, with newly diagnosed OSAS. OSAS was defined as ≥ 4% oxygen desaturation index (ODI) > 7.5 events/hour and an ESS ≥ 9. (chapter 2, section 2.3.3 for full details of the ESS). 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/Forced vital capacity (FEV_1 / FVC) ratio <60%
- Substantial problems with sleepiness driving (in those who are still driving)
- Currently using heavy good vehicle (HGV) or professional service vehicle (PSV) driving license
- Shift work
- Any very severe complication of OSAS such that CPAP therapy was mandatory
- Inability to give informed consent or comply with the protocol

3.3.2 Screening

All patients potentially eligible to participate in the trial were identified from sleep and respiratory clinics predominantly by the principal investigator (PI) 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 PI 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 reason(s) for non-inclusion.

3.3.3 Informed consent

Patients completed written informed consent at the enrolment visit (a copy of the patient information from and consent form are given in appendix 1.

3.4 Interventions

Patients were randomised to receive CPAP plus BSC or BSC alone (see chapter 2, section 2.2 for a full description of the each treatment modality). Details of the randomisation are given in section 3.8.

3.5 Assessment

Both groups had identical visit schedules. Structured clinical assessments were performed at baseline, 3 months and 12 months. Assessment visits were carried out at each local centre. Occasionally, research staff agreed to see a patient in their own home when the patient 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, side effects and to optimise CPAP adherence. Additionally, all patients completed monthly diaries recording their ESS, functionality, quality of life, healthcare usage, change in medication, caffeine and alcohol intake, frequency of exercise, and any side effects.

All patients enrolled in the trial completed a domiciliary overnight respiratory polygraphy study (chapter 2, section 2.5.2) prior to treatment allocation which was scored centrally. Domiciliary overnight, pulse-oximetry was completed at 3 and 12 months (chapter 2, section 2.5.1). Table 3.1 summarises the assessment completed at each time point.

Table 3.1: Summary of assessments by time point

Assessments and Measurements	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 (Epworth Sleepiness Scale)		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Objective sleepiness (Oxford Sleep Resistance) test		*				*									*
Quality of life (European Quality of Life-5 Dimensions)		*		*	*	*	*	*	*	*	*	*	*	*	*
Generic quality of life (SF-36)		*				*									*
Disease specific quality of life (SAQLI)		*				*									*
Mood (Hospital Anxiety and Depression Scale)		*				*									*
Functionality (Townsend Disability Scale)		*		*	*	*	*	*	*	*	*	*	*	*	*
Nocturia		*		*		*			*						*
Mobility (Timed Up and Go Test)		*				*									*
Accidents		*		*		*			*						*
Cognitive function (MMSE, TMT-B, DSS, RT)		*				*									*
Anthropometry, blood pressure and resting pulse		*				*									*
Fasting bloods		*				*									*
Vascular events		*				*									*
Health care usage and change in medication		*		*	*	*	*	*	*	*	*	*	*	*	*
Caffeine and alcohol intake		*		*	*	*	*	*	*	*	*	*	*	*	*
Exercise		*		*	*	*	*	*	*	*	*	*	*	*	*
Continuous positive airway pressure compliance			*			*									*
Continuous positive airway pressure side effects			*	*	*	*	*	*	*	*	*	*	*	*	*
Adverse events			*	*	*	*	*	*	*	*	*	*	*	*	*

SF-36: Medical Outcomes Study Short Form-36, SAQLI: Sleep Apnoea Quality of Life Index, MMSE: Mini Mental State Examination, TMT-B: Trail Making Test B, DSS: Digit Symbol Substitution, RT: Reaction Time (simple and 4 choice reaction time)

3.6 Outcome measures

3.6.1 Co-primary outcomes

The first co-primary outcome was the change in subjective sleepiness from baseline to 3 months, measured by the mean ESS score at 3 and 4 months. Additionally the ESS was measured monthly throughout the trial.

The other co-primary 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 QALYs using the EQ-5D (Euroquol group. Health Policy 1990) and Short Form six dimensions (SF-6D) derived from the Short Form 36 (SF-36) (Brazier, Roberts et al. 2002) as an alternative scenario (details of the EQ-5D, SF-36 and QALYs are given in chapter 2, section 2.3.5).

Patients reported health-related quality of life 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. Healthcare resource use was recorded in the monthly diaries completed by the patients (see appendix 2 for a copy of the diary). Costs were evaluated in UK pounds sterling at 2012 prices from the UK NHS perspective (HM Treasury 2011).

3.6.2 Secondary outcomes

These included (for full detail of each test see chapter 2 section 2.3):-

- Subjective sleepiness at 12 months, measured by the mean ESS score of months 10, 11 and 12.

Plus the following outcomes recorded at the 3 and 12 months assessments.

- Objective sleepiness measured by the Oxford Sleep Resistance test (OSLER).
- Generic quality of life assessed by the Short Form -36 (SF-36).
- Disease specific quality of life was assessed using Sleep Apnoea Quality of Life Index (SAQLI).
- Mood assessed using the Hospital Anxiety and Depression Scale (HADS).
- Functionality assessed by the Townsend Disability Scale (TDS).
- Nocturia, the patients were asked if they had to pass urine and on average the number of times each night and if they had been incontinent and how many times in the last month
- Mobility measured using the Timed Up and Go test (TUG).
- Domestic and road traffic accidents. Domestic accidents were recorded in the CRFs and driving accidents were self-reported confidentially at each assessment.
- Cognitive function was assessed using the following 4 tests: - Mini Mental State Examination (MMSE), Trail Making Test B (TMT–B), Digit Symbol Substitution Test (DSST) and Simple and four-choice reaction time.

- Cardiovascular risk factors: systolic and diastolic office BP, fasting glucose, lipids, and HbA1c.
- New cardiovascular events: including angina, newly diagnosed hypertension, atrial fibrillation, myocardial infarction, heart failure, diabetes, stroke, transient ischaemic attack and peripheral vascular disease.

3.6.3 Tertiary outcome

Treatment compliance was measured objectively by downloading a smart card in the CPAP machine at the 3 and 12 month visits (for full details see chapter 2, section 2.6).

3.7 Data collection and monitoring

Data generated by all centres were collected on case report forms (CRF), 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 Centre 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 manually for inconsistencies in range and missing data. Missing or ambiguous data were queried with individual research nurses and resolved wherever 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 completed by the chief investigator, trial manager and clinical research fellow. Interim monitoring visits were completed for 5 centres and source data verification was completed during those visits. 11 close-out visits were completed remotely and 4 centres were visited. All adverse events (AEs) were reviewed by the Independent Data Monitoring Committee (IDMC).

3.8 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 (see below) once the baseline data collection was completed.

The randomisation program 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 > 13 v ≤ 13), functionality using the TDS >1 v $\leq$1 and recruitment centre. In the analysis baseline ESS and TDS 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 only recruit a single patient.

3.8.1 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. 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 data analysis. Patients continued to see other health care professionals unrelated to the trial for their usual medical care.

3.9 Sample size

The primary analysis was the difference between the two treatment groups in the mean change of ESS from baseline to 3 months. The ESS is a scale from 0 to 24 and a one 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 (McDaid, Griffin et al. 2009) the effect of CPAP treatment on the difference in ESS in middle-aged patients with mild OSA was -1.07 (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 one point change in ESS (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 randomised trials with a similar design the loss to follow-up rate was approximately 5%. Since the PREDICT trial was of longer duration and in older people with co-morbidity 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).

3.10 Statistical methods

The statistical analysis plan was finalised and approved by the Trial Management Group (TMG) (the list of members are in included in appendix 4). The analysis was completed by a statistician, Daniel Bratton Medical Research Council Clinical trials Unit at University College London, Institute of Clinical Trials and Metholodolgy.

Statistical significance was tested at the 5% level for all analyses. All analyses were adjusted for the minimisation factors (enrolment ESS > 13 v ≤ 13, functionality using the TDS >1 v ≤1 and recruitment centre) to optimise power and reduce bias. In addition to the minimisation factors age, gender, ODI and BMI were also adjusted for in an additional analysis of the primary outcome. All analyses were intention-to-treat (ITT) 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 due to 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, 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^{TM}12.0 (StataCorp LP, College Station, Texas, USA).

3.10.1 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, standard deviation (SD) or median, 25th and 75th percentiles as appropriate.

3.10.2 Co-primary outcomes analysis

Subjective sleepiness: Subjective sleepiness was assessed using the ESS. The mean of month 3 and 4 ESS score was calculated for each patient and compared to baseline. The ESS score is the sum of its eight components and therefore if one of the components was missing the ESS was set to missing. If any non-integer values were given these were included in the sum and the final ESS rounded up or down to the next integer. Any scores obtained outside the pre-specified window of 2 to 5 months after randomization were excluded. If either the 3 or 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 and follow-

up ESS 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 GP visits during the trial. The cost-effectiveness analysis was completed by a health economist, Ms Rita Neves De Faria at the Centre for Health Economics, University of York.

3.10.3 Secondary outcome analyses

Subjective sleepiness at 12 months, the mean ESS 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 to 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 measured by Oxford Sleep Resistance Test (OSLER): Two tests were conducted at each visit (baseline, 3 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 and 12 months with log-rank tests used to compare survival curves. The difference in the mean time to fall asleep at each follow-up visit compared to baseline was compared between treatment groups.

Generic quality of life was assessed by the SF-36: The mental and physical component scores (MCS and PCS) summary scores were calculated. Were any of the 36 questions not answered, the MCS and PCS were set to missing along with any of the 8 summary scores dependent on the missing answers.

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 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 was assessed by the TDS: Each of the 9 items of the TDS 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 out of 18 (Townsend 1979). If at least one of the components was missing the TDI was also set to missing.

Mobility was assessed by the TUG, 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 were assessed: The proportion of patients experiencing any accidents was analysed adjusting accident history at baseline (whether they had an accident at home in the month before enrolment or while driving in the three months before enrolment).

Cognitive function was assessed using the MMSE, TMT-B, DSST and the simple and 4 choice reaction time test: The change in the score for each of the 4 tests was analysed.

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 (SF36, 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 was not an issue and could 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.

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.

3.10.4 Tertiary outcomes analyses

CPAP 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 25^{th} and 75^{th} percentiles. Patients who had stopped CPAP during follow-up and were missing adherence data were assumed to have zero 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.

3.10.5 Sensitivity analyses

Patients who were randomised to BSC only and who subsequently started CPAP therapy during the follow-up potentially dilute the results of the ESS comparisons. Sensitivity analyses of the primary and secondary ESS outcomes were performed in which BSC patient who swapped to CPAP were

excluded from the analysis if CPAP therapy had been started before the visit at which the observation was recorded.

3.10.6 Multiple imputation analyses

Multiple imputations could be used to impute missing ESS scores over follow-up and produce an unbiased analysis under a Missing at Random (MAR) assumption. MAR 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 MAR assumption was explored by comparing observed data in those patients with and without the outcome of interest.

All the monthly ESS scores were entered into an imputation model along with the minimisation variables and the previously listed covariates (age, gender, 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 fifty imputation models were created using the *'ice'* command in Stata. In analyses secondary to those described above, the primary and secondary ESS outcomes were reanalysed on the imputed datasets and the results combined using Rubin's rules.

The MAR 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, MNAR) was considered. The ESS 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.

3.10.7 Exploratory analyses

Effect of CPAP adherence on ESS: 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 to the BSC group in a single model on the change in the primary ESS outcome. The minimisation variables were adjusted and a global test was used to determine whether the treatment effect in each of the three CPAP groups differed. A similar analysis was conducted on the secondary ESS 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 at each time point was also modelled using multivariable fractional polynomial models (Royston and Sauerbrei 2008) adjusting for the minimisation variables. Since the BSC group had no compliance data the mean change in ESS in this group was displayed on a fractional polynomial plot.

3.10.8 Interaction analyses

The variation of the effect of CPAP therapy compared to BSC on the primary ESS outcome was investigated over age, BMI, ODI and ESS at baseline. Fractional polynomials (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 (AIC) (Royston and Sauerbrei 2004). 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% 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.

3.10.9 Analysis of monthly diaries

A longitudinal analysis of the effect of CPAP compared to 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 as the response variable and ‘month’ and ‘baseline ESS’ as fixed effects with patient-specific and month-specific random intercepts (with the latter nested within the former). This model makes the assumption that all trial visits and monthly diaries are completed on the expected dates. An unstructured covariance matrix was used. From the model a plot of the treatment effect and its 95% confidence interval at each month was constructed.

3.11 Summary of changes to the protocol

Changes to the trial documents following NREC approval in October 2009 are summarised below:-

1. Substantial Amendment SA01 (approved by the REC on 04/11/2009). Change of the version number of the Patient information sheet (PIS) mentioned in the consent form to match the PIS v. 2.0 already approved.

2. Substantial Amendment SA02 (approved by the REC on 02/12/2009). Change of 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 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 delivery of CPAP/service provision and clarified the procedure for returning the driving questionnaire.

3. Substantial Amendment SA03 (approved by the REC on 10/05/2010). Updating staff and committee membership and contact details, minor editing and administrative changes. Further information added to the PIS. Standard letters inviting patients to attend their 3 and 12 month visit were introduced at the request of the participating centres. The Sleep diaries were updated and information regarding Sibutramine was removed from the BSC booklet. Clarification were required for the blinding procedure, one of the exclusion criteria, minimisation criteria, trial treatment, loss to follow-up, procedure for assessing safety, quality control and adverse events section.

4. Non-substantial amendment NA04 (acknowledged by the REC on 14/05/2010). One of the minimisation criteria had been changed in error and was corrected.

5. Substantial Amendment SA05 (approved by the REC on 24/02/2011). Updated staff and 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 not completed more than 3 months before randomisation. Amended the co-enrolment guidelines and listed the bloods tests. Updated the monitoring, amendments and safety reporting section so that it refers to a device trial rather than an Investigational Medicinal Product trial.

6. Substantial Amendment SA06 (approved by the REC on 20/06//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 08/06/2012). Clarification of how the cardiovascular risk would be measured, the ESS calculations and the analysis plan. Corrections of the statistical calculations, update of the trial manager's details and admin corrections.

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

3.12 Trial conduct

3.12.1 Trial organisation

The trial was managed and co-ordinated from the National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, UK (Professor Mary Morrell and Dr Alison McMillan) and the Oxford Respiratory Trial Unit (ORTU) (Magda Laskawiec-Szkonter). Dr Renata Riha University of Edinburgh was co-primary investigator on the NIHR, HTA grant that funded the trial. 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 Group (TSG) carried overall responsibility for the safe delivery of the trial. They initially met every six months until they were satisfied trial recruitment was achievable and thereafter annually to provide overall supervision of the trial.

The Trial Management Group (TMG) was responsible for the management of the trial and met frequently. An Independent Data Monitoring Committee (IDMC) was also appointed.

Membership of the TMG, TSC and IDMC are listed in appendix 4

3.12.2 Patient involvement

A patient representative on the TSC and patients from the London centre were invited to an annual Patient Public Involvement (PPI) event at the Royal Brompton Hospital (once their direct involvement in the trial was over) to provide feedback on their experiences.

3.12.3 Trial Finances

The PREDICT trial was funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment Program (project number 08/56/02). Subcontracts were established between Imperial College London, ORTU, University of Edinburgh and York and each of the recruitment centres. Trial patients travel expenses were paid.

3.12.4 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.

3.12.5 Working with industry

CPAP 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 chapter 2, section 2.2.1.

The CPAP machine and associated equipment (masks, tubing, filters and humidification units) were supplied by ResMed (UK) Ltd, they also provided on loan the sleep diagnostic equipment (Embletta^{TM}). 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 they 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 (£100) 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 was 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.

The PREDICT trial offers numerous examples of good practice in the industry, putting the needs of the trial 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 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, who provided their 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. The loan of Embla GOLD equipment and software was approximately £103,485 generating a total cost saving of £226,381.

3.13 Results

3.13.1 Recruitment

Recruitment took place between 24th of February 2010 and the 30th May 2012. The overall recruitment rate is shown in (Figure 3.2). 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 as 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 randomization prior to the official stop date. The TMG agreed the additional patients should be included.

The CONSORT (Consolidated Standards of Reporting Trials) diagram shows the flow of patients through the trial (Figure 3.3) 'Withdrew consent' means that the patients withdrew from the treatment and trial and 'discontinued treatment' means that patient stopped their allocated treatment but remained in the trial.

In total, 1614 individuals were screened as potential patients: of these 541 (33%) were eligible and subsequently 278 (51%) were randomised. 245 (88%) completed their 3 months follow-up and 231 (83%) completed their 12 month follow-up and completed the trial.

Data collected on the screening logs enabled the 1073 ineligible patients to be group 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 FEV1/FVC <60% N=171 (16%).
- Being a professional driver, reporting sleepiness whilst driving, shift work or any severe symptom of Obstructive sleep apnoea syndrome for which the referring physician felt CPAP was mandatory N=216 (20%).
- No information or incomplete data N=165 (15%).

Figure 3.2: Cumulative recruitment

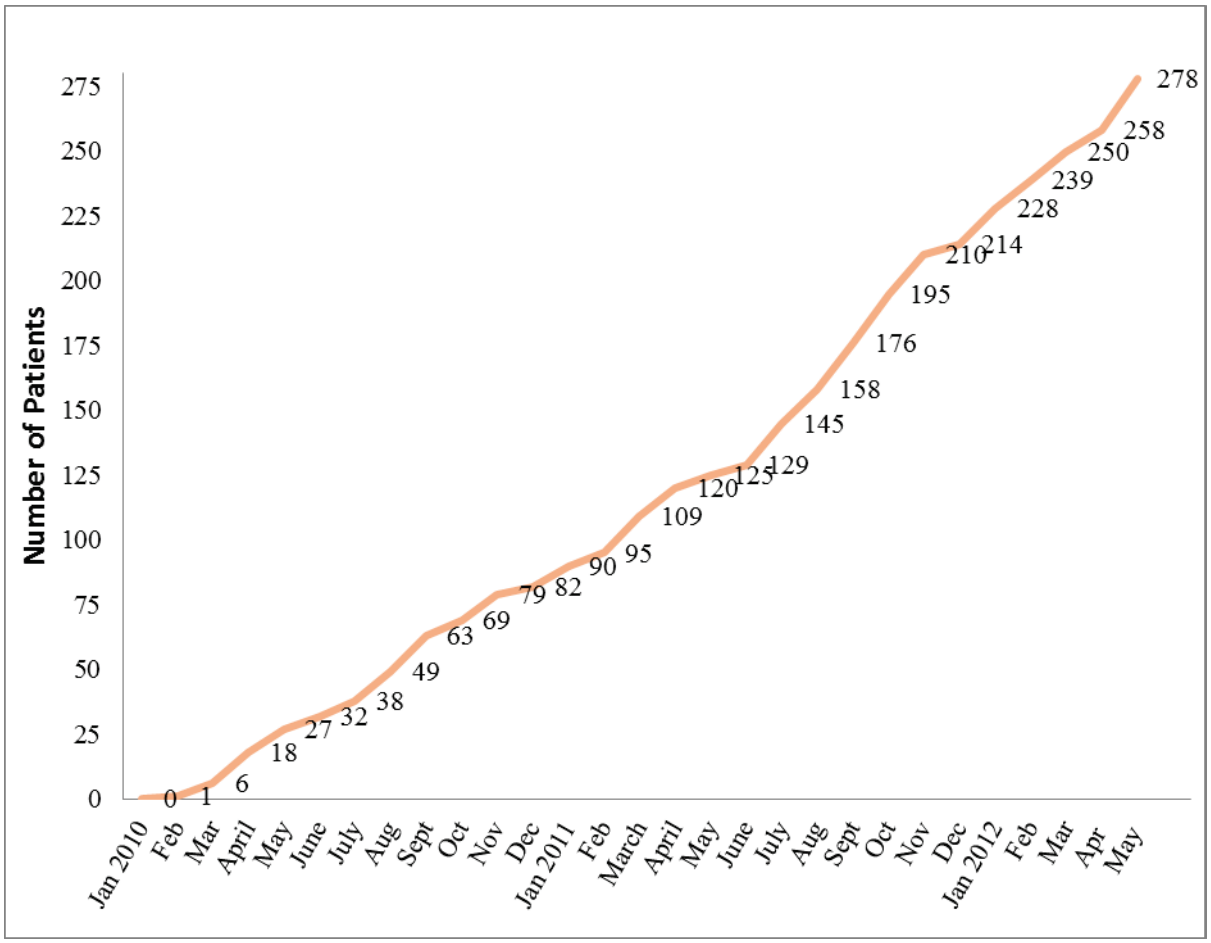
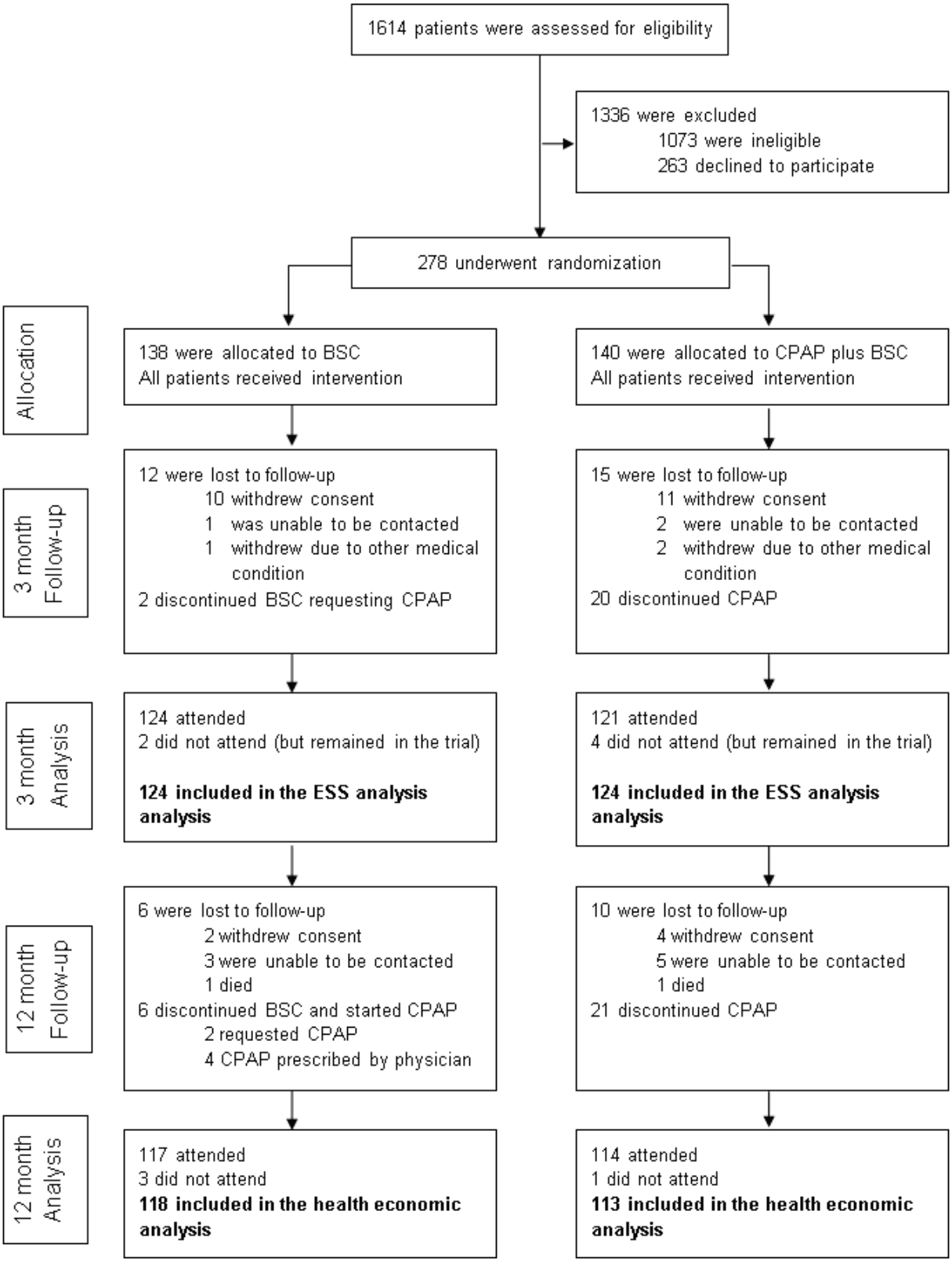


Figure 3.3: Trial screening, enrolment, randomisation and follow-up



3.13.2 Baseline data

As stated above, 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 ranging from 65 to 89 years and had on average moderate OSAS; ESS mean (SD) 11.6 (3.7) and oxygen desaturation index (ODI) 28.7 (19.1) events/hours. The majority of patients were white (96%), obese and had on average 11 years of education and normal MMSE. 228 (82%) were current drivers, and 146 (53%) slept alone. Interestingly the self-reported alcohol intake was low and weekly exercise frequency was high. This data was subjective and may also represent trial participation bias although was similar in both groups.

Baselines demographic are shown in Table 3.2, clinical characteristics in Table 3.3, sleep characteristics in Table 3.4 and sleep measurements in Table 3.5. None of the baseline data between groups were considered different.

Table 3.2: Baseline demographics

		Best Supportive Care	Continuous positive airway pressure
Number		138	140
Age (years)		70.3 (68.0-73.8)	69.5 (67.1-74.1)
Male sex N (%)		109 (79)	120 (86)
Education (years)		11 (10-14)	11 (10-15)
Mini Mental State Examination		29 (28-30)	29 (27-30)
Current drivers N (%)		111 (80)	117 (84)
White		134 (97)	133 (95)
Asian		3 (2)	5 (4)
Other		1 (1)	2 (1)
Body mass index (kg/m^2)		33.6 (6.4)	33.9 (5.7)
Neck circumference (cm)		42.6 (4.0)	44.0 (4.4)
Waist size (cm)		114.1 (15.5)	115.3 (13.6)
Hip size (cm)		115.7 (12.8)	116.6 (12.1)
Waist to hip ratio		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		5.1 (2.7)	5.2 (2.6)
Alcoholic drinks/wk		0 (0-2)	0 (0-2.3)
Exercise frequency (defined as lasting over 10 minutes) N (%)	5-7 times/wk	67 (49)	69 (49)
	2-4 times/wk	37 (27)	37 (26)
	Once/wk	9 (7)	10 (7)
	<Once/wk	5 (4)	8 (6)
	None	19 (14)	16 (11)

Data are mean (SD), median (25th-75th percentiles) or N (%) as appropriate

Table 3.3: Clinical characteristics

	Best Supportive Care	Continuous positive airway pressure
Number	138	140
Asthma/Chronic Obstructive Pulmonary Disease	34 (25)	31 (22)
Other chronic lung diseases	13 (9)	9 (6)
Ischaemic Heart Disease	49 (36)	42 (30)
Hypertension	104 (75)	98 (70)
Diabetes	43 (31)	40 (29)
Peripheral Vascular Disease	32 (23)	26 (19)
Atrial fibrillation	41 (30)	28 (20)
Heart failure	11 (8)	7 (5)
Cerebral vascular Disease	19 (14)	16 (11)
Systolic blood pressure (mmHg)	140.4 (20.0)	137.7 (17.7)
Diastolic blood pressure (mmHg)	77.6 (12.4)	77.7 (10.2)
Forced expiratory volume in 1 sec % predicted	84.5 (19.9)	86.5 (19.4)
Forced vital capacity % predicted	5.1 (2.7)	5.2 (2.6)
FEV1/FVC	83.6 (13.4)	82.4 (12.8)
Nocturia (no. of times/night)	2.1 (1.3)	1.9 (1.3)
Incontinent overnight N (%)	8 (6)	10 (7)
Townsend Disability Scale	2.5 (1-7)	2.5 (1-5)

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N (%) as appropriate

Table 3.4: Sleep characteristics

		Best Supportive Care	Continuous positive airway pressure
Number		138	140
Epworth sleepiness score		11.6 (3.9)	11.6 (3.4)
Oxford Sleep Resistance Test (minutes)		20.3 (9.4-37.5)	22.4 (13.3-40.0)
Sleep Apnoea Quality of Life Index		4.7 (1.2)	4.8 (1.2)
Self-reported sleep duration (hours)		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		7 (3-7)	7 (3-7)
Duration of each nap (minutes)		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 apnea N (%)	Yes	97 (70)	105 (75)
	No	25 (18)	19 (14)
	Unknown	16 (12)	16 (11)

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N (%) as appropriate

Table 3.5: Sleep measurements

	Best Supportive Care	**Continuous positive airway pressure**
Number	138	140
Time in bed (hours)	8.7 (1.4)	8.5 (1.4)
Apnea index (/hour in bed)	7.4 (2.7-17.3)	7.1 (1.7-17.4)
Obstructive	6.5 (1.9-15.7)	6.0 (1.4-15.5)
Central	0 (0-0.1)	0 (0-0)
Mixed	0 (0-0.5)	0 (0-0.2)
Hypopnea index (hour in bed)	18.6 (12.4-25.7)	17.8 (11.6-28.4)
Total (per hour in bed)	29.4 (18.9-46.0)	28.1 (16.3-47.7)
Mean overnight O2 Saturation (%)	92.6 (90.9-93.7)	92.6 (91.0-93.7)
Lowest O2 Saturation (%)	79 (73-83)	79 (73-83)
Average Desaturation (%)	6.3 (5.3-7.5)	6.3 (5.4-7.8)
Saturation < 90% (% of total sleep time)	8.8 (3.3-26.3)	8.6 (2.8-26.7)
Oxygen Desaturation Index (>4% events/hour)	24.4 (15.2-39.2)	28.1 (13.3-46.0)

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N (%) as appropriate

3.13.3 Co-primary outcomes

Subjective sleepiness

The primary outcome, the change in subjective sleepiness between groups at 3 months, is shown in Table 3.6. CPAP resulted in a mean change (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 was statistically significant (p<0.001). An additional analysis adjusting for age, gender, BMI and baseline ODI did not alter this result.

Table 3.6: Change in Epworth sleepiness scale (ESS) at 3 months

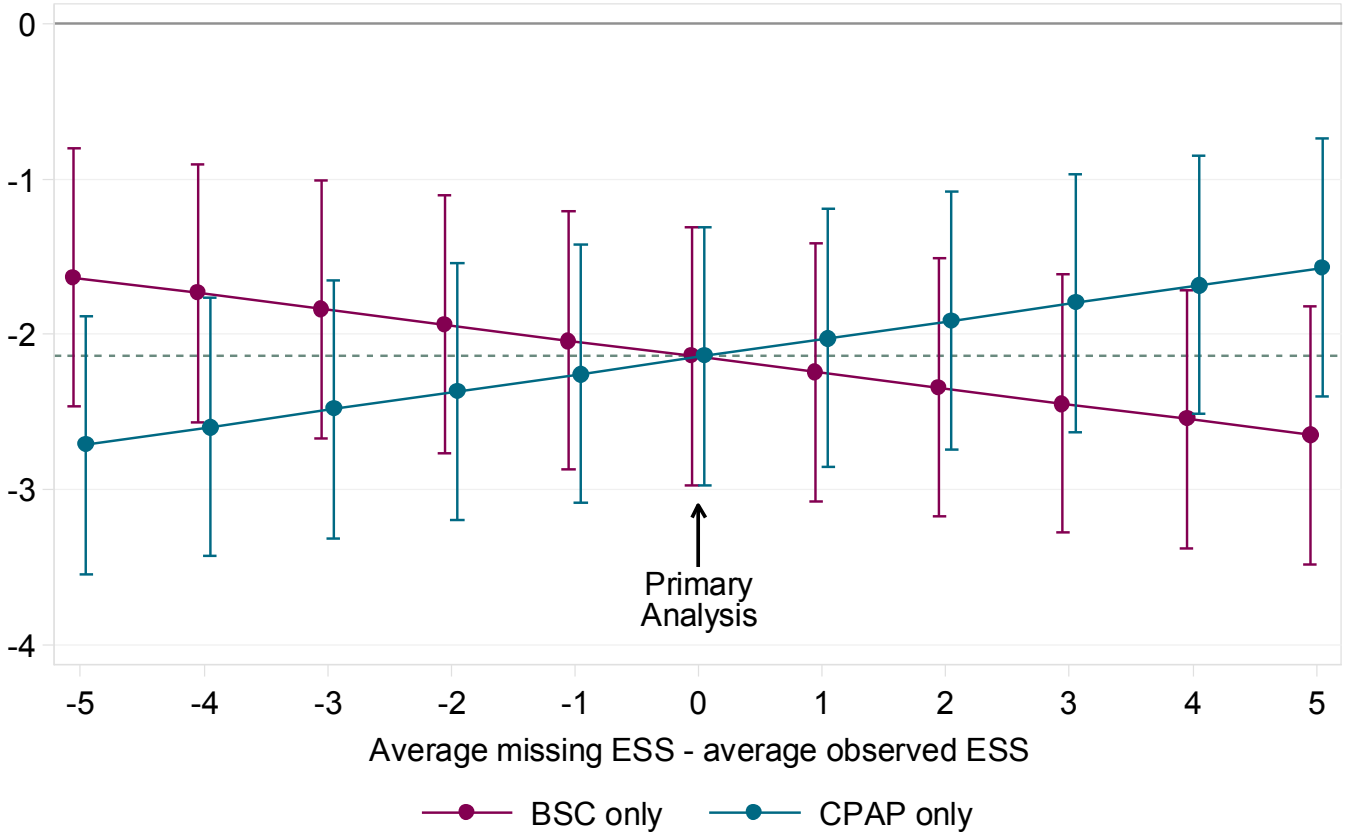
	Best Supportive Care	**Continuous positive airway pressure**
Number randomised	138	140
Number analysed	124	124
Baseline (at randomization)	11.4 (4.2)	11.5 (3.3)
Month 3	9.8 (4.7)	7.7 (4.1)
Month 4	9.7 (4.2)	7.7 (4.3)
Mean of months 3 and 4	9.8 (4.3)	7.7 (4.0)
Mean change from baseline (SE)	-1.6 (0.3)	-3.8 (0.4)
Treatment effect (95% CI) p-value	-2.1 (-3.0,-1.3) p<0.001	

Data are quoted as mean (SD)

Sensitivity Analysis: Sensitivity analyses were performed i) excluding 2 patients who swapped from BSC to CPAP prior to the 3 month assessment; and ii) including all randomized patients by replacing missing values using multiple imputation. Excluding the 2 patients that 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.

Results from the imputation analyses calculating the effect of the incomplete ESS data reported by 14 patients, estimated a change of -2.0 (95% CI -2.8, -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 3.3 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.

Figure 3.3: Sensitivity analysis of the primary outcome to missing data



ESS: Epworth Sleepiness scale; BSC: Best supportive care; CPAP: Continuous positive airway pressure

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

A full description of CPAP adherence which was a tertiary outcome is given in section 3.13.6

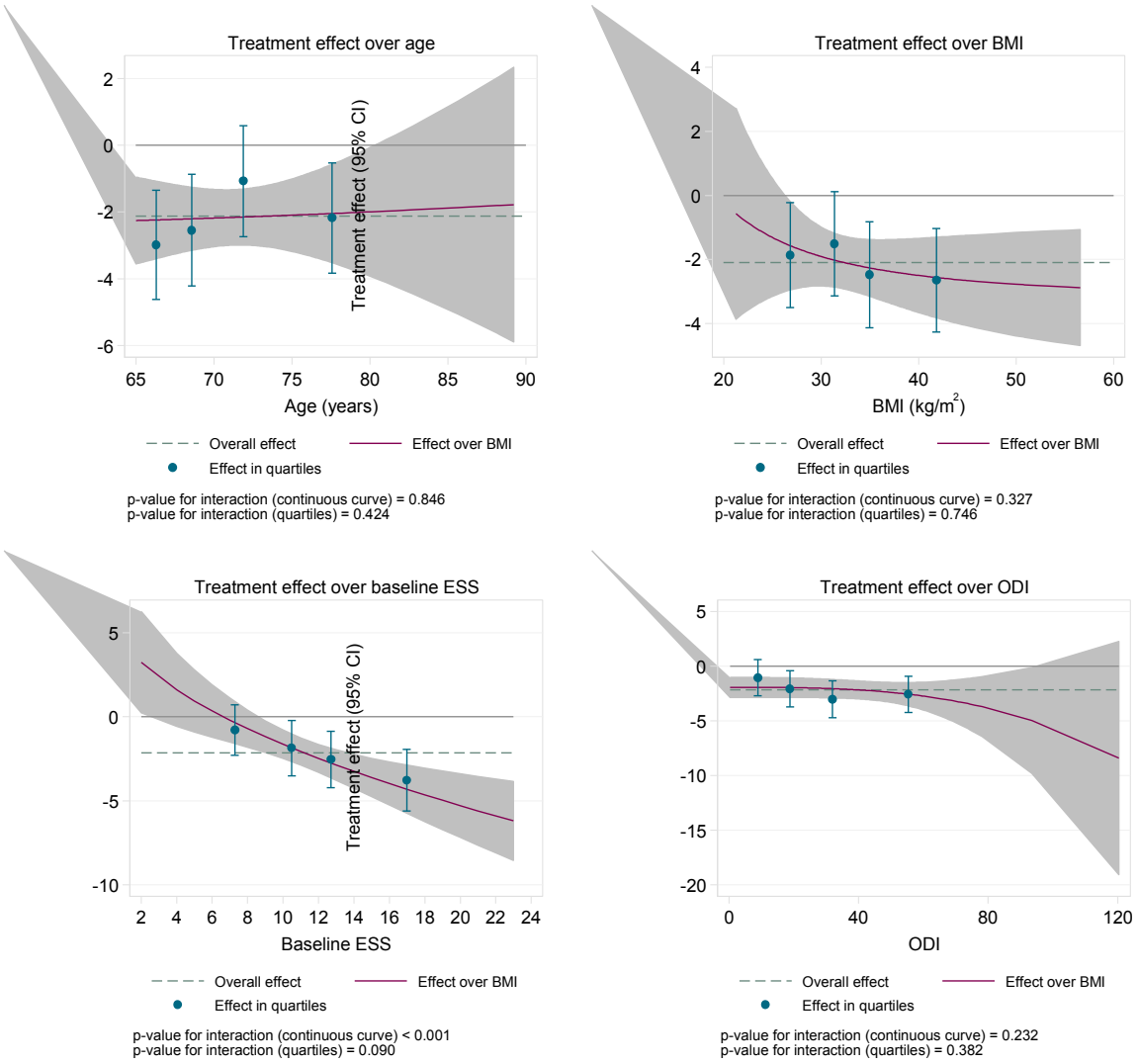
Table 3.7: The effect of the Continuous Positive Airway Pressure use on the Epworth sleepiness score over the month prior to 3 month assessment.

	Best supportive care	Continuous positive airway pressure		
		1st tertile	2nd tertile	3rd tertile
Number	124	38	37	41
Mean usage (hours/night) (min-max)	-	0 (0-0)	1.9 (0.001-4.6)	6.4 (4.6-8.6)
Baseline ESS	11.4 (4.2)	10.6 (3.0)	12.0 (3.9)	11.4 (2.7)
Months 3 ESS	9.8 (4.3)	8.0 (3.9)	9.0 (4.5)	6.1 (2.7)
Change	-1.6 (2.9)	-2.6 (3.9)	-3.1 (4.3)	-5.3 (3.4)
Treatment effect (95% CI)	-	-1.3 (-2.4, 0.1)	-1.3 (-2.4, -0.1)	-3.7 (-4.8, -2.6)
p-value	-	0.032	0.034	<0.001

Data are mean (SD), ESS: Epworth sleepiness scale.

The effect of CPAP therapy compared to BSC on the primary ESS outcome was also assessed separately over age, BMI, ESS and ODI at baseline using fractional polynomials and is shown in Figure 3.4. The treatment effect was larger in patients with higher ESS at baseline (p<0.001).

Figure 3.4: Interactions between primary treatment effect on Epworth sleepiness score (ESS) and age, Body Mass Index, baseline ESS and Oxygen desaturation index



BMI: Body Mass Index; ESS: Epworth Sleepiness scale; ODI: Oxygen desaturation index

3.13.4 Cost Effectiveness

The primary outcome of cost-effectiveness is show in Table 3.8. There was small difference between those treated with CPAP and those treated with BSC. The average costs per patient allocated to CPAP were +£1,363 (95%CI +£1,121 to +£1,606) and +£1,389 (95%CI +£1,116 to +£1,662) for BSC. Overall the CPAP group accrued on average £35 (95%CI -£390 to £321) lower costs which were 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.

The average QALYs obtained using the EQ-5D were +0.680 (95%CI +0.638 to +0.722) and SF-36 +0.678 (95%CI +0.664 to +0.691) for CPAP and +0.666 (95%CI +0.627 to +0.705) and +0.658 (95%CI +0.643 to +0.673) for BSC. The relative increase in QALYs with CPAP was EQ-5D QALYs +0.005 (95%CI -0.034 to +0.044, NS) and SF-36 QALYs +0.018 (95%CI +0.003 to +0.034) compared to BSC.

Overall, the probability that the intervention was cost-effective at the thresholds conventionally used in the NHS of £20,000 per QALY gained was 0.61 using EQ-5D QALYs, and 0.96 using the SF-36 QALYs. The improvements in QALYs were small, albeit statistically significant for the SF-36. The improvement of 0.005 QALYs was equivalent to 2 days in full health and of 0.018 QALYs to 7 days. Overall CPAP appeared to have improved health outcomes as well as reduced overall costs to the NHS.

Table 3.8: Cost-effectiveness of Continuous positive airway pressure (CPAP) compared to Best supportive care (BSC) over 12 months

	Best supportive care (BSC)	**Continuous positive airway pressure (CPAP)**
Costs of CPAP treatment	0	£201
Costs of healthcare resource use Mean (SD)	£1,363 (£123)	£1389 (£139)
EQ-5D QALYs Mean (SD)	0.666 (0.020)	0.680 (0.021)
SF-6D QALYs Mean (SD)	0.658 (0.008)	0.678 (0.007)
CPAP versus BSC (Difference in)		
Costs Mean (SE) 95% CI	-£35 (£180, -£390 to £321)	
EQ-5D QALYs Mean (SE) 95% CI	0.005 (0.020, -0.034 to 0.044)	
SF-6D QALYs Mean (SE) 95% CI	0.018 (0.008, 0.003 to 0.034)	

EQ-5D: European Quality of Life – 5 Dimensions, SF-36: Medical Outcomes Study Short Form-36

3.13.5 Secondary outcomes

Subjective sleepiness

The change in subject sleepiness as measured by the mean ESS of months 10, 11 and12, is shown in Table 3.9. CPAP resulted in a mean change (SD) -4.2 (4.1) in ESS from an average of 11.4 (3.4) at baseline to 7.2 (3.6) at 12 months. BSC showed a change of -2.1 (3.6) from a baseline of 11.3 (4.0) to 9.2 (4.0) at 12 months. The difference between the two groups at 12 months was -2.1 (95% CI -2.8 to -1.2) in favour of CPAP which was statistically significant (p<0.001). A sensitivity analysis excluding 8 patients who swapped from BSC to CPAP was performed but this did not alter the conclusion, the difference between the two groups remained -2.1 (95% CI -3.0 to -1.3); p<0.001 in favour of CPAP.

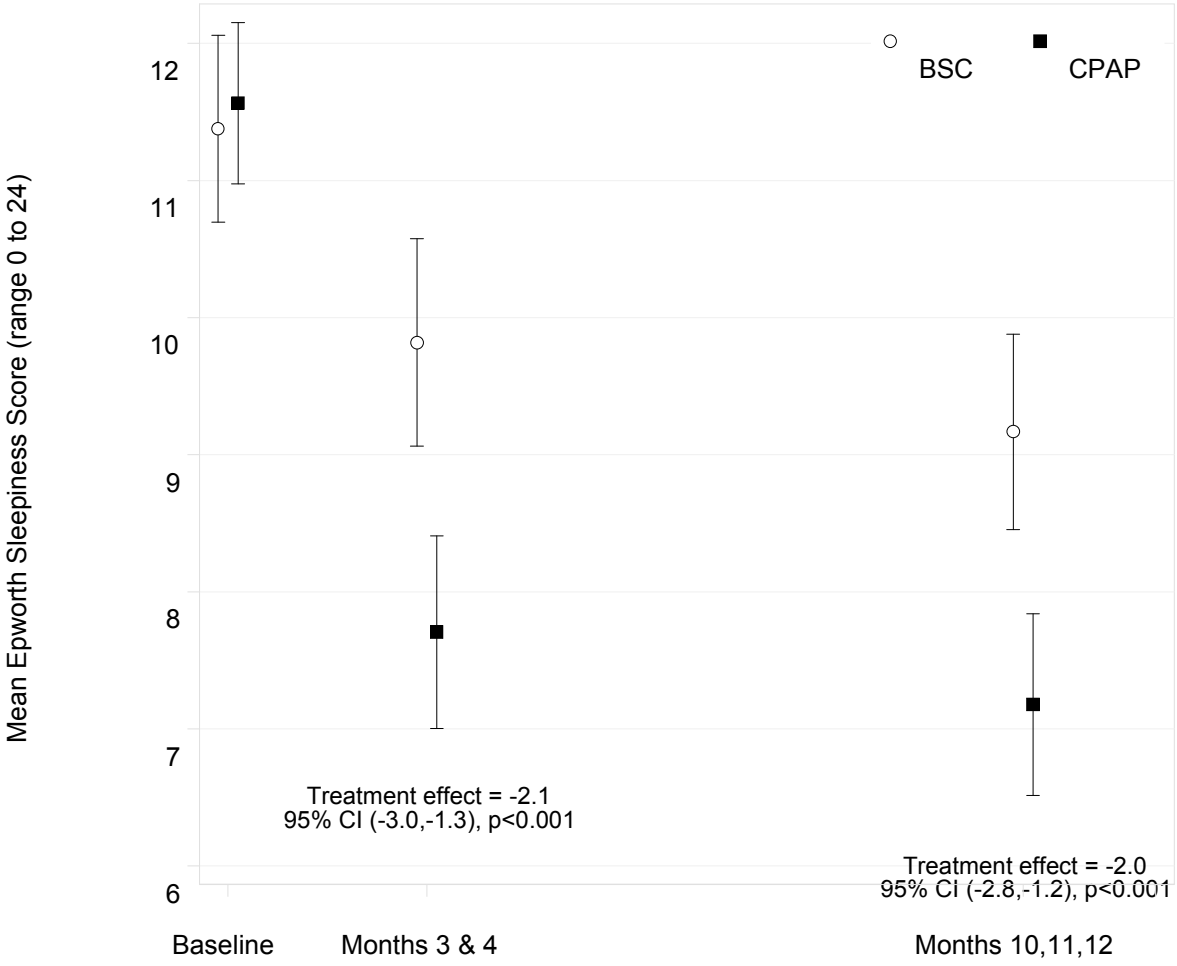
CPAP reduced subjective sleepiness at 3 months and the effect was maintained at 12 months and was statistically significant (p<0.001) this is shown graphically in Figure 3.5. Likewise the effect was larger in patients with greater CPAP use. The analysis by CPAP use is given in Table 3.10.

Table 3.9: Change in Epworth sleepiness scale at 12 months

Timed assessed	**Best Supportive Care**	**Continuous positive airway pressure**
Number randomised	138	140
Number analysed	122	116
ESS baseline (at randomization)	11.3 (4.0)	11.4 (3.4)
ESS month 10	9.3 (4.3)	7.3 (4.1)
ESS month 11	9.6 (4.4)	7.2 (4.1)
ESS month 12	9.0 (4.1)	7.0 (3.8)
Mean of months 10, 11 & 12	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	-2.1 (-2.8, -1.2) p<0.001	

Data are mean (SD), ESS: Epworth Sleepiness Scale

Figure 3.5: The treatment effect of Continuous Positive Airway Pressure compared to best supportive care on subjective sleepiness



Adjusted treatment effects of Continuous positive airway pressure (CPAP) and Best supportive care (BSC) and their 95% CI on the mean Epworth sleepiness score (ESS) of months 3 and 4 (co-primary outcome) and of months 10, 11 and 12 (secondary outcome). Lower scores indicate an improvement.

Table 3.10: The effect of the Continuous Positive Airway Pressure use on the Epworth sleepiness score over the 3 months prior to 12 month assessment.

	Best supportive care	Continuous positive airway pressure		
		1st tertile	2nd tertile	3rd tertile
Number	122	52	30	30
Mean usage (hours/night) (min-max)	-	0 (0-0)	2.3 (0.002-4.4)	6.3 (4.5-8.9)
Baseline Epworth sleepiness scale	11.3 (4.0)	11.2 (3.5)	11.4 (4.0)	11.8 (2.6)
Month 10,11 and 12 Epworth Sleepiness scale	9.2 (4.0)	8.1 (3.9)	7.3 (3.5)	5.6 (2.6)
Change	-2.1 (3.6)	-3.0 (4.4)	- 4.2 (3.4)	-6.2 (3.3)
Treatment effect (95% CI)	-	-1.0 (-2.0, 0.1)	-2.0 (-3.2, -0.7)	-3.6 (-4.9, -2.4)
p-value	-	0.063	0.002	<0.001

Data are mean (SD)

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 3.11a and b, (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 3.6.

Table 3.11a: Oxford Sleep Resistance test at 3 months

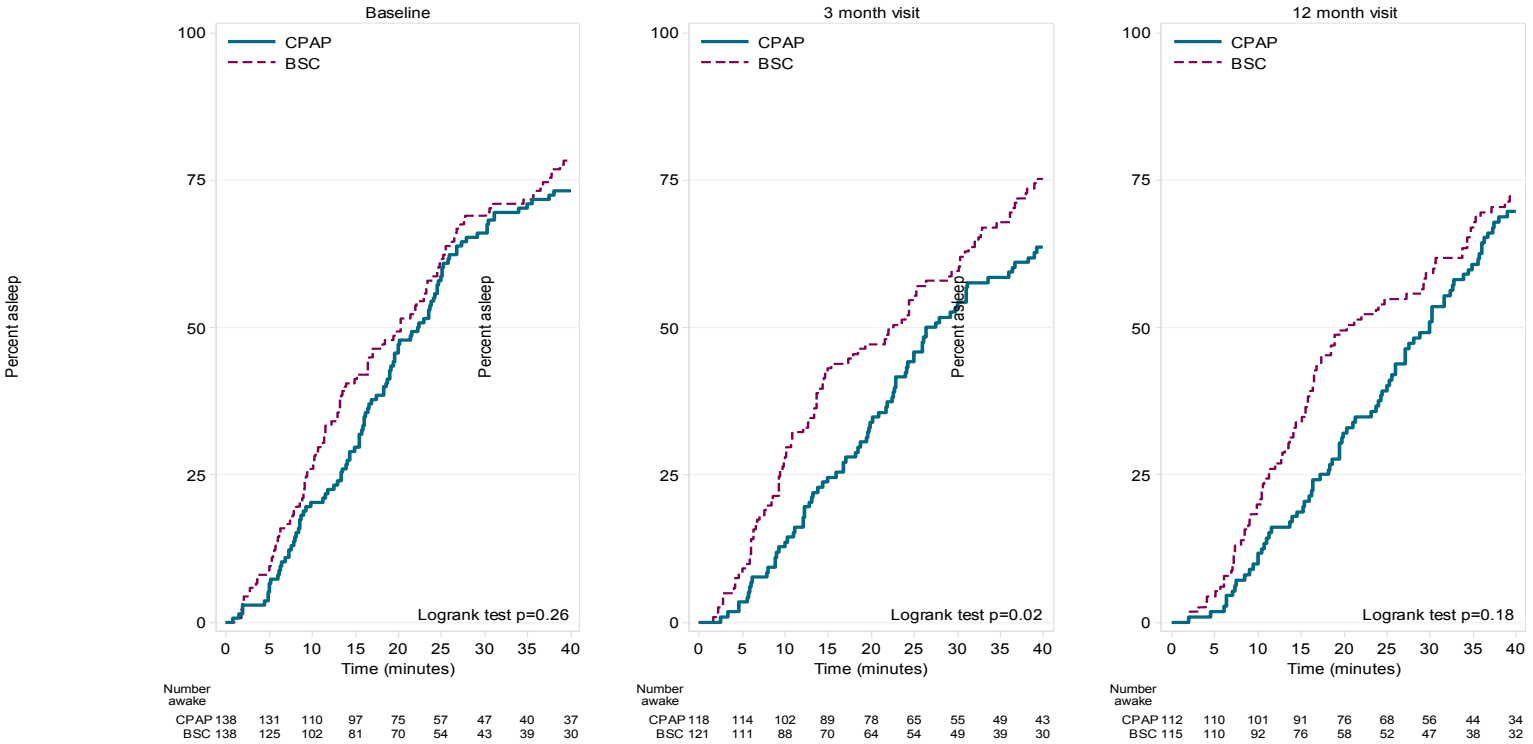
	Best supportive care	**Continuous positive airway pressure**	**Treatment effect (minutes)** **(95% CI)**	**p-value**
Number	121	116	2.8 (0.4, 5.2)	0.024
Baseline Mean time to sleep (minutes)	21.5 (13.4)	23.6 (12.7)		
Month 3 Mean time to sleep (minutes)	22.8 (13.9)	27.3 (12.4)		

Table 3.11b: Oxford Sleep Resistance test at 12 months

	Best supportive care	**Continuous positive airway pressure**	**Treatment effect (minutes)** **(95% CI)**	**p-value**
Number	115	110	2.6 (-0.1, 5.3)	0.058
Baseline Mean time to sleep (minutes)	21.4 (13.3)	24.5 (12.7)		
Month 12 Mean time to sleep (minutes)	23.8 (13.4)	27.8 (11.6)		

Data are mean (SD)

Figure 3.6: Kaplan-Meier plot of average time taken to fall asleep for each patient at baseline, 3 and 12 months



BSC: Best supportive care, CPAP: Continuous positive airway pressure

Quality of life and mood

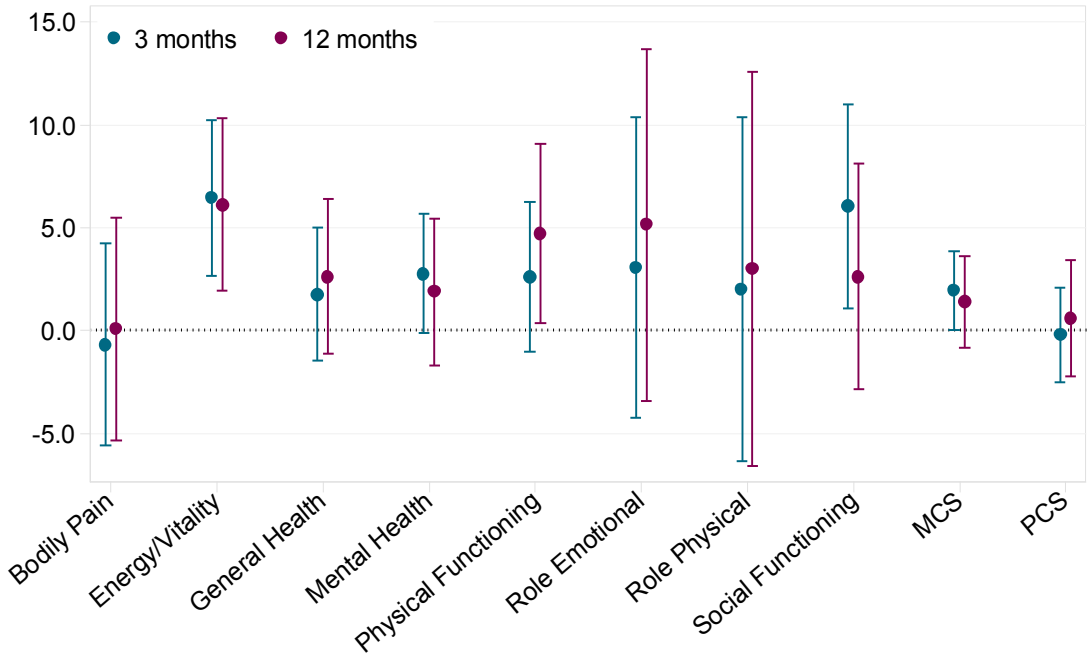
Generic quality of life was assessed using the SF-36, at 3 and 12 months. The difference between groups in the energy/vitality domain was statistically significant at 3 months (p=0.001) and 12 months (p=0.004) in favour of CPAP. The mental component score was also statistically significant at 3 months (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 3.7.

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 (p=0.005) and 12 months (p=0.001).

Mood was assessed using the HADS which was summarised into an anxiety 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.

The SF-36, SAQLI and HADS scores are shown in Tables 3.12a and 3.12b, (3 and 12 months respectively).

Figure 3.7: Short-Form 36 questionnaire treatment effects at 3 and 12 months



Adjusted treatment effects and their 95% CI, Continuous positive airway pressure versus Best supportive care, on the mental component score (MCS), physical component score (PCS) and the eight individual components at 3 and 12 months. Higher score indicate an improvement.

Table 3.12a: Quality of life and mood questionnaires at 3 months

Outcome	Best supportive care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 3		
Short form 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, 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, 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, 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, 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, 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, 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, 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, 11.0)	0.017
Mental Component Score	118	51.2 (9.9)	51.5 (10.0)	119	51.9 (10.1)	54.1 (8.9)	1.9 (0.0, 3.8)	0.046
Physical Component Score	118	31.0 (13.6)	31.7 (15.1)	119	34.2 (13.8)	34.2 (14.3)	-0.2 (-2.5, 2.1)	0.84
Sleep Apnoea Quality of Life Index	119	4.7 (1.2)	5.0 (1.1)	121	4.8 (1.2)	5.3 (1.1)	0.3 (0.1, 0.5)	0.005
Hospital anxiety and depression scale								
Anxiety	125	5.5 (3.7)	4.9 (3.5)	123	5.3 (4.0)	4.2 (3.4)	-0.5 (-1.1, 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, 0.1)	0.17

Data are mean (SD)

Table 3.12b: Quality of life and mood questionnaires at 12 months

Outcome	Best supportive care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 12	N	Baseline	Month 12		
Short form 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, 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, 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, 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, 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, 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, 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, 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, 8.1)	0.35
Mental Component Score	114	51.1 (9.8)	52.0 (10.4)	108	52.1 (10.2)	53.9 (9.4)	1.4 (-0.8, 3.6)	0.22
Physical Component Score	114	31.3 (13.2)	30.9 (15.3)	108	33.8 (13.9)	33.7 (14.9)	0.6 (-2.2, 3.4)	0.68
Sleep Apnoea Quality of Life Index	114	4.7 (1.2)	5.1 (1.1)	113	4.8 (1.2)	5.5 (1.1)	0.4 (0.2, 0.6)	0.001
Hospital anxiety and depression scale								
Anxiety component	117	5.5 (3.6)	4.5 (3.5)	114	5.2 (3.9)	4.1 (3.5)	-0.2 (-0.9, 0.5)	0.58
Depression component	116	4.4 (3.0)	4.2 (3.2)	114	4.6 (2.9)	3.9 (3.1)	-0.4 (-1.0, 0.3)	0.23

Data are mean (SD)

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 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), 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 -0.1seconds (95% CI -0.9 to 0.7) in favour of CPAP but 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 road traffic accidents 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 Table 3.13a and 3.13b.

Table 3.13a: Functionality (Townsend Disability Scale); nocturia, mobility (Timed up and go test); and accidents at 3 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 3		
Townsend Disability Scale	118	4.0 (4.5)	4.7 (4.8)	120	3.6 (4.0)	3.9 (4.1)	-0.4 (-1.0, 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, 0.3)	0.64
Timed up and go test (seconds)	117	12.0 (4.5)	12.5 (5.3)	117	11.4 (4.6)	11.3 (3.9)	-0.8 (-1.4, -0.1)	0.029
Domestic accidents N of patients (%)	124	12 (9.7)	14 (11.2)	121	6 (5.0)	18 (14.9)	1.53 (0.71, 3.31)	0.28
Driving accidents N of patients (%)	88	2 (2.3)	1 (1.1)	81	1 (1.2)	0		
All accidents N patients (%)	124	13 (10.5)	15 (12.1)	121	7 (5.8)	18 (14.9)	1.42 (0.67, 3.03)	0.36

Table 3.13b: Functionality (Townsend Disability Scale); nocturia, mobility (Timed up and go test); and accidents at 12 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 12		
Townsend Disability Scale	115	4.0 (4.3)	4.8 (5.2)	115	3.7 (4.1)	4.2 (4.5)	-0.1 (-0.9, 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, 0.3)	0.74
Timed up and go test (seconds)	107	11.7 (4.2)	12.0 (4.6)	108	11.5 (4.7)	11.8 (4.5)	-0.1 (-0.9, 0.7)	0.80
Domestic accidents N of patients (%)	117	12 (10)	18 (15)	113	6 (5)	9 (8)	0.49 (0.21, 1.18)	0.11
Driving accidents N of patients (%)	77	2 (3)	1 (1)	73	1 (1)	2 (3)		
All accidents N of patients (%)	117	13 (11)	19 (16)	113	6 (5)	11 (10)	0.59 (0.26, 1.32)	0.20

Data presented mean (SD), N (%)

Cognitive function

Cognitive function was assessed at 3 and 12 months with the following tests:- Mini-mental state examination, Trail making B, the Digit Symbol Substitution test and simple and four-choice reaction time. The results are shown in Table 3.14a and 3.14b. The difference between the groups was not statistically significant for any of the four tests at 3 or 12 months.

Table 3.14a: Cognitive function at 3 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 3		
Mini Mental State Examination	123	28.5 (2.1)	28.7 (1.8)	120	28.2 (2.1)	28.3 (2.1)	-0.2 (-0.6, 0.2)	0.25
Digit Symbol Substitution Test	123	38.7 (11.1)	39.6 (11.6)	119	37.5 (11.9)	39.5 (11.2)	0.8 (-0.9, 2.5)	0.36
Trail Making B (sec)	123	117.9 (58.9)	108.6 (49.7)	117	117.7 (55.0)	109.7 (42.7)	0.7 (-7.2, 8.5)	0.87
Simple reaction time (sec)	95	382.9 (111.5)	394.4 (129.2)	102	379.5 (85.4)	380.4 (89.9)	-12.8 (-39.9, 14.3)	0.35
4-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, 0.4)	0.82
Mean time for correct answers (sec)	100	680.8 (207.9)	666.6 (181.4)	102	682.3 (155.9)	699.4 (174.2)	32.0 (-0.7, 64.8)	0.055

Table 3.14b: Cognitive function at 12 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 12	N	Baseline	Month 12		
Mini Mental State Examination	116	28.5 (2.0)	28.5 (1.7)	113	28.3 (2.0)	28.5 (1.9)	0.1 (-0.3, 0.5)	0.65
Digit Symbol Substitution Test	116	39.4 (10.4)	40.6 (11.3)	113	37.2 (11.7)	40.0 (10.7)	1.1 (-0.6, 2.7)	0.22
Trail Making B (sec)	115	113.7 (55.8)	107.6 (47.2)	111	119.9 (57.9)	116.6 (54.9)	6.2 (-3.4, 15.8)	0.21
Simple reaction time (sec)	99	379.4 (108.1)	388.1 (108.1)	98	376.2 (84.6)	370.0 (94.6)	-16.4 (-39.1, 6.2)	0.16
4-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, 0.8)	0.26
Mean time for correct answers (sec)	100	681.9 (204.2)	688.4 (215.7)	99	678.8 (204.2)	688.1 (166.0)	1.8 (-33.6, 37.2)	0.92

Data presented as mean (SD)

Cardiovascular risk factors

The cardiovascular risk factors at 3 and 12 months are shown in Tables 3.14a and 3.14b respectively. CPAP reduced total cholesterol at 3 months compared to BSC by -0.2 mmol/litre (95%CI -0.3 to 0.0) (p=0.048). This was driven by a reduction in the LDL cholesterol of -0.15 mmol/litre (95%CI -0.29 to -0.01) (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 further reduced 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 blood pressure in the BSC group not seen in the CPAP group which lead to a difference between the groups of +3.7mmHg (95%CI +0.2 to +7.3) 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 3.15a and 3.15b. 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 3.15a: Cardiovascular risk factors at 3 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 3		
Systolic blood pressure (mmHg)	123	141.3 (19.8)	137.4 (16.3)	120	137.5 (18.1)	136.3 (15.9)	0.7 (-2.5, 3.8)	0.69
Diastolic blood pressure (mmHg)	123	78.2 (12.6)	76.4 (11.0)	120	77.2 (10.2)	76.1 (10.0)	0.1 (-1.9, 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, 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, 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, -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, 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, 0.5)	0.54
HbA1c (mmol/mol)	111	46.6 (11.7)	47.2 (12.3)	109	46.2 (11.2)	46.5 (11.6)	-0.3 (-1.6, 1.1)	0.70

Data presented as mean (SD)

Table 3.15b: Cardiovascular risk factors at 12 months

Outcome	Best support care			Continuous positive airway pressure			Treatment effect (95% CI)	p-value
	N	Baseline	Month 12	N	Baselines	Month 12		
Systolic blood pressure (mmHg)	116	141.7 (20.3)	135.5 (17.3)	113	138.0 (18.2)	137.5 (15.6)	3.7 (0.2, 7.3)	0.04
Diastolic blood pressure (mmHg)	116	78.5 (12.9)	76.2 (12.0)	113	77.8 (10.6)	76.2 (9.9)	0.2 (-2.1, 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, 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, 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, 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, 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, 0.4)	0.93
HbA1c (mmol/mol)	104	46.6 (11.8)	47.7 (14.9)	102	46.5 (11.2)	46.8 (12.5)	-0.9 (-3.1, 1.4)	0.45

Data presented as mean (SD)

Table 3.16a: Cardiovascular events at 3 months

Adverse Cardiovascular Event	Best support care			Continuous positive airway pressure			Odds ratio (95% CI)	p-value
	N	Baseline	Month 3	N	Baseline	Month 12		
Myocardial Infarction 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 CV events N (%)	124	60 (48)	5 (4)	121	56 (46)	7 (6)	1.54 (0.47, 5.06)	0.48

Data presented as N number (%)

Table 3.16b: Cardiovascular events at 12 months

Adverse Cardiovascular Event	Best support care			Continuous positive airway pressure			Odds ratio (95% CI)	p-value
	N	Baseline	Month 12	N	Baseline	Month 12		
Myocardial Infarction 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 CV events N (%)	117	56 (48)	17 (15)	114	51 (45)	14 (12)	0.87 (0.40, 1.88)	0.72

Data presented as N (%)

3.13.6 Tertiary outcome

Of the 140 patients randomized to CPAP treatment 120 (86%) at 3 months, and 99 (71%) at 12 months, reported they were still using CPAP. Actual CPAP data was obtained in 117 patients at 3 months with median usage of 1:52 hours/night (IQR 0:19 to 5:12), and 102 patients at 12 months with median usage of 2:22 hours/night (IQR 0:10 to 5:09). 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) at 3 months and 1:26 hours/night (IQR 0:04 to 4:45) at 12 months. CPAP usage data is shown in Table 3.17.

Table 3.17: Continuous positive airway pressure usage over 3 and 12 months

	Over first 3 months	Over 12 months
Number randomised	140	140
Number (%) analysed	117 (84%)	102 (73%)
Median use (mean hours/night)	01:52 (00:19-05:12)	02:22 (00:10 - 05:09)
Using CPAP >4 hours/night N (%)	41/117 (35)	36/102 (35)
Missing data and stopped CPAP N (%)	7/140 (5)	12/140 (9)
Median use (hours/night) Including patients with missing data	01:33 (00:13-05:00)	01:26 (00:04 - 04:45)

Data presented as number of patients N (%), median (IQR)

3.13.7 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 which included 2 deaths, 1 in the CPAP group and 1 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.

3.13.8 Self-reported side effects

This trial involved the use of an approved medical device which is the main stay of treatment for OSAS in middle aged populations. Therefore the TSC did not anticipate 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 independent data monitoring committee and trial steering committee and presented in Table 3.18. Treatment side effects are also incorporated in the SAQLI questionnaire (chapter 2, section 2.3.5).

Table 3.18: Self-reported side effects attributable to Obstructive sleep apnoea syndrome or its treatment

	Best supportive care	Continuous positive airway pressure
Number	138	140
Possibly related to Obstructive sleep apnoea syndrome (OSAS)		
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 ischemic attack, heart failure, angina)	5 (4)	2 (1)
Road traffic accidents	1 (1)	0
Probably related to Continuous positive airway pressure treatment (CPAP)		
Interface-related issues (e.g. claustrophobia, dislike of mask, leaking air, red/watery eyes, sore skin, pressure uncomfortable)	0	33 (24)
Upper airway problems (e.g. dry mouth, runny or stuffy nose, sinus problems, nose bleeds)	0	47 (34)
Abdominal bloating	0	4 (3)
Anxiety/dyspnoea related to CPAP	0	4 (3)
General inconvenience or intolerance of CPAP or accident using the CPAP machine	0	4 (3)
Possibly related to either OSAS or CPAP		
Disturbed sleep (e.g. insomnia, noisy equipment)	0	2 (1)
Social issues (e.g. partner disturbed, inconvenience)	0	2 (1)
Probably unrelated		
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)	0	2 (1)
Upper respiratory tract infection	0	7 (5)

Data presented as number of patients N (%)

3.14 Discussion

3.14.1 Main findings

The PREDICT trial was designed to assess the clinical efficacy of CPAP in older people with OSAS at 3 months and the cost-effectiveness over 12 months. CPAP improved sleepiness after 3 months by 2.1 points on the ESS compared to BSC. The beneficial effects were maintained at 12 months, and the magnitude of the improvements were similar to those seen in middle-aged patients with equivalent disease severity (McDaid, Griffin et al. 2009). This subjective improvement in sleepiness was corroborated by the improvement in objective sleepiness at 3 months.

CPAP also improved quality of life, both generic and disease specific. The CPAP related improvement was statistically significant for the QALYs calculated with the SF-6D, but not for EQ-5D, equating to one week and 2 days, respectively. The CPAP group also accrued marginally lower health care costs compared to BSC alone over 12 months. Overall the economic benefit of CPAP was linked to the reduced healthcare 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 due to the EQ-5D being a less sensitive measure of the changes in health status attributed to sleepiness compared to the SF-36 (from which the SF-6D is derived) (Jenkinson, Stradling et al. 1997).

3.14.2 Additional findings

The secondary outcomes related to cognitive function did not show any difference between the two groups despite improvements in sleepiness in the CPAP group. The baseline cognitive scores were often within the age-adjusted normative range, which may have resulted in a ceiling effect and limited the ability of the tests to find a significant difference between the two groups. Cognitive dysfunction is well recognised in middle-aged OSAS patients (Engleman 2004, Twigg, Papaioannou et al. 2010) potentially linked to changes in brain morphology (Morrell, Jackson et al. 2010). Although the impact of OSAS on cognitive function, separate from its effects on sleepiness and vigilance, is debated (Ferini-Strambi, Baietto et al. 2003, Rosenzweig, Williams et al. 2013). Additionally, in older patients with OSAS, cognitive dysfunction may be the result of a combination of multiple risk factors, and the aging process, and hence the capacity for neuronal recovery may be limited (Ayalon, Ancoli-Israel et al. 2010).

The cardiovascular risk factors showed a small improvement 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 (Robinson, Stradling et al. 2004). CPAP resulted in no improvement in blood pressure. In the BSC group there was a small improvement in the systolic blood pressure at 12 months. This finding echoes the results of a recent randomised controlled trial of cardiovascular risk in mild asymptomatic patients (Craig, Kohler et al.

2012) where CPAP usage, more specifically low usage, seems to slightly raise BP. We speculate this could be due to 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 (Douglas, Young et al. 2013). We speculate that the expected lack of improvement in nocturia with CPAP may have been due to the multifactorial nature of this symptom in older people (Guilleminault, Lin et al. 2004).

3.14.3 Treatment Adherence

The CPAP adherence was low at 3 and 12 months, which is likely to have diluted any treatment effect between the groups (Aloia, Ilniczky et al. 2003). Indeed, exploratory analyses revealed that the treatment effect was larger in patients with greater CPAP usage. The mean CPAP usage, and the percentage of patients using CPAP at 12 months was similar to another randomized controlled trial in the UK, all-be-it of a shorter duration in minimally symptomatic OSA (Craig, Kohler et al. 2012). Some authors have suggested that the minimal optimal usage of CPAP is 4 hours per night (Weaver et al. 2007) Although others supports a dose-response relationship between CPAP use and its benefits (McNicholas 1997).

The CPAP machines used in the PREDICT trial were auto-adjusting. Based on previous studies it is unlikely that the auto-adjusting machines resulted in the reduced CPAP usage (Massie, McArdle et al. 2003, Senn, Brack et al. 2003, Aloia, Stanchina et al. 2005). Furthermore as technology improves contemporary CPAP devices provide accurate usage data as opposed to the self-reported measures used previously in trials.

In the PREDICT trial we adopted a clinical approach to initiating and managing CPAP treatment, which may have resulted in a lower CPAP usage, compared to a more intensive trial protocols or shorter duration studies (Kushida, Nichols et al. 2012). However, by adopting our approach we have ensured that the PREDICT outcomes reflect clinical practice in the UK, which in turn strengthens the validity and applicability of the health economic assessment.

We speculate a further factor that may have contributed to the low CPAP usage in older people was 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 (Gagnadoux, Le Vaillant et al. 2011), however we knew just over half the patients slept alone.

3.14.4 Strengths and weaknesses

PREDICT was designed as a pragmatic trial, recruiting older OSAS patients with co-morbidity 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 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 so patients were not blinded to their treatment. Therefore the observed outcomes on sleepiness may be due to reporting bias or the 'placebo effect' of CPAP. However, the results of the objective sleep resistance test and the observation of a therapeutic dose response relationship between the treatment effect and CPAP usage supports a real effect. Furthermore, any placebo effect there might have been in the CPAP group is very likely to have disappeared at 12 months. Additionally the trial may have been too small to evaluate many of the secondary endpoints and no adjustments for multiple testing were made, hence the statistical significance of the secondary outcomes were interpreted cautiously.

3.14.5 Generalisability

With respect to generalisability, the PREDICT 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 at baseline, they were sufficiently symptomatic to seek treatment. At the other end of the disease spectrum exclusion of highly symptomatic OSAS patients in whom CPAP was considered mandatory is likely to have diminished the effect size. Patients with a higher ESS at baseline had a greater treatment effect in the exploratory analysis. Equally the marginal improvement in cost-effectiveness was greater in the more symptomatic patients.

CPAP 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 prior to treatment and additionally in those the patients who use CPAP treatment more.

3.14.6 Implication for health care

Clinical guidelines play an important role in improving healthcare for people with long term conditions however it is well recognised they often fail to address the effect of co-morbidity and polypharmacy (Hughes, McMurdo et al. 2013). There is also an inequality of research in older people with OSAS (McMurdo, Roberts et al. 2011), the PREDICT trial attempts to addressed this. The high quality data 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 growing older population. The results clearly support the use of CPAP for the treatment of OSAS in older people and I recommend CPAP treatment should be routinely offered to older patients with OSAS, and that current clinical guidelines should be modified accordingly.

3.15 Conclusion

The PREDICT trial has been the longest and most comprehensive randomised controlled treatment trial in older OSAS patients to date, assessing both the therapeutic and economic impact of CPAP treatment. The trial addressed the lack of research in older people with OSAS and the results 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.

Chapter 4: Brain morphology and cognitive function in older people with obstructive sleep apnoea after continuous positive airway pressure treatment

(The Brain MRI study)

4.1 Introduction

4.1.1 Overview

Cognitive impairment can be described as a collection of symptoms, including a decline in memory, reasoning and communication associated with a gradual loss of skills needed for daily activities. It is not a single identity with one cause but can be thought of as a spectrum of diseases or disability arising from multiple risk factors such as age, environment, genes and pathologies such as smoking, head injury and cardiovascular disease (Petersen, Stevens et al. 2001) which leads to structural and chemical changes in the brain (Dementia NICE guidelines no.42).

Obstructive Sleep Apnoea (OSA) is a disease that increases in prevalence with aging. Intermittent hypoxia and sleep fragmentation secondary to OSA are both known to affect neurogenesis. Therefore, despite the high prevalence of OSA in older people as discussed earlier in section 1.4.2 and the increased prevalence of cognitive impairment in older people (see below in section 4.2.2) there is a paucity of research on the relative benefits or risks of CPAP therapy on cognitive function in older people with OSA.

Cognitive dysfunction is frequently recognised in patients with OSAS which will be discussed in section 4.3, and although has been studied since the 1980's the pathogenesis and clinical presentation remain hotly debated. (Gozal 2013, Rosenzweig, Williams et al. 2013). The structural neuronal sequel of OSA is controversial and various imaging techniques have been used to examine metabolic and structural changes and subsequently the potential response to CPAP therapy which will be discussed in section 4.4.

4.2 Cognitive function

4.2.1 Description of cognitive impairment

An accepted definition of mild cognitive impairment is the maintenance of overall cognitive function with no significant impact on activities of daily living but impairment in at least one neuropsychological test. Mild cognitive impairment is a pathological impairment of memory, beyond that seen in normal aging (Morris and Price 2001). Epidemiological data confirms mild cognitive impairment represents a transitional phase between normal aging and dementia for many individuals. The symptoms of mild cognitive impairment may be subtle and unrecognised as they have developed over the years insidiously or accepted as an expected consequence of aging. Indeed normal aging is associated with changes in cognitive function such as less effective learning (Fisk, Rogers et al. 1997) reduced ability for abstract and complex problem solving, reasoning, mental inflexibility, behavioural slowing (Lezak

1983) and the ability to encode new memories (Hedden and Gabrieli 2004). Often patients, family or friends may have reported worsening memory but equally this may not be apparent.

4.2.2 The prevalence of cognitive impairment in the general population

There are no clear prevalence figures for mild cognitive impairment although it is estimated the prevalence increases with age, roughly doubling every five years over the age of 65. The age-specific prevalence of dementia as reported by the Alzheimer's Society UK reported 0.1% for all those aged 40-64 years, 2% aged 65-69 years, 5% aged 70-79 years and 20% for those aged 80 and over.

4.2.3 The aetiology of cognitive impairment

The aetiology of cognitive impairment is thought to be multifactorial including increasing age and genetic factors, such as having a common genetic polymorphism. The apolipoprotein E (ApoE) gene Q4 allele greatly increases the risk of developing dementia; although 25% of the population has one or two copies of polymorphism (Saunders and Roses 1993). Genetic risk is also influenced by the environment (Breitner et al 1995), limited education (Ott el al 1995) and head injury (Mortimer et al 1991, Mayeux at al 1995). Vasular disease (Skoog et al 1996), vascular risk factors (Kivipelto et al 2001) and smoking (Ott et al 1998) are all recognised in contributing to chemical and structural changes in the brain that can produce neural cell death (Dementia NICE guidelines no.42).

4.3 Cognitive function in Obstructive sleep apnoea

4.3.1 Cognitive impairment in Obstructive sleep apnoea

The evidence for impaired cognitive function in OSAS is established although the extent of the cognitive deficits in patients with OSAS is complex and debated. Recent reviews (Sforza and Roche 2012, Ferini-Strambi, Marelli et al. 2013) and a meta-analysis (Bucks, Olaithe et al. 2013) have been completed in this area. To simplify and summarise the data obtained from cognitive studies, these review categorizes cognition into four discrete domains: intellect, memory, attention and executive function. There is a general consensus that OSAS impacts on attention and executive functioning, plus possibly effects on sub-components of memory, but overall there appears to be a negligible effect of OSAS on intellect. The four domains and the relevant meta-analysis are summarised below. The individual cognitive tests which can be used in each domain are not discussed as there are a large number of different validated cognitive tests which have been used.

Intellect: A meta-analysis of 25 studies including 1092 OSA patients and 899 controls by Beebe *et al* 2003, showed no significant impairment in intellectual function in OSA patients compared with control subjects and normative data. Furthermore (Alchanatis, Zias et al. 2008) reported that OSA patients

with high intellect scores in the 90th percentile had normal attention. The authors suggested that high intelligence may be protective, due to cognitive reserve.

Memory: Several studies have shown impairment in short-term and long-term memory (Bedard, Montplaisir et al. 1991, Ferini-Strambi, Baietto et al. 2003, Naegele, Launois et al. 2006) and verbal but not visual memory (Kloepfer, Riemann et al. 2009, Twigg, Papaioannou et al. 2010). It is general accepted the impact of OSA on specific memory components it still not fully understood.

Attention: Overall it is accepted OSA impairs attention (Mazza, Pepin et al. 2002, Bawden, Oliveira et al. 2011, Shpirer, Elizur et al. 2012). OSA may also impact motivation, which in turn manifests as a lack of attention.

Executive function: Many studies have shown impairment in executive function a recent systematic review suggested that this domain was the most sensitive and most impaired in OSA (Kilpinen, Saunamaki et al. 2014). The most recent meta-analysis by (Bucks, Olaithe et al. 2013) echoed this finding more over the meta-analysis suggested it was independent of age and disease severity.

One of the difficulties in comparing data in this field is there is no agreed definition of cognitive impairment and indeed no consensus on how to measure or quantify cognitive impairment. Large observational cohort studies have not found a relationship between OSA and cognitive impairment. . Moreover age, obesity, and cardiovascular disease are all known risk factors for cognitive impairment in the general population. Studies in this area also vary by sample size and characteristics, methodology and design and in addition the large numbers of different cognitive tests have been used making comparison difficult. The categorisation of cognitive tests into domains may be helpful but it is also an over simplification as each test measures different aspects of cognitive function to a greater or lesser degree. Never-the less it is important to understand the impact of OSA on cognitive function and the effect of treatment due to the clinical and public health relevance.

4.3.2 The aetiology of cognitive impairment in obstructive sleep apnoea

Several mechanisms have been proposed in the pathogenesis of cognitive impairment in OSA. In earlier studies excessive daytime sleepiness was the proposed mechanism by influencing attention. The field now accepts that cognitive impairment extends beyond the simple association with sleepiness. The focus recently has been on intermittent nocturnal hypoxaemia and sleep fragmentation and their effect on neuronal function.

Findley et al observed that greater hypoxemia was associated with poorer memory performance (Findley, Barth et al. 1986). More recently a 5 year observational cohort of 298 older women suggested intermittent hypoxia and not sleep fragmentation or duration was associated with mild cognitive impairment or dementia (Yaffe 2011).

Sleep fragmentation has also been proposed as a mechanism (Ayalon, Ancoli-Israel et al. 2009). This has been supported by animal models showing both sleep fragmentation (Sportiche, Suntsova et al. 2010), and intermittent hypoxia (Gozal, Row et al. 2003) can independently lead to poorer cognitive function. The latter study showing neural loss or apoptosis in the hippocamous and prefrontal cortex, these areas being associated with memory processes and executive functions. Furthermore animal models of intermittent hypoxia in Apolipoprotein E (ApoE) deficient mice and wild mice confirmed both groups had cognitive impairment, although the ApoE deficient mice had an increased oxidant and inflammation response and increased deposits of beta amyloid the pathophysiological hallmark of neurodegenerative disease (Kheirandish, Row et al. 2005). This proposed mechanism has not been confirmed in humans.

The severity of OSA (sleep fragmentation, sleepiness, AHI or the degree of hypoxemia) does not appear to be linked to performance in cognitive tests (Olson, Cole et al. 1998, Sauter, Asenbaum et al. 2000). In addition the neurcognitive symptoms of excessive sleepiness, depression, disturbances in attention, dysmetria of thought and affect, executive and verbal memory deficits would support the involvement of the hippocampus although there have been inconsistent findings which will be discussed in section 4.4. Patients with severe OSA may have minimal sleepiness and no detectable cognitive dysfunction, while those with mild OSA can be markedly symptomatic. In summary the pathogenesis is probably multifactorial, and as yet there is a weak correlation between disease severity, duration and cognitive impairment.

4.3.3 Cognitive function in older people with Obstructive sleep apnoea

In older people the research surrounding cognitive impairment and OSA is confusing due to the confounding factor of normal aging and the impact it has on cognitive impairment. Mathieu et al 2007 found cognitive impairment was independently related to both OSA severity and increasing age (Mathieu, Mazza et al. 2008), but the coexistence of both factors did not result in increased cognitive dysfunction, as severity of OSA was more strongly related to cognitive decline in younger patients. Ayalon et al 2010 showed cognitive dysfunction, on performance of the Go-No-Go cognitive task, in older subjects with OSA. However, no significant impairment was found when OSA and increasing age were considered separately (Ayalon, Ancoli-Israel et al. 2009). Finally, Cohen-Zion et al found a significant association between the severity of OSA and self-reported severity of daytime somnolence, but including other variables (e.g. cognitive impairment) in the model, only the relationship between cognitive impairment and excessive somnolence remained significant (Cohen-Zion 2001). More recently poorer sleep quality has been associated with factors that may accelerate cognitive decline in older people. Ideally longitudinal studies should be carried out to address this issue, although in older people this may be problematic due to high level of co-morbidity, drop outs and death.

In summary as both the prevalence of OSA and cognitive impairment increases with age establishing the association between OSA and cognitive impairment is complex and more data is required.

4.3.4 OSA in patients with cognitive impairment.

The prevalence of OSAS is higher among patients with dementia. (Ancoli-Israel, Klauber et al. 1991). The results of an early population based longitudinal study by Cohen *et al* suggested that declining cognitive function, as measured by the MMSE was associated with both the increasing severity of OSA (measured by the respiratory disturbance index) and self-reported increasing daytime sleepiness. Unfortunately there were several limitations to this study, there was a very high attrition rate; out of the 427 participants enrolled, after 15 years of follow up only 25 patients remained and the authors concluded that the remaining sample was not necessarily representative of the population seen in a sleep clinic. Once other variable were included in the analysis only the relationship between cognitive impairment and excessive somnolence remained significant (Cohen-Zion, Stepnowsky et al. 2001).

Studies reporting OSA in patients with mild cognitive impairment are often based on patient or bed partner's interviews without objective or diagnostic measures of cognitive impairment or OSA. Additionally in studies were a diagnostic test was completed OSA was often grouped with other dysomnias contributing to sleep disturbance. The prevalence of primary sleep disorders such as rapid eye movement (REM) sleep behaviour disorders (RBDs), restless legs syndrome (RLS), periodic limb movements (PLMs) increases with age and cognitive impairment (Bombois, Derambure et al. 2010).

Moving through the spectrum of cognitive impairment to those patients with a diagnosis of dementia but still living in the community, reports suggest between 19 - 44% of these patients complain of sleep disturbance the wide range reflecting the lack of clear diagnosis.

Patients institutionalised with dementia could be considered the extreme end of the spectrum of cognitive impairment. This group of patients have been better characterised and studied particularly by the author Ancoli-Israel *et al.* who reported 70 – 80% had an AHI ≥ 5 events/hr, and up to 48% had an AHI ≥ 20 events/hr. The most common cause of dementia is Alzheimer's disease (AD) representing 60-70% of the dementias. Ancoli-Israel went on to measure the prevalence of SDB in a smaller group of patients with mild to moderate AD, 53% had an AHI ≥ 10 events/hr. This high prevalence of SDB in patients diagnosed with AD was also reflected in a study by Rose *et al.* 59 patients with geriatrician diagnosed dementia with nocturnal agitation behaviour underwent 2 nights of in-home attended PSG, 49% had SDB defined as AHI > 15 events/hr (Rose 2011).

ApoE gene is a common genetic risk factor for Alzheimer's Disease and subsequent cognitive impairment. ApoE has been associated with an increased risk of developing OSA. Analysis of data from the Wisconsin Sleep Cohort Study showed a significantly higher probability of moderate to severe OSA (AHI ≥ 15) with ApoE independent of age, sex, BMI and ethnicity than in subjects with an AHI < 15 (Kadotani, Kadotani et al. 2001). The Sleep Heart Health study also showed the same gene was associated with an increased odds ratio for OSAS (Gottlieb, DeStefano et al. 2004). Although a meta-analysis suggested the association was weak (Thakre, Mamtani et al. 2009).

In summary the prevalence of OSA in patients with cognitive impairment may be up to 50%. Given the already high prevalence of sleep disordered breathing in older people, this association and its subsequent consequences needs further clarification as currently there are no treatments available that cure, or even alter the progressive course of dementia. It has been speculated that CPAP treatment may offer a way of slowing the progressive course of dementia.

4.4 Brain morphology in obstructive sleep apnoea

The structural neurocognitive sequel of OSA is controversial. The most commonly used techniques for examining brain morphology and metabolic function are structural and functional magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and positron emission tomography (PET). This section of my thesis will summarise the studies using an MRI analysis technique called Voxel-based morphometry (VBM) which was the technique used in the study presented in this chapter (section 4.9), although the discussion will be limited as the Brain MRI data is currently being analysed and cannot be presented in this thesis.

A review of the current literature carried out in 2013, identified several imaging studies that have shown OSA patients have reduced grey and white matter in several brain regions that regulate memory and executive functions. The neuroanatomical regions most commonly reported as affected are summarised in Table 4.1. The most consistent finding is a reduction of grey matter in the left hippocampus, although there is high variability in the results across studies and the findings are not always concordant between different neuroimaging methods. Most studies were small with fewer than 50 patients, with the exception of one study by (Morrell, Jackson et al. 2010). The patient samples are heterogeneous in respect to diagnostic criteria, intelligence, age and imaging analysis methods. All studies were in sleepy patients and predominantly men.

When cognitive function is preserved in OSA patients functional brain MRI imaging has revealed that brain activation is increased, compared to the activation that occurs in healthy controls performing the same task. The association between preserved cognitive function, and greater activation in OSA patients, suggests that increased cerebral recruitment is required to maintain to same level of cognitive performance in these patients (Ayalon, Ancoli-Israel et al. 2006). Similar preservation of cognitive function, with compensatory increased cerebral activation has been found in normal older subjects; however older patients with coexistent OSA show decreased cerebral activation with cognitive function (Ayalon, Ancoli-Israel et al. 2009). This suggests that age and OSA may have a synergistic effect on cerebral activation or the older brain is no longer able to compensate or up-regulate.

Table 4.1: Summary of Brain MRI studies (Voxel based morphometry) in Obstructive Sleep Apnoea

Study	Macey et al 2002	Morrell et al 2003	O'Donoghue et al 2005	Yaouhi et al 2009	Morrell et al 2010	Joo et al 2010	Canessa et al 2011	Torelli et al 2011
Sample size	21 OSAS 21 Controls	7 OSAS 7 Controls	27 OSAS 24 Controls with comorbidities	16 OSAS 14 Controls	60 OSAS 60 Controls	36 OSAS 31 Controls	17 OSAS 15 controls	13 OSAS 9 controls
OSA Severity AHI (events/hr) Mean (SD)	34 (20)	Median 28 (Range 25-40)	71 (17)	38 (14)	55 (95% CI 48-61)	52.5 (Range 31.6-105.9)	56 (19)	52.5 (26)
Statistical threshold	p<0.001 uncorrected for multiple comparisons	p<0.01 corrected for multiple comparisons	P<0.05 corrected for multiple comparisons	p<0.005 uncorrected for multiple comparisons	P<0.05 corrected for multiple comparisons	P<0.05 corrected for multiple comparisons	P<0.05 corrected for multiple comparisons	P<0.05 corrected for multiple comparisons
Changes in grey matter concentration	Diffuse changes across the entire brain: frontal & parietal cortices, temporal lobe, anterior cingulate, hippocampus and cerebellum	No significant reductions. Focal reduction within the left hippocampus (p=0.01)	No significant reductions	Bilateral prefrontal cortex, inferior parietal gryrus, right temporal cortex, occipital cortex, thalamus, basal ganglia,hippocampus and cerebellum	Left cerebellum, right temporal gyrus	Diffuse changes across the brain.	Left posterior-parietal cortex, right superior-frontal gyrus, left hippocampuS	Left hippocampus, bilateral temporal lobe

OSAS: Obstructive sleep apnoea syndrome. Table adapted from Glasser et al Breathe 2011, volume 7, no. 3 (Hermes syllabus)

4.5 The role of CPAP treatment in modifying cognitive function

As discussed earlier (section 1.7) it is now accepted that CPAP normalizes oxygen desaturation and sleep fragmentation and modifies the symptoms of excessive daytime sleepiness in middle aged people. There is also a general assumption that CPAP improves cognition in patients with OSAS. However, although there have been numerous studies, reviews and meta-analysis looking at effect of CPAP on cognition since the early 80s. To date there has not been a unanimous finding.

The most recent, largest and longest RCT treatment trial to studying the effect of CPAP specifically on cognition in patients with OSA was the The Apnea Positive Pressure Long-term Efficacy Study (APPLES) (Kushida, Nichols et al. 2012). This was a 6-month, randomized, double-blind, sham-controlled multicentre trial. 1,105 people with OSA were randomized, and 1,098 contributed to the analysis of the primary outcome measures. The mean age of patients was 52 years. Three cognitive variables used were:

- Attention and psychomotor function (Pathfinder number test-total time)
- Learning and memory (Buschke selective reminding test-sum recall)
- Executive & frontal-lobe function (Sustained working memory test-overall mid-day score)

The primary analysis showed CPAP improved only executive and frontal-lobe function at 2 months, but no difference on any of the other outcomes at 6 months. CPAP was shown to reduce sleepiness measured subjectively by the ESS and objectively by the maintenance of wakefulness test. The findings were confirmed when the analysis was stratified by OSA severity (AHI or oxygen saturation parameters). The authors concluded CPAP use resulted in mild, transient improvement in executive and frontal-lobe function for those with severe OSA (AHI>30). This study had some limitations; there was some evidence of worsening in the sham arm at 2 month. Furthermore, the population studied may not have been reflective of patients seen in clinical practice as some patients were recruited from advertisements.

The results of the most recent meta-analysis and are summarised below.

Meta-analysis: (21 studies) OSA vs. controls, 19 pre & post CPAP. Executive function is impaired in OSA, and improved with treatment independent of age and disease severity (Olaithe and Bucks 2013)

Meta-review: (5 studies) CPAP treatment improves executive dysfunction, delayed long-term verbal and visual memory, attention/vigilance and global cognitive function (Bucks, Olaithe et al. 2013)

Meta-analysis: CPAP had a small but significant effect on attention, a non-significant effect on other domains (Kylstra, Aaronson et al. 2013).

Finally there have been a several small preliminary studies of CPAP treatment in people with OSA and cognitive impairment (Chong, Ayalon et al. 2006, Ancoli-Israel, Palmer et al. 2008). The study by Ancoli-Israel *et al*. randomised 78 patients with mild to moderate Alzheimers disease to CPAP treatment versus sham CPAP and concluded it was well tolerated and reduced daytime sleepiness. Later (Cooke, Ayalon et al. 2009) from the same group completed a smaller follow up study in the original study group and studied 10 of the original patients; 5 of whom continued CPAP treatment, and 5 who discontinued CPAP. This preliminary study raised the possibility that CPAP treatment may slow cognitive deterioration although the patient selection was highly selective and assessments were subjective and provided by the care givers.

In summary, there are many factors that may contribute to cognitive impairment and possible responses to CPAP therapy. Baseline cognitive function can vary significantly between individuals, but is thought to generally stable within individuals. Individuals may have a different vulnerability or protection to impairment from sleep loss, fragmentation and intermittent hypoxia. Which patients benefit from treatment, what duration of treatment is required, and when the optimal intervention period occurs remain unknown. Moreover, older patients with OSA may be more vulnerable and may have insufficient cognitive reserve capacity to overcome hypoxia-induced neural changes.

4.6 Aims

The aim of the study presented in chapter 4 was to investigate the impact of CPAP treatment on cognitive function in older people with OSA. The design of the study was to investigate cognitive function in more detail than the earlier PREDICT trial (chapter 3, section 3.13.5). Additionally I wanted to study the effect of CPAP therapy on brain morphology in older people with OSA. I tested the hypothesis that CPAP could modify cognitive function and/or brain morphology in older patients with OSA.

The specific aims of the study were to determine if:-

- Treating intermittent hypoxia secondary to OSA with CPAP was associated with an improvement or stabilization in cognitive function at 6 months.

- Treating OSA was associated with changes in brain morphology studying overall brain volume, plus white and grey matter in pre-defined areas of the brain at 6 months.

- If the changes in cognitive function were associated with changes in brain morphology

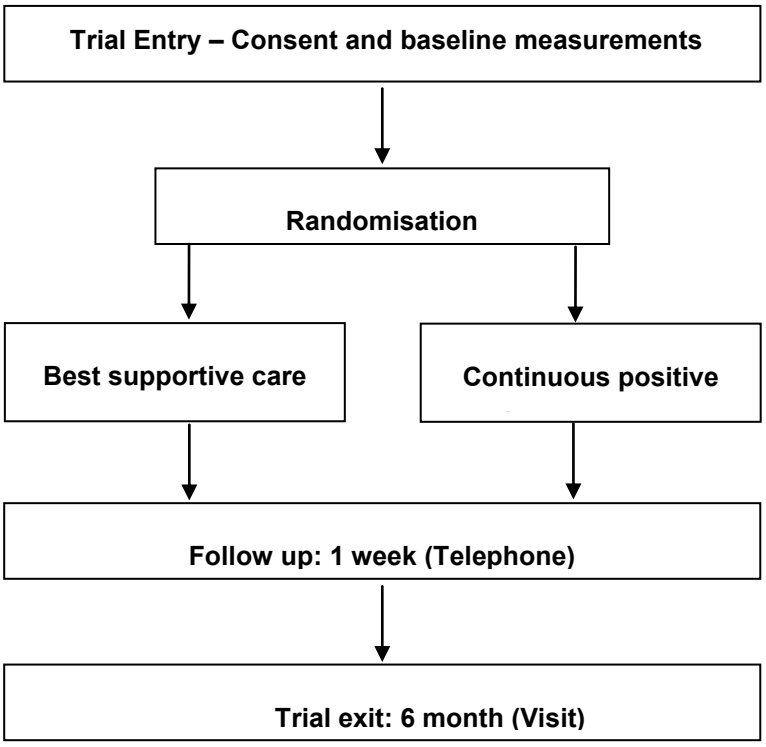
In this chapter I will present the results of the cognitive tests, the brain MRI scans are currently being analysed and hence are not available to be presented in this thesis.

4.7 Methods

4.7.1 Trial design

This study was a pragmatic, single-blinded (investigator blinded), parallel group, single centre, randomised controlled trial (RCT) of 6 months duration (Figure 4.1). All patients were randomised to receive CPAP, plus best supportive care (BSC), or BSC only. The trial design is shown in Figure 4.1

Figure 4.1 Trial Design



4.7.2 Recruitment

Recruitment took place within the Royal Brompton and Harefield NHS trust. Patients had been referred for assessment and diagnosis of OSA. The study was completed in the Royal Brompton Hospital research laboratory and Clinical Research Facility. The brain MRI scans were completed in the Radiological Sciences Unit at Charing Cross Hospital, Imperial College Healthcare NHS trust.

4.7.3 Ethical considerations

The study was given a favourable ethical opinion from the national research ethics service, London. Research Ethics Committee (REC) reference 10/H0711/101. A copy of the approval is provided in appendix 3. Sponsor insurance and indemnity was provided by Imperial College London. NHS research and development and site specific approval was obtained for the Royal Brompton and Harefield NHS Foundation trust and the Imperial College Healthcare NHS trusts.

4.7.4 Eligibility criteria

Patients were invited to participate if they were aged 65 years or older at the enrolment visit, with a diagnosis of OSA. OSA was defined as ≥ 4% Oxygen desaturation index (ODI) > 7.5 events/hour, the ESS was measured although an ESS criterion was not set. Patients were not admitted to the trial if any of the following criteria applied:-

- Arterial awake oxygen saturation <90% on room air
- Forced expiratory volume in 1 second/Forced vital capacity (FEV_1 / FVC) ratio <60%
- Substantial problems with sleepiness driving (in those who are still driving)
- Currently using heavy good vehicle (HGV) or professional service vehicle (PSV) driving license
- Shift work
- Any very severe complication of OSAS such that CPAP therapy was mandatory
- Inability to give informed consent or comply with the protocol

These exclusion criteria were similar to the PREDICT trial in chapter 3, section 3.3.1. In addition as this study was examining cognitive function and brain morphology the following additional exclusion criteria were required.

- Previous or current psychiatric disorders (including alcohol or drug abuse)
- Psychotropic medications (including all sedating medications, anxiolytics, major tranquilizers, antipsychotics, hypnotics, anticonvulsants)
- Neurological disorders
- Previous head injury resulting in loss of consciousness or notable cognitive deficit

Furthermore as a Brain MRI scan was going to be completed any contraindication to undergoing an MRI scan, were also exclusion criteria. The main exclusion criteria for MRI were:-

- Pacemaker or pacing wires
- Aneurysm clips in the head
- Artificial heart valves or coronary stents
- Metal implants
- Cochlear implants
- Programmable shunts, deep brain stimulator or neurostimulator
- Shrapnel or metal fragments in the body or eyes

Imperial College Healthcare NHS trust provided a standard NHS Brain MRI consent form which is included in appendix 2

4.7.5 Screening

All patients potentially eligible to participate in the study were identified from sleep and respiratory clinics by myself attending outpatient clinics and were initially assessed either by review of case notes or in person. Once the diagnosis of OSA was confirmed they were contacted and offered trial entry. Consecutively eligible patients were offered trial entry. Screening logs were kept documenting the number of patients assessed for eligibility and, if applicable, the reason(s) for non-inclusion.

4.7.6 Informed consent

Patients completed written informed consent to the trial and brain MRI scan at the enrolment visit. Consent for the Brain MRI was also reassessed independently by staff completing the brain MRI scan.

4.8 Intervention

Patients were randomised to receive CPAP plus BSC or BSC alone. The interventions have been previously described in chapter 2, section 2.2.

4.9 Assessments

Both groups had identical visit schedules, Table 4.2. Structured clinical assessments were performed at baseline and 6 months. All patients received a telephone call at 1 week to optimize CPAP adherence and offered additional support via telephone or additional visits as required. All patients enrolled in the trial completed a NPSG prior to treatment allocation the following morning. Domiciliary

overnight, pulse-oximetry was completed at 6 months. Table 4.3 summarizes the assessment completed at each time point.

Assessment visits were carried out in the Royal Brompton Hospital research laboratory and clinical research facility. The brain MRI scans were completed on a 3T scanner (Siemens, Germany) in the Radiological Sciences Unit at Charing Cross Hospital, Imperial College Healthcare NHS trust. The brain scan sequence was approximately 60 minutes and included T1 and T2 weighted and diffusion tension imaging. All MRI scans were done on the afternoon prior to the NPSG and randomization. The cognitive test panel was conducted in a quiet laboratory at 19.00 before their NPSG. Patients were asked to abstain from caffeinated beverages for the duration of their stay.

Occasionally, research staff agreed to see a patient in their own home when the patient was unable to attend the hospital.

Table 4.2 Visit schedule

Time	Event
Day 1	
13.00	Patient arrival Royal Brompton Hospital Consent and enrolment
14.00	The Oxford Sleep Resistance Test
15.00	Taxi to Charing Cross Hospital
16.00	Brain MRI scan
18.00	Patient returns to Royal Brompton Hospital Enrolment completed
18.30	Evening meal
19.00	Cognitive tests
20.00	Set up for Nocturnal Polysomnogram
Day 2	
08.00	Fasting bloods
08.30	Breakfast
09.00	Randomised and intervention delivered

Table 4.3 Summary of assessments by time point

Assessments and Measurements	Screening	Baseline	Week	Month
			1	6
Eligibility and exclusions	*			
Informed consent and enrolment	*	*		
Nocturnal polysomnogram		*		
Overnight pulse oximetry				*
Overnight respiratory polygraphy	*			
Clinical assessment visit including sleep history		*		*
Demographics		*		
Caffeine and alcohol intake		*		*
Exercise history		*		*
Anthropometry		*		*
Blood pressure and resting pulse		*		*
Fasting bloods		*		*
Subjective sleepiness (Epworth Sleepiness Scale)		*		*
Objective sleepiness (Oxford Sleep Resistance test)		*		*
Disease specific quality of life (SAQLI)		*		*
Mood (Hospital Anxiety and Depression Scale)		*		*
Cognitive function		*		*
Telephone call			*	
Continuous positive airway pressure adherence			*	*
Continuous positive airway pressure side effects			*	*
Adverse events			*	*

4.10 Outcome measures

4.10.1 Primary outcome

The primary outcome was the change in cognitive function from baseline to 6 months as measured by the cognitive test panel described in chapter 2, section 2.4.

4.10.2 Secondary outcomes

These included the change from baseline in:-

- Brain morphology. The volume of the whole brain and predefined areas of gray and white matter within the temporal and parietal lobes were measured. In particular the medial temporal lobe, hippocampus, parahippocampal gyrus, amygdalar and entorhinal cortex. The measurements will be processed using the automated techniques voxel-based morphometry (VBM) and region of interest analysis (ROI). VBM is used to analyse MRI scans and characterize structural differences in grey and white matter volume across the whole brain. Detection of a reduction or increase in brain matter reflects neuronal change; this technique has been validated and used in a number of different brain diseases and previously used within our group to examine brain morphology.
- Subjective sleepiness measured by the ESS score (chapter 2, section 2.3.3).
- Objective sleepiness measured by the Oxford Sleep Resistance test (OSLER) (chapter 2, section 2.3.4).
- Disease specific quality of life was assessed using Sleep Apnoea Quality of Life Index (SAQLI) (chapter 2, section 2.3.5).
- Mood assessed using the Hospital Anxiety and Depression Scale (HADS) (chapter 2, section 2.3.5).
- Functionality assessed by the Townsend Disability Scale (TDS) (chapter 2, section 2.3.6)
- Treatment compliance was measured objectively by downloading a smart card in the CPAP machine at the 6 month visits (chapter 2, section 2.6).

4.11 Data collection

Data generated was collected on case report forms (CRF) included in appendix 2 and entered on to a database with help from staff in the research laboratory. The member of 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% check was conducted for the inclusion criteria. 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 and resolved wherever possible. Quality control of CRF data entry was completed on a regular basis throughout the duration of the study.

4.12 Randomisation

Patients were randomised after completing their enrolment visit, the morning after they had completed the NPSG. Patients were allocated on a one to one basis, using block randomisation stratified by disease severity (enrolment ESS > 9 v ≤ 9) and Oxygen desaturation index ODI (ODI >15 v ≤15).

4.12.1 Blinding

As discussed earlier in chapter 3, section 3.8.1 this was a physical device trial, and hence the treatment allocation for the individual patients could not be concealed.

4.13 Sample size

A recent cross-sectional study from our own department compared cognitive function in healthy participants and OSA patients reported mean differences and standard deviations for several different tests Twigg *et al* 2010. The values for the cognitive tests that were used in the present study are listed in table 4.4

Table 4.4 Cognitive tests with sample sizes

Test	**Sample 1**		**Sample 2**		**Sample Size in both groups**
	Mean	**Sd**	**Mean**	**Sd**	
Spatial Span Forwards	8	2	6	1	10
Spatial Span Backwards	8	2	5	1	5
Logical Memory (immediate)	43	10	36	22	94
Logical Memory (delayed)	27	7	22	7	31

These data indicate that between group differences can be calculated at an alpha error level of 5% (corresponding to a 95% confidence interval) and a beta error level or Statistical Power [1 - Beta] of 80% assuming CPAP treatment reverses any reduction in cognitive function in older patients with OSA to levels comparable to those seen in these healthy people. 20 Patients in each group would demonstrate a difference in spatial span forwards and backwards test.

In addition a recent study using the STROOP test has shown that the mean time to complete the test is 39 seconds in OSAS patients vs. 23 seconds in controls SD 8.1 (Canessa, Castronovo et al. 2011). Assuming a more conservative difference of 8 seconds between the 2 groups. Using an alpha error levels of 5% and a Beta error or 80% it is calculated 17 patients are required in each group to detect this difference.

Several investigators have examined the neuroanatomy of OSA patients using structural MRI (Macey, Henderson et al. 2002, Morrell, McRobbie et al. 2003, Morrell, Jackson et al. 2010). In these studies changes in grey matter have been identified using sample sizes ranging from 7 to 21 patients. However, none of the patients in these studies were over the age of 65.

One previous study (O'Donoghue, Briellmann et al. 2005) has investigated the effect of 6 months CPAP treatment on grey matter changes. In this study 27 male patients with severe OSA and no other related illness were compared to 24 age matched controls. The OSA patients were then given CPAP treatment 21 of the OSA patients underwent a further MRI scans after 6 months of CPAP treatment. No evidence of gray matter changes was found between the groups at baseline or in the group who received 6 months of CPAP treatment, although a slight decrease in whole brain volume did occur after CPAP treatment. In this study the average age was 43 years Taken together these findings suggest that between 7 and 21 OSA patients are needed to show within subject differences in brain morphology, following 6 months of CPAP treatment.

Assuming a 10% drop out and failure of data collection such as MR images (e.g. due to claustrophobia) or sleep data (e.g. due to difficulty sleeping in the laboratory). I studied a minimum of 22 participants for each group; 44 in total in order to ensure 20 patients in each group.

4.14 Statistical methods

The cognitive tests will be presented as summary data. The data which is normally distributed will be expressed as a means $\pm$ standard deviation (SD) and non-normally distributed as median (range).

Group comparisons of the intervention group (CPAP) versus control group (BSC) were assessed at baseline and at 6 months using one way analysis of variance (ANOVA) with repeated measures. The threshold for statistical significance was $P< 0.05$. No adjustments for multiple testing were made.

Changes in the brain morphology at baseline and 6 months are being analysed using statistical parametric maps assuming the data is normally distributed. Initially the analysis will be at a threshold $p<0.001$ uncorrected for multiple comparisons. Thereafter inferences about regionally specific grey mater volume loss will be made using a significance threshold level of $p<0.05$, corrected for topological false discovery rate across the whole brain.

All statistical analysis was performed using SPSS statistical software (version 21.0, SPSS Inc., Chicago, Illinois, USA).

4.15 Results

4.15.1 Recruitment

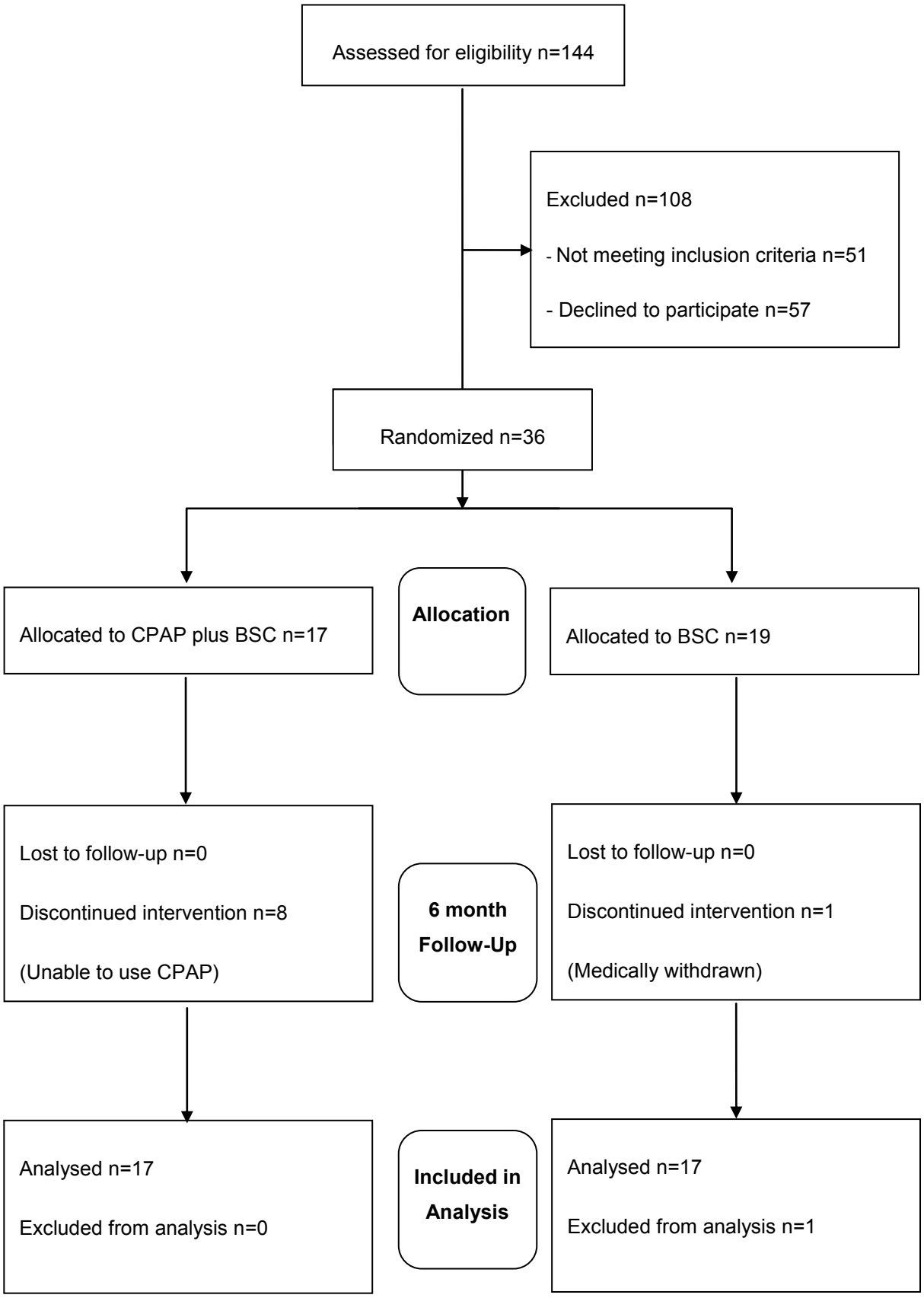
Screening and recruitment was completed between January and December 2012. 2568 patients were seen in outpatient clinics with an interest in sleep medicine within the Royal Brompton and Harefield NHS trust. Of those 767 (30%) were over 65 years of age. There were 150 (20%) new patients over the age of 65 with a potential diagnosis of OSA.

The CONSORT diagram shows the flow of patients through the study (Figure 4.2). In total 144 individuals were screened as potential patients: of these 93 (65%) were eligible. Although the trial was powered for 44 patients, 36 (39%) patients were randomised. 1 patient subsequently was medically withdrawn and 1 patients was found not to have OSA (AHI <5 events/h) and was excluded from the analysis. The 6 month visits and trial exit were completed by August 2013. 34 patients completed the study; therefore analysis was performed on 34 patients.

The main reasons for non-inclusion were:-

- Declined trial entry n=57 (53%)
- Pacemaker or stents excluding them from an MRI scan n=18 (17%)
- Unable to make contact after initial contact and providing a patient information sheets n=14 (13%)
- Limited English and unable to participate in the cognitive tests n=8 (7%)
- Various other exclusion criteria n=11 (10%)

Figure 4.2 Trial screening, enrolment, randomisation and follow-up



4.15.2 Baseline data

In total 36 patients were randomised; 17 to the CPAP with BSC and 19 to BSC alone. All 36 patients completed the baseline enrolment visit. The majority of patients were male 28 (83%), with a mean age of 71 ranging from 65 to 77 years and had on average minimally symptomatic OSAS (ESS mean (SD) 9.4 (4.3) and oxygen desaturation index (ODI) 27 (20) events/hours). The majority of patients were white 28 (82%), obese BMI 30.8 (4.9) kgm^2 and had on average 15 years of education. The groups were not considered different for age, years of education, BMI and neck circumference, office BP, mood and functionality as shown in the demographic in Table 4.5, clinical characteristics in Table 4.6 and mood and functionality in Table 4.7.By chance the patients randomised to the CPAP group had a statistically different Arousal Index (events/TST) (p=0.01), 4% Apnoea /hypopnoea Index (p=0.02), Obstructive events/h (p=0.04) and 4% Oxygen Desaturation index (p=0.01) although subjective sleepiness, objective sleepiness and obstructive sleep apnoea symptoms were similar. The Sleep measurements are shown in table 4.8.

Table 4.5: Baselines demographics

		Best Supportive Care N=17	Continuous positive airway pressure N=17	Independent T test p value
Age (years)		70.8 (3.3)	70.8 (4.1)	0.96
Male sex N (%)		12 (71%)	16 (94%)	Not tested
Education (years)		15 (6)	14 (4)	0.36
White N		15	14	Not tested
Asian N		1	1	Not tested
Other N		1	2	Not tested
Body mass index (kg/m^2)		31.4 (3.8)	30.1 (6.0)	0.46
Neck circumference (cm)		42 (4)	43 (4)	0.63
Caffeinated drinks /day		4 (3)	5 (3)	Not tested
Alcoholic drinks/week		4 (0-12)	3 (0-6)	Not tested
Smoking status N	Never	6	10	Not tested
	Ex	11	5	Not tested
	Current	0	2	Not tested
Exercise frequency (defined as lasting over 10 minutes) N	5-7 times/wk	9	8	Not tested
	2-4 times/wk	3	3	Not tested
	Once/wk	1	3	Not tested
	<Once/wk	2	1	Not tested
	None	2	2	Not tested

Data are mean (SD), median (25th-75th percentiles) or N number (%) as appropriate. As patients were randomised any differences that occurred between groups at baseline will be the result of chance. Statistical analysis by group was only completed after data collection was completed in parameters that may influence cognitive function. Parameters with small numbers were not tested.

Table 4.6 Baseline clinical characteristics

	Best Supportive Care N=17	**Continuous positive airway pressure N=17**	**Independent T test p value**
Asthma/COPD N	4	1	Not tested
Ischaemic Heart Disease N	7	7	Not tested
Hypertension N	11	13	Not tested
Diabetes N	4	5	Not tested
Cerebral vascular Disease N	1	2	Not tested
Systolic blood pressure (mmHg)	140.9 (22.4)	134.1 (17.5)	0.33
Diastolic blood pressure (mmHg)	81.7 (11.6)	81.5 (15.1)	0.97

COPD: Chronic Obstructive Pulmonary Disease

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N number (%) as appropriate. As patients were randomised any differences that occurred between groups at baseline will be the result of chance. Statistical analysis by group was only completed after data collection was completed in parameters that may influence cognitive function. Parameters with small numbers were not tested.

Table 4.7 Baseline mood and functionality

	Best Supportive Care N=17	**Continuous positive airway pressure N=17**	**Independent T test p value**
Hospital anxiety and depression scale	11.6 (8)	9.2 (5.6)	0.33
Anxiety	6.4 (4.5)	5.1 (3.7)	0.36
Depression	5.2 (4.4)	4.1 (2.8)	0.38
Townsend disability Scale	3.4 (4.2)	3.1 (4.5)	0.84

Data are mean (SD). As patients were randomised any differences that occurred between groups at baseline will be the result of chance. Statistical analysis by group was only completed after data collection was completed in parameters that may influence cognitive function. Parameters with small numbers were not tested.

Table 4.8 Baseline sleep measurements

	N	Best Supportive Care	N	Continuous positive airway pressure	Independent T test p value
Epworth sleepiness score	17	9.4 (4.8)	17	9.4 (3.9)	1.0
Oxford Sleep Resistance Test (minutes)	16	26.6 (14.5)	16	26.6 (15.8)	0.99
Sleep Apnoea Quality of Life Index	17	4.8 (1.5)	17	5.2 (0.9)	0.30
Total sleep time (TST) (minutes)	14	291.5 (99.5)	15	352.7 (91.8)	0.097
Sleep efficiency (%)	14	55.8 (16.6)	15	66.8 (13.1)	0.06
Arousal index (events/TST)	15	17.1 (9.4)	15	30.9 (16.8)	0.01
4% Apnoea /hypopnoea index (events/TST)	17	19.3 (15.4)	17	34.1 (20.2)	0.02
Apnoea index	17	6.6 (2.3 - 12.9)	17	23.9 (8.3 - 44)	0.06
Obstructive events/h	17	4.7 (1.2-9.3)	17	14.9 (4.8 – 31.6)	0.04
Central events/h	17	0.5 (0.05 – 1.7)	17	1.1 (0.2 -6.4)	0.5
4% Oxygen Desaturation index	17	18.3 (14.6)	17	35.1 (21.5)	0.01
SpO2 Time < 90% (minutes)	17	62.6 (12.7-87.7)	17	73.5 (6.4-148.7)	0.72

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N number (%) as appropriate. As patients were randomised any differences that occurred between groups at baseline will be the result of chance. Statistical analysis by group was only completed after data collection was completed in parameters that may influence cognitive function.

4.15.3 Primary outcomes

Global cognitive function (Intellect)

Global cognitive function was assessed at baseline and 6 months using the ACE-R which also included the MMSE. The results are shown in Table 4.9. One point is rewarded for each correct answer, higher scores represent an improvement. Although the ACE-R was lower in the CPAP group at baseline, this was not statistically different and the MMSE although a less sensitive measure was the same. In the subcomponents of the test there were trends towards improvement in attention and orientation and visuospatial in favour of the CPAP group although these were not statistically significant. There was no statistically significant difference in any of the sub-components of the ACE-R.

Table 4.9: Addenbrooke's Cognitive Examination – Revised (ACE-R)

Outcome	**Best support care**		**Continuous positive airway pressure**		**Independent T test p value**
	Baseline N=17	**Month 6 N=17**	**Baseline N=17**	**Month 6 N=17**	
Addenbrooke's Cognitive Examination - Revised	91.7 (6.1)	90.9 (6.3)	85.4 (9.5)	85.3 (11.6)	0.62
Attention and Orientation	17.5 (0.5)	17.5 (0.5)	17 2(0.8)	17.6 (0.6)	0.11
Memory	23.7 (2.4)	23 4 (2.7)	20.8 (4.9)	19.9 (5.4)	0.56
Fluency	11 0 (2.7)	10.5 (3.3)	10.1 (2.7)	10 (2.9)	0.61
Language	24.6 (1.7)	24.6 (1.9)	23.2 (3.7)	23.0(3.9)	0.74
Visuospatial	14.8 (1.4)	15 0 (1.1)	13.7 (1.9)	14.7 (2.1)	0.08
Mini Mental State Examination	28.2 (1.8)	28 1 (1.6)	27.7 (1.8)	27.8 (1.6)	0.68

Data are mean (SD)

Attention

This was measured using the following three tests: - Spatial span forward, Trail making test (TMT) and STROOP. These tests are listed in order of increasing complexity and the results are shown in table 4.10.

Spatial span forward: This is considered the simplest test as it requires the participant to follow a visual spatial pattern. One point is rewarded for each correctly completed sequences, the higher the score the better the performance. Both groups were similar at baseline and there was no significant difference between groups at 6 months. This is in keeping with the literature which suggests the tests remains relatively stable regardless of the level of impairment (discussed in chapter 2, section 2.4.7)

Trail making test consist of two parts A and B, both are reported. The score for each test is the time taken to complete the task measured in whole seconds. A lower score represents a better or quicker performance.

Part A is considered the screening part of the test as it is a measure of the participant's ability to count and complete the test. The CPAP group at baseline performed more slowly although the difference was not statistically significant. At 6 months the difference between groups was not statistically significant which would be expected if the test was completed correctly.

Part B, the BSC group at baseline performed more slowly which was not statistically significant but the BSC group improved more than the CPAP group. This difference at 6 months was statistically significant in favour of the BSC group. This was confirmed by looking at the differential of the two tests. At baseline the BSC group were slower but improved more and the CPAP group deteriorated this difference was statistically significant in favour or BSC group which was unexpected. Although is keeping with the results from the PREDICT trial chapter 3, section 3.6.2 which did not suggest a difference after 3 or 12 months of CPAP therapy.

The STROOP test is the most complex and challenging test of attention. It is a test with 3 components each with increasing complexity. The score for each test is the number of correct responses in 90 seconds. A higher scores represents a better performance. The first part of the test like the TMT part A is considered the screening test as it measures the participant's ability to read and if performed correctly there should not be a significant different between the groups at 6 months.

Overall at baseline the BSC group performed better in all three components of the test although their performance deteriorated over the 6 months. The CPAP group improved in the 2^{nd} and 3^{rd} components of the test and the difference was statistically significant at 6 months in favour of the CPAP group.

In summary there was no difference in attention as measured by the simplest test (spatial span forward) but when measured with tests of increasing complexity, there was a statistically significant

difference in favour of the BSC group with the TMT. Although the STROOP test, which is considered the most complex task was statistically in favour of the CPAP group.

Table 4.10: Spatial span forwards, Trail making test and STROOP

Outcome	**Best support care**		**Continuous positive airway pressure**		**Independent T test p value**
	Baseline N=17	**Month 6 N=17**	**Baseline N=17**	**Month 6 N=16**	
Spatial span forwards	7.2 (1.9)	7.4 (1.9)	7.5 (1.6)	7.1 (1.7)	0.24
Trail making test (seconds)					
Part A	31.9 (8.7)	33.2 (8.9)	36.8 (18.3)	35.5 (15.2)	0.34
Part B	93.1 (47.7)	83.2 (44.6)	87.7(48.6)	94.3 (55.6)	0.05
Difference between A and B	61.2 (42.7)	50.1 (39.6)	52.8 (35.9)	60.4 (43.5)	0.05
STROOP (number of correct answers in 90 seconds)					
Part 1 (Word)	93.7 (15.7)	93.8 (17.4)	88.1(13.1)	87.9 (18.1)	0.94
Part 2 (Color)	55.7 (12.9)	52.3 (12.8)	53.7 (18.3)	60.7 (16.7)	<0.001
Part 3 (Colorword)	30.1 (10.2)	28.6 (10.7)	28.3 (9.4)	32.5 (10.4)	0.03

Data are mean (SD)

Memory tests

Episodic memory

This was measured using Logical memory and Verbal paired associates. The results are shown in table 4.11

Logical memory, 3 components of the test are reported: - Immediate recall, Delayed recall and Percentage retention. Each correct answer scores one point, a higher score represent a better performance. Both groups improved from baseline in all components of the test, the difference between groups was not statistically significant at 6 months.

Verbal paired associates, 4 components of the test are reported. Once again each correct answer scores one point, a higher score represent a better performance. In the recall component the BSC group improved and the CPAP group remained the same; the difference between groups was statistically significant at 6 months ($p=0.02$). There were no other statistically significant differences in the other components of the test, the trends suggested BSC group improved and CPAP group stayed the same.

Table 4.11 Logical memory and Verbal paired associates

Outcome	Best support care		Continuous positive airway pressure		Independent T test p value
	Baseline N=17	Month 6 N=17	Baseline N=17	Month 6 N=17	
Logical memory					
Immediate recall total score	34.1 (10.5)	38.7 (10.4)	31.1 (11.3)	35.3 (12.2)	0.91
Delayed recall total score	16.5 (9.1)	24.6 (8.8)	14.1 (7.8)	19.2 (9.8)	0.37
Percentage retention %	60.8 (26.8)	82.9 (15.6)	57.9 (19.9)	70.7 (21.7)	0.33
Verbal paired associates					
Recall total score	14.9 (9.1)	19.4 (9.2)	14.9 (8.8)	14.8 (9.8)	0.02
Delayed recall total score	4.9 (3.1)	6.1 (2.4)	4.3 (2.4)	4.5 (3.0)	0.25
Recognition total scores	22.5 (5.8)	23.9 (0.2)	22.2 (5.8)	22.1 (5.9)	0.29
Percentage retention %	74.7 (38.2)	90.1 (28.1)	72.0 (31.3)	71.9 (37.8)	0.19

Data are mean (SD)

Working memory

This was measured using Letter number sequencing, Digit Symbol Substitution Test and Spatial Span backwards. The results are shown in table 4.12

Letter number sequences, each correct sequences scores one point, a higher score represents a better performance. At baseline both groups were similar, the BSC group improved and the CPAP group marginally deteriorated the difference was statistically in favour of the BSC group at 6 months (p=0.04).

Digit Symbol Substitution Test, the score is the number of correct symbols completed in 90 seconds. The higher the score the better the performance. Both groups deteriorated from baseline the difference between the groups was not statistically significant at 6 months.

Spatial span backwards, one point is rewarded for each correctly completed sequences, the higher the score the better the performance. The BSC group improved and the CPAP group stayed the same the difference between the groups was not statistically significant at 6 months.

Table 4.12: Letter number sequencing, Digit Symbol Substitution Test and Spatial Span

Outcome	**Best supportive care**		**Continuous positive airway pressure**		**Independent T test p value**
	Baseline N=17	**Month 6 N=17**	**Baseline N=17**	**Month 6 N=17**	
Letter number sequencing	8.9 (2.7)	9.2 (2.4)	9.1 (2.2)	7.8 (2.9)	0.04
Digit Symbol Substitution Test	45.3 (10.5)	43.1 (12.7)	42.1 (13.5)	39.1 (16.7)	0.65
Spatial span backwards	6.1 (1.6)	6.8 (1.4)	6.6 (1.7)	7.0 (1.5)	0.43

Data are mean (SD)

Non-verbal memory

This was measured using the test Faces, which is a two part test with a delayed component. Each correct response scores 1 point; the maximum score for each part is 48. Both groups were similar at baseline, there were trends that the BSC group improved in all components of the tests and the CPAP group deteriorated. The difference between the groups was not statistically significant at 6 months and shown below in table 4.13

Table 4.13: Faces

Outcome	**Best supportive care**		**Continuous positive airway pressure**		**Independent T test p value**
	Baseline N=17	**Month 6 N=17**	**Baseline N=17**	**Month 6 N=17**	
Faces					
Recognition	34.6 (5.7)	36.5 (4.7)	32.8 (4.1)	32.9 (9.8)	0.45
Delayed recognition	32.7 (3.4)	34.6 (3.5)	31.8 (4.4)	30.6 (9.4)	0.15
Percentage retention	91.6 (8.7)	93.3 (8.8)	92.4 (8.9)	83.7 (24.4)	0.07

Data are mean (SD)

Summary of memory tests

One component (total recall score) of the episodic memory test (Verbal paired associates) and one out of the three working memory tests (Letter number sequencing) improved statistically in favour of the BSC group. There were no statically significant differences between groups in the less sensitive measure of non-verbal memory. Overall these results suggest that there was no difference in memory between the groups after 6 months of CPAP treatment.

4.15.4 Secondary outcomes

Subjective sleepiness was assessed using the ESS at baseline and at 6 months. At baseline both groups had similar scores and both groups improved at 6 months, with the mean (SE) change from baseline being CPAP -2.1 (0.8), BSC -0.7 (0.7). The difference between the two groups was not statistically significant at 6 months (p=0.26).

Objective sleepiness was not assessed in all patients completed due to technical problems, of the results available the BSC group improved, in the CPAP group there appeared to be a deterioration, although the difference between groups at 6 months was not statistically different. The results are shown below in table 4.14

Table 4.14 Epworth sleepiness score and the Oxford Sleep Resistance Test at 6 months

Outcomes		**Best supportive care**			**Continuous positive airway pressure**		**Independent T test**
		Baseline	**Month 6**		**Baseline**	**Month 6**	**p-value**
ESS	N=17	9.4 (4.8)	8.7 (4.7)	N=17	9.4 (3.9)	7.3 (4.7)	0.26
OSLER	N=13	24.8 (15)	33.4 (11.7)	N=12	26.8 (16.4)	24.2 (12.8)	0.10

ESS: Epworth sleepiness score; OSLER: Oxford Sleep Resistance Test

Data are mean (SD)

Continuous positive airway pressure usage

The overall CPAP use was measured at 6 months and results are shown in table 4.15. Of the 17 patients randomised to CPAP 7 patients had stopped using CPAP or had low CPAP use, although at the end of the trial 12 patients (including 2 with low use) requested they continue using CPAP. Only 5 patients had over 4 hours a night of CPAP use. The median daily use was 3.4 (2.2) hours.

The oxygen desaturation index was statistically different between groups at 6 months in favour of CPAP 3.0 (10.7) vs. BSC 20 (18.3) events/hour $p<0.01$

Table 4.15: Continuous positive airway pressure usage over 6 months

	Over 6 months
Number randomised	17
Number (%) analysed	17 (100%)
Number of patient who used CPAP less than 1 months or stopped	7 (41%)
Number of patients who requested to continue using CPAP	12 (71%)
Number using CPAP >4 hours/night N (%)	5 (29%)
Median daily use (mean hours/night)	3.4 (2.2)

Data are mean (SD) or N number (%) as appropriate

Quality of life

Disease specific quality of life was measured using the SAQLI, a sleep apnoea specific questionnaire which also incorporates side effects associated with CPAP. The CPAP group showed an improvement and the BSC group deteriorated although the differences between the groups at 6 months was not statistically significant (p=0.06)

Mood

This was assessed using the HADS which was summarised into an anxiety and a depression score. Overall the BSC group showed an improvement in their scores and the CPAP groups a deterioration. The difference between the groups at 6 months was statistically significant (p=0.03) in favour of BSC.

Functionality

The average TDS was similar in both groups at baseline and higher in both groups at 6 months. The difference between the groups at 6 months (p=0.13) was not statistically significant.

The SAQLI, HADS and TDS scores are shown in Tables 4.16

Table 4.16 Disease specific quality of life, mood and functionality

Outcome	**Best supportive care**		**Continuous positive airway pressure**		**p-value**
	Baseline N=17	**Month 6 N=17**	**Baseline N=17**	**Month 6 N=17**	
Sleep Apnoea Quality of Life Index	4.8 (1.5)	5.1 (1.4)	5.3 (0.9)	4.7 (1.8)	0.06
Hospital anxiety and depression scale total score	11.6 (8.2)	10.5 (8.4)	9.2 (5.7)	10.2 (6.7)	0.03
Anxiety	6.4 (4.5)	5.7 (4.8)	5.1(3.7)	5.3 (4.2)	0.14
Depression	5.2 (4.3)	4.8 (4.1)	4.1(2.8)	4.9 (3.7)	0.08
Townsend disability Scale	3 (4)	4 (4)	3 (5)	4 (5)	0.13

4.15.5 Exploratory analysis

The baseline demographic of the patients in the Brain MRI study who were recruited from a single centre The Royal Brompton and Harefield NHS trust were compared to the patients in the PREDICT trial which was UK multicentre trial presented in chapter 3. The groups were similar in age, male predominance, ethnicity, and MMSE. The patients recruited to the Brain MRI study had more years of education and were less obese, although the percentage of men in both groups was similar. They also rated themselves as less sleepy, although the oxygen desaturation index (ODI) was similar. Results are shown in table 4.17.

Table 4.17: Baseline demographic of the Brain MRI study compared to the PREDICT trial

	Brain MRI study	**PREDICT trial**
Number	34	278
Age (years)	71 (65-77)	70 (65 to 89)
Male sex N (%)	22 (83)	229 (82)
White N (%)	28 (82)	267 (96)
Asian N (%)	2 (6)	8 (3)
Other N (%)	3 (9)	3 (1)
Education (years) (%)	14 (11-17)	11 (10-15)
Mini mental state examination	29 (27-29)	29 (27-30)
Body mass index (kg/m^2)	30.8 (4.9)	33.8 (6.1)
Oxygen desaturation index events/hours	27 (20)	28.7 (19.1)
Epworth sleepiness scale	9.4 (4.3)	11.6 (3.7)

Data are mean (SD), median (25^{th}-75^{th} percentiles) or N (%) as appropriate

I then compared older OSA patients, to data obtained from younger OSA patients and normal controls from previously studies in our group Twigg *et al*. shown in Table 4.18. The older OSA patients compared to the younger OSA patients were less obese, although the percentage of men was less and they reported less sleepiness for a similar ODI. All groups had similar years of education.

The Trail making tests (TMT) part A is considered the screening part of the test as it is a measure of the participant's ability to count and complete the test; this was similar across the groups which would be expected if the test was completed correctly. The older OSA performed more slowly in part B of the TMT. Likewise the older OSA patients' performance in the memory tests was also impaired compared to the younger OSA patients.

Table 4.18 Older compared to younger Obstructive sleep apnoea patients and age-matched normal controls

		Obstructive sleep apnoea		Normal controls
		Older	Younger	
Number		34	102	59
Age (years)		71 (68-74)	50 (43-57)	50 (43-57)
Sex (male)		28 (82%)	94 (92%)	48 (83%)
Years of education		15 (5)	14 (3)	15 (3)
BMI (kg/m^2)		31 (5)	33 (6)	25 (6)
AHI (events/hr)		27 (19)	35 (25)	2 (1)
ODI ≥ 4%		27 (20)	27 (30)	1 (1)
ESS		9 (4)	12 (5)	6 (4)
Trail making test (seconds)	Part A	34 (14)	35 (13)	35 (11)
	Part B	96 (58)	75 (31)	77 (28)
Logical Memory	Immediate	32 (11)	37 (10)	43 (9)
	Delayed	15 (9)	23 (7)	27 (7)

Data are mean (SD) or N (%) as appropriate

I then compared the older OSA patients TMT to published normative values, results shown in table 4.19. The TMT is the most commonly available cognitive test with normative values in older people, although the data sets are not screened for sleep disorders. The older OSA patients took 10 seconds longer to complete the TMT part B than their age and education matched normal controls.

Table 4.19 Older Obstructive sleep apnoea patients compared normal controls matched for age and years of education

		Obstructive sleep apnoea	**Normal controls** (Tombaugh *et al* 2004)		
Number		34	32	30	34
Age range		68-74	65-69	70-74	75-79
Age (years)		71 (4)	67 (1)	72 (2)	77 (2)
Years of education		15 (5)	16 (2)	15 (2)	15 (2)
Epworth sleepiness scale		9 (4)	Not available	Not available	Not available
Trial making test (seconds)	Part A	34 (14)	34 (7)	40 (15)	42 (15)
	Part B	96 (58)	67 (9)	86 (24)	101 (44)

Data are mean (SD) or N (%) as appropriate

4.15.6 Serious adverse events and self-reported side effects

No serious adverse events were reported and self-reported side effects were encapsulated in the SAQLI questionnaire. Although there was in improvement in the SAQLI in favour of CPAP the difference between groups was not significantly different.

4.16 Discussion

4.16.1 Main findings

The main finding of this study was that in older people with minimally symptomatic OSA, CPAP therapy showed an improvement in only one complex measure of attention and executive function. There were no improvements in the less sensitive measures. OSA patients randomised to BSC showed significant improvements in a sub components of episodic memory and working memory tests. There were no statically significant differences between groups in any of the other tests of memory or the less sensitive measures of non-verbal memory. Overall the results in the memory tests were inconsistent with no clear trends in favour of CPAP treatment. Taken together these findings do not support any changes in memory between groups after 6 months of CPAP treatment.

The global cognitive function tests used in this study showed trends towards improvement in attention and orientation and visuospatial domains in favour of the CPAP group although these were not statistically significant. There was no difference in overall ACER or MMSE scores at 6 months. Interestingly the baseline cognitive scores were impaired compared to published normative data or normalized scores provided with the test results.

In summary CPAP improved only one component of attention and executive function but overall there were no significant difference in memory or global cognitive function after 6 months of CPAP therapy. These results are consistent with the recent meta-analysis by Kylastra et al 2013 and the findings of the PREDICT trial reported in chapter 3 (see section 3.13.5).

Additional findings

The secondary outcomes in this study related to subjective and objective sleepiness did not show any difference between the two groups. This may have been due to group being minimally symptomatic, although they did present with symptoms requesting treatment.

Other secondary outcomes which showed no statistically significant difference between the two groups, at 6 months were quality of life and functionality. Interestingly the patients in this trial randomised to CPAP had a statistically significant worsening of mood, on a background of baseline scores being elevated in both groups. Once I again I speculate that the lack of improvement in quality of life and functionality but worsening of mood was related to the group being minimally symptomatic. The BSC group may have been relieved that they had been randomised to BSC, likewise the CPAP unhappy with the lack of perceived benefit.

Treatment adherence

It could be argued that the mean CPAP use of less than <4 hours per night might account for lack of improvement in the other cognitive outcomes. Although the CPAP use was low (3.4 hours) it was higher than the PREDICT trial (1.3 hours) (see chapter 3, section 3.13.6) but lower than the APPLES

trial (4.2 hours) (see earlier section 4.5). The arbitrary threshold of at least four hours per night of CPAP usage is often quoted as a bench mark to determine adequate CPAP use, although the relationship between duration of use and improvement in cognitive function in younger patients groups remains uncertain. In earlier studies, CPAP adherence was often not measured objectively. There is one study by Zimmerman *et al.* 2006 in OSA patients with impaired memory which suggested optimal users (>6 hours of use a night) were eight times more likely to have improved memory function compared with poor users at 3 months, it could also be interpreted that poor CPAP use was reflective of poor memory function. Furthermore there is no clear consensus on the ideal duration of exposure to CPAP within the literature there is a range from 1 week Bardwell et al 2001 to 12 months Munoz et al 2000.

Strengths and weaknesses

The study presented in this chapter was designed as a pragmatic study, recruiting older OSA patients with co-morbidity. The findings are therefore relevant to what would be seen in clinical practice, 65% of the patients approached were eligible for trial entry. The duration of the study was considerably long for a RCT of CPAP therapy. The baseline clinical and sleep characteristics of the group were well defined with all patients completing a NPSG.

The most notable limitation of the study was that the patients randomised to CPAP by chance had significantly greater markers of OSA severity. Although the study groups were heterogeneous, including multiple co-morbidities, these were equally distributed between the groups. In addition the target sample size was not achieved. A further limitation of the trial was that sham CPAP was not used so patients were not blinded to their treatment, this has been discussed previously (see chapter 3, section 3.14.4). Finally no corrections were made for multiple comparisons and the statistical significance of the secondary outcomes were interpreted cautiously due to the number of secondary analyses performed and the sample size was low.

Generalisability

The was a study of minimally symptomatic older people with OSA, although the patients studied had a relatively low mean ESS at baseline; they were sufficiently symptomatic to seek treatment and were representative of the patients referred from primary care to the Royal Brompton and Harefield NHS trust. At the other end of the disease spectrum exclusion of highly symptomatic OSAS patients in whom CPAP was considered mandatory may have diminished the effect size.

4.17 Conclusion

The results of this study showed that in older patients with minimally symptomatic OSA, 6 months of CPAP therapy may improve attention and executive function, as measured by a highly sensitive test, irrelevant of changes in subjective and objective sleepiness, but overall there were no significant difference in memory or global cognitive function.

Chapter 5: General Discussion

5.1 Summary of main findings

Continuous positive airway pressure (CPAP) therapy is established as an efficacious and cost-effective treatment for middle-aged patients with moderate to severe OSAS, the benefits in older people are less clear. The aim of this thesis was to address this evidence gap.

The first study presented, the PREDICT trial was a 12 month multicentre randomised controlled trial of CPAP therapy in older people with OSAS. It was designed to evaluate the efficacy of CPAP in reducing daytime sleepiness, while determining its cost-effectiveness. A number of secondary outcomes, focusing on the important consequences of untreated OSAS were also measured, including cognitive function, road traffic accidents, changes in blood pressure and metabolism. More general aspects thought to reflect successful treatment of a chronic condition, such as improvements in mobility, quality of life and the use of health-care resources such as the visits to the general practitioner or hospital for treatment were also measured. The adherence to CPAP therapy was the tertiary outcome measure. Patients also recorded side-effects to CPAP therapy.

The PREDICT trial showed 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 those seen in middle-aged patients treated with CPAP therapy.

The reduction in subjective sleepiness was corroborated by a significant improvement in objective sleepiness measured by the OSLER test at 3 months. CPAP also produced superior quality of life outcomes which were significant using the SAQLI and SF-36 at 3 and 12 months.

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 utilise in this disease-group.

Secondary outcomes related to cognitive function did not show any differences between the two groups despite improvements in sleepiness in the CPAP group. Additionally, mood, which may impact on cognitive function, did not change. Other secondary outcomes, nocturia, and accidents, also did not improve with CPAP and may reflect their multifactorial aetiologies.

In terms of the cardiovascular outcomes there was a significant improvement in total cholesterol at 3 months on CPAP, not sustained at 12 months. CPAP produced no improvement in blood pressure. In the BSC group systolic blood pressure fell, an observation previously reported.

The mean CPAP usage was low at 3 and 12 months, although similar to other trials in OSAS patients. Adopting a standard clinical approach as compared to an intensive trial approach may have resulted

in lower CPAP use. Additionally other factors, such as reduced social support may contributed to lower CPAP adherence, since 50% of the patients reported sleeping alone.

The second study the Brain MRI study was a 6 month single centre randomised controlled trial designed to investigate the impact of CPAP therapy on cognitive function and brain morphology in older people with minimally symptomatic OSA.

The results of the second study suggested CPAP partially modified attention and executive function as measured by the STROOP test in older patients with minimally symptomatic OSA, irrespective of changes in subjective and objective sleepiness. Overall there were no significant differences in memory or global cognitive function, although mood significantly deteriorated in the CPAP group. My interpretation of these data is that there is a complex relationship between OSA, cognitive function and the response to treatment in older people. As the patients were minimally symptomatic, the lack of perceived benefit with CPAP therapy, in addition to the increased burden of treatment may have been reflected in the deterioration of their mood. Equally the BSC group many have been reassured. It is also possible the treatment period or the cognitive test battery was insufficient to show a relationship. Additional there was a small sample size and the study was under powered to detect changes in all of the cognitive tests.

Finally an alternative explanation would be that CPAP was ineffective in treating cognitive impairment in older people with minimally symptomatic OSA, as older brains may have less plasticity to respond to treatment once the cognitive insult has occurred.

5.2 Implication for future research

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. Suggestions to improve trail design have been to incorporate run in periods, to identify non-adherence early (e.g. the SAVE trial) or alternatively CPAP withdrawal studies in which treatment is withdrawn from a selected group of patients who are known to use CPAP optimally. Both techniques would have recognised methodological weaknesses although the technique could be used in clinical effectiveness trials to answer direct questions regarding cause and effect.

Studies have also been carried out to investigate how the patient acceptability of CPAP can be promoted. 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.

5.3 Conclusion

Overall, the findings from the studies presented in this thesis support the use of CPAP therapy in reducing the symptom of excessive daytime sleepiness and improving quality of life in older people with obstructive sleep apnoea syndrome. The magnitude of the improvements with CPAP was similar to those seen in middle-aged patients with similar disease severity.

In older people with minimally symptomatic OSA, CPAP therapy may improve subtle aspects of attention and executive function irrespective of sleepiness although there were no significant changes in memory or global cognitive function, suggesting there is a complex relationship between OSA, cognitive function and the response to treatment in older people.

Based on the findings presented in this thesis I recommend that CPAP therapy should be routinely offered to older patients with OSAS. The response to treatment should be assessed and success judged by improvements in symptoms and quality of life. There should be a focus on how to best optimise CPAP delivery in the older patient to improve compliance. .

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Appendix

Appendix 1:

Patient and GP information sheets, consent forms

Royal Brompton & Harefield NHS
NHS Trust

PREDICT: Patient Information Sheet

A randomised controlled trial of continuous positive airway pressure treatment in older people with obstructive sleep apnoea / hypopnoea syndrome (PREDICT)

Centre No: 1.0

Ethics Ref: 09/H0708/33

ISRCTN No: 90464927

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1. Invitation

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

This Patient Information Sheet is in two parts. Part 1 tells you about the study. Part 2 gives you more information if you are thinking of taking part in the study.

PART 1

2. What is the purpose of the study?

This trial has been designed to establish if there are any benefits from using nasal continuous positive airway pressure (CPAP) for older people with obstructive sleep apnoea (OSA).

What is Nasal continuous positive airway pressure (CPAP)? Your doctor (or nurse) will explain fully the CPAP treatment and show you what it looks like, but to summarise it involves breathing pressurised air through a mask (like an oxygen mask). The air pressure is automatically adjusted so that it is just enough to keep your breathing regular, without being excessive. The pressurised air is produced by a machine which is about the size of a tissue box and can be placed at the side of your bed. The machine is attached to the mask on your face by a tube. Your doctor (or nurse) will fit you with a comfortable mask. You may also have a humidifier connected to your machine to make the air you breathe moist; sometimes people find this more comfortable.

We know CPAP works well in younger people with OSA, but we do not know if it helps in older people who may feel unwell for other reasons, or who may not be as sleepy as younger people. Therefore, we need to compare the responses in some patients who are using CPAP, with those who are receiving standard care. Only in this way can we establish if the CPAP is advantageous to health (or not) in older people with OSA.

3. Why have I been chosen?

You have been chosen to consider taking part in this trial because you have OSA and you are over 65 years.

4. Do I have to take part?

No. Your participation in this study is voluntary. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. Should you wish to stop taking part at any stage of this study you are free to do so without giving a reason. If you do stop taking part, we will ask you if we can keep the records relating to the treatment given to you up to this point, as this is still valuable to the study. A decision to stop treatment at any time, or a decision not to take part, will not affect the quality of care you receive.

5. What will happen to me if I take part?

If you decide to take part, we will review your history, which includes questions about your general health, medications, smoking, alcohol and caffeine intake. We will also ask you about your sleeping habits, memory and schooling, how much exercise you take and how many times you pass urine at night. Other routine tests, such as measuring your blood pressure, heart rate, height, weight, collar size and waist will be performed. As part of the research study you will be asked to undergo a number

of other tests. These are listed below and outlined in the chart at the end of the information sheet. *These additional tests will provide us with detailed information about you and your OSA.*

Treatment: Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. We put people into groups and give each group a different treatment; the results are compared to see if one is better. To make sure the groups on each treatment are similar to start with, each patient is put into a group by chance (randomly); this gives a fair comparison. The results are then compared. If you agree to take part you will be asked to sign a consent form and then put in one of two groups through a randomised process normally involving a computer.

One group will be asked to use the CPAP whilst the other group will continue with their normal medical treatment; we call this *best supportive care*. Both groups will be asked to undergo similar follow-up visits and investigations.

Follow-up: Regardless of which group you are put in you will be asked to return to the hospital at least 3 times during the study, as shown in the study outline (at the end of this document). You will also be contacted by phone at one week, one month and six months after you enrol in the study, to see how you are doing. In addition to this, we would like to know how you have been feeling each month and if you have needed to see your GP or hospital doctors. Therefore, we will ask you to complete a monthly diary that will be returned to us in a stamped addressed envelope. If we do not receive the diary we will phone you in case it has got lost in the post. This study will last for 12 months.

Additional tests for your study participation – These will be done on your first visit and on subsequent visits after 3 and 12 months

Sleepiness: This will be assessed by asking you to fill in a short questionnaire, and also by seeing how long you can stay awake. This is called the '***maintenance of wakefulness test***'. The test is carried out in the sleep laboratory. It involves lying comfortably on a bed in a quiet room for up to 40 minutes. During this time you will be asked to watch a small light which will light up at random intervals, when it does you are required to press a button.

Quality of life questionnaires: You fill in a number of questionnaires that assess your quality of life, mood and any accidents you may have had. These are called the '***Short-Form 36 Questionnaire***', the '***Sleep apnoea quality of life questionnaire***', the '***Townsend disability Scale***', the '***Hospital anxiety and depression score***', the '***EQ-5D***' and a '***General accident questionnaire***'. These questionnaires will take approximately 15 minutes to answer.

Blood tests: 30ml (6 teaspoons) of your fasting blood will be taken to check a number of factors such as cholesterol and glucose levels, kidney, liver, bone and thyroid function as well as a full blood count. These tests will be carried out as part of the standard care. In addition, we will carry out some **genetic**

tests (see below). All of these blood samples can be taken at the same time in one go. Very occasionally gene tests do not give a clear result, for technical reasons (rather than a problem with the genes themselves). If this happened we might ask you to give a further 10ml (2 teaspoons) of blood, although there would be no obligation on your part to do so. The samples will not be tested for HIV or chronic infectious disease.

Blood samples for genetic testing will be frozen and stored indefinitely in a Human Tissue Bank, in the Oxford Centre for Respiratory Medicine. The samples will be stored with trial numbers and no personal identifiers (coded anonymised). We will use the samples to study genetic factors that may be important in OSA. For example, why some people are more likely than others to develop OSA, what determines symptoms and disease progression, and why there are differences in cardiovascular responses to low oxygen levels and sleepiness. We will probably use the samples to study other genes as they are discovered and we are asking your permission for this at this stage. In the first instance we will analyse small portions of your genetic code; though in the future we hope to carry out whole genomic screening. This means identifying your entire genetic code. Any research on these samples will be coordinated by the Trial Team. Some of these studies may be performed with commercial organisations. This blood sample will be stored separately from your name and address so that nobody will be able to trace the results of these tests back to you and the results of the genetic research need not be declared on insurance or mortgage applications. The anonymisation process protects your confidentiality, but also means we will not be able to give you your individual test results.

Cognitive Function: We would like to test your memory by asking you some simple questions which form part of the ***Mini Mental State Examination***. We would also like to test the speed at which you react to information by asking you to complete several tasks. One of these tasks is called the ***Simple and four-choice reaction time test***. This is done by asking you to react to a flashing X in a box on a computer screen. A second test called ***Trail making B*** is a dot to dot connecting numbers and letters. The last test is the ***Digit symbol substitution test***, which is a coding exercise where you will be asked to substitute a symbol for a random number, with the aim of filling out as many boxes as you can in 90 seconds. Each test will be fully explained and you will be given a practice until you feel comfortable at completing them.

Mobility Test: This is a timed test in which you start by sitting in a chair. When asked you stand up and walk at your normal pace around a marker at 3 meters walk back and sit down again in the chair.

Overnight breathing patterns: You will be shown how to attach an overnight breathing monitor. This will be two stretchy elastic bands that fit round your waist and chest to measure your breathing, a small clip that fits onto your finger to measure the oxygen in your blood, and a sensor that fits just under your nose to measure your airflow. You will be asked to put the breathing sensors on before you go to bed at your normal time. They will be attached to a recording box (about the size of a large match box). In the morning you can get up as normal, remove the sensors yourself and return the monitoring kit to the hospital.

6. What do I have to do?

If you agree to take part in the study we will help you with arranging your visits to the hospital. There are no restrictions to lifestyle or diet and we would ask you to continue your usual medications. We would like to review your progress regularly by keeping in contact with you over the phone (e.g. 1 week, 1 month and 6 months) and by completion of a monthly diary which we will ask you to return to us in stamped addressed envelopes provided. *We will reimburse all your travel expenses that are incurred in taking part in this trial. This includes the cost of additional hospital visits.*

7. What is being tested?

In this study we are testing whether CPAP is a useful treatment for OSA in older people.

8. What are the alternatives for treatment?

Participating in the study will not change your diagnosis. We also aim to ensure that you are on the best treatments for your OSA. In younger people the treatment for OSA is CPAP; however in older people we do not know if this treatment is beneficial.

9. What are the unwanted side-effects of any treatment received when taking part?

CPAP is generally very well tolerated. Sometimes it can cause nasal dryness/discomfort, nasal discharge, a dry mouth (and dribbling), facial discomfort and, rarely, ulceration due to poor mask fitting. These effects can be minimised by the use of humidification and careful mask fitting. All the nurses and doctors involved in this trial are experienced in using CPAP and minimising these unwanted side-effects.

If you do decide to take part in the study, please report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this sheet for you to phone if you become worried at any time.

10. What are other possible disadvantages and risks of taking part?

The main disadvantage of taking part in this study is the time commitment to attend hospital for the visits. There is the small discomfort of having blood samples taken. Some private medical insurers require to be notified of participation in clinical trials.

11. What are the possible benefits of taking part?

All people taking part will receive detailed advice on managing their OSA with improved diet, exercise and regular sleep patterns. You will also have regular and detailed health assessments. We may find during the tests that something needs further investigation or treatment that would not have otherwise been found. If this is the case then we will organise appropriate further care in liaison with your GP.

12. What happens when the research study stops?

After the end of the research study, you will be followed up by your GP and / or hospital clinicians, as usual.

13. What if there is a problem?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Chief Investigators by contacting the **UKCRN Oxford Clinical Trials Unit at** rtu@orh.nhs.uk**).** The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Governance Office.

This completes Part 1 of the Information Sheet. If this has interested you and you are considering participation, please continue to read the additional information that follows before making any decision. This provides more information about how we run the study.

PART 2

14. What if new information becomes available during the study?

Sometimes during the course of a study, new information becomes available on the condition being studied. If this happens, the study team will review the information and let you know if it affects the study. If the study changes as a result and you decide to continue in it, you will be asked to sign an updated consent form.

15. What will happen if I don't want to carry on with the study?

You are free to withdraw entirely from this study at any stage. If you withdraw from the study, you can ask us to destroy all your identifiable samples, but we would seek your permission to keep and use information and samples collected up to your withdrawal. If you have registered with the NHS Central Register (NHSCR), we would also seek your permission to continue this.

16. Will my taking part in this study be kept confidential?

If you consent to join the study, your medical records may be looked at by representatives of the Sponsor (Imperial College London), the coordinating trials office, the Regulatory Authorities and/or Research Ethics Committees, for the purposes of checking the study is being carried out correctly. All of these individuals will have a duty of confidentiality to you as a research participant.

As part of your participation in the study, information will be collected about you for analysis by the Sponsor's trial team and other collaborators involved in the study. This will include information about your health and other details such as your date of birth and gender. You will be allocated a study number to identify you, which means that you will not be identifiable from the study database.

However, some identifiable details, such as your full name, address and NHS number may be transferred to the Sponsor's trial team or the trial co-ordinating centre in Oxford on paper or electronic records, where this cannot be prevented and where necessary for the purposes of monitoring and follow-up. In these instances, the information that identifies you will be kept completely secure and accessible only to authorised individuals within the Sponsor's trial team or the co-ordinating centre in Oxford. In line with Good Clinical Practice guidelines, at the end of the study, your identifiable data will be securely archived for a minimum of 10 years. Arrangements for confidential destruction will then be made.

Finally, the information held by the NHS and records maintained by the NHS Information Centre may be used by the Sponsor's trial team to keep in touch with you and follow up your health status.

17. Informing your General Practitioner (GP) and other clinicians

We will ask your permission to inform your GP, other medical practitioners and carers involved in your care that you are participating in this study. Where it is appropriate, we will liaise with your family, GP and any relevant carers in completing the information for the study.

18. What will happen to any samples I give?

If you consent to take part in this study, new blood samples will be taken specifically for the study and will be stored as previously described. These samples are regarded as a 'gift' to the research team. Samples used for genetic analysis will be coded so they cannot be identified as yours, other than by the trial team. Scientists working with the samples will only know their code number and would not be able to trace the sample to you. Your samples may be stored indefinitely.

Samples will be used for the purposes indicated in this information sheet, as well as for research investigating OSA in the future, in studies for which ethical committee approval has been given. Future research may include working with commercial organisations, or tests in laboratories outside our study centres and the European Union. All tests will still be under the control of the Oxford Clinical Trials Unit, Imperial College London and Edinburgh University and results of any tests remain strictly confidential at all times. Any information gained will be held securely on paper and electronically at your hospital under the provisions of the 1998 Data Protection Act. Your data will not be passed to anyone else outside the team or the NHS Information Centre who is not involved in the trial.

The information collected about you may also be shown to authorised people from the UK Regulatory Authorities and Sponsor (Imperial College London). This is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

19. What will happen to the results of this study?

As results of the study become available, we will make them public through presentation in scientific journals and conferences. We will also intermittently provide a summary of the study progress for patients through patient support groups such as Help The Aged. In all instances the data will be anonymous and none of the patients involved in the study will be identified in any report or publication.

20. Who is organising and funding this clinical trial?

The trial is run by the Oxford Respiratory Trials Units in conjunction with the Medical Research Council Clinical Trials Unit, Imperial College London and Edinburgh University. The trial is being funded by the NHS National Institute for Health Research Health Technology Appraisal Programme. ResMed UK are supplying the CPAP machines; this company is not involved in running the study. Independent experts will regularly monitor the progress of the trial in terms of both safety and benefits from the trial treatment. No payment will be made to any of the doctors or nurses taking part in this trial.

21. Who has reviewed the study?

This study was given favourable ethical opinion for conduct in the NHS by: **Royal Brompton Harefield and NHLI Research Ethics Committee.** A local Ethics committee in each hospital taking part in this trial has also reviewed the trial.

22. Contact for further information

You are encouraged to ask any questions you wish, before, during or after your participation in the study. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the procedures involved. If you wish to see more detailed background to the study, we are happy to provide a copy of the full study protocol.

If you require any further information or have any concerns while taking part in the study, please contact one of the following people:

Prof. Mary Morrell PhD, Professor of Sleep & Respiratory Physiology, Academic Unit of Sleep and Ventilation, Royal Brompton Hospital, Fulham Road, London, SW3 6NP. Tel: +44 (0) 20 7352 8121 (ext 4023), m.morrell@imperial.ac.uk

Dr RL Riha, Consultant and Honorary Senior Lecturer, Department of Sleep Medicine, Royal Infirmary Edinburgh, 51 Little France Crescent, Edinburgh, Scotland EH16 4SA. Tel: 0131 2423882, rriha1@staffmail.ed.ac.uk

23. Consent

If you decide you would like to take part, please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes and one will be filed with the study records. You can have more time to think this over if you are at all unsure. Thank you for taking the time to read this information sheet and considering our study.

Study Outline

First contact with the PREDICT Team

If you have been diagnosed with obstructive sleep apnoea / hypopnoea syndrome and excessive daytime sleepiness (based on your clinic's usual practice) and you are over 65 years you may have been invited to take part in our study and complete the consent form

You will be asked to arrive for your 1st hospital visit at 8:30am, having had nothing to eat & drink since midnight the night before. You will be free to leave at around 12.30pm. We will offer you breakfast and pay your travel costs

- We will take your blood first and then give you breakfast.
- Your height, weight, waist and neck circumference and current medications will be noted. We will ask about your medical history, smoking, alcohol and caffeine intake, how much you exercise and how many times you urinate at night. We will measure your blood pressure and how strong your lungs are. We will also measure how sleepy you are using some questions and a short test.
- We will ask you to fill in several questionnaires to measure the quality of your life, numbers of road traffic, domestic and work accidents, the number of times you visit your GP, hospital visits, and A&E visits
- We will also test you mobility, memory, reaction times, and ask you about your schooling.
- You will then be assigned to receive either CPAP and best supportive care, or best supportive care only; we call this process randomisation.
- If you are randomised to best supportive care the research nurse/doctor will explain this to you and give you a packet of information for you to take away with you, including a monthly diary which should be mailed back to us (stamped addressed envelopes will be provided) The diary will ask you how you are feeling each month.
- You will then be shown how to put on a monitor that will measure your breathing when you are asleep. We will give you the monitor to take home and wear when you are asleep. This is a home sleep study. You will be asked to return it the next morning.
- If you are randomised to CPAP treatment you will be set up with your equipment to take home to use and also the diary that will ask you how you are feeling each month. If you prefer, this can be carried out the next day after the home sleep study.

Next Morning

Follow up: 1 week and 1 month (Telephone)

We will call you after one week and again at one month. You are of course free to call us at any other time and we have provided a phone number you can ring at the end of this sheet. If you are using CPAP we will ask how you are getting on with it and if you are experiencing any difficulties with it. We will also ask about any exercise and life style changes you may have had. We will then complete a sleepiness questionnaire with you and some simple questions about health care usages and accidents. We will offer you optional clinic visits if you would like them. If you are not using CPAP we will still call and ask how you are. You will be asked all the same questions except the ones relating to the CPAP machine

Follow up: 3 months (Clinic Visit)

This visit will be similar to the 1st visit, except that you will be asked to bring your machine (if you have one). We will ask you about treatment side effects and read information on the machine about how much you have used it. At the end of the visit you will be asked to take home an oxygen monitor to wear that night and return the

Return of monthly diary (by pre paid post)

Your diary will ask you to assess your sleepiness and general health over the past month, any treatment side effects, and any changes in your medications; if you have visited your GP or hospital or had any traffic, domestic and work accidents.

Follow up: 6 months (Telephone)

Follow up: 12 months (Clinic Visit)

Brain MRI: Patient Information Sheet

Brain morphology and cognitive function in older people with obstructive sleep apnoea after continuous positive airway pressure treatment

Chief Investigator: Professor Mary Morrell

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1. Invitation

You are being invited to take part in a research study. Before you decided whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

This Patient Information Sheet is in two parts.

Part One tells you the purpose of this study.

Part Two gives you more information if you are thinking of taking part in the study.

PART ONE

2. What is the purpose of this study?

This study has been designed to establish if the treatment continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) has any effect on brain structure and memory in older people.

In this study we will be examining brain structure before and after treatment with a MRI scan and different aspects of your memory in particular how you process information and complete tasks.

We know CPAP works well in younger people with OSA, but we do not know if it is helpful in older people who may feel unwell for other reasons, or who may not be as sleepy as younger people. Therefore, we need to compare the responses in some patients who are using CPAP, with those who are receiving normal medical treatment. Only in this way can we establish if the CPAP is beneficial to health (or not) in older people with OSA.

3. Why have I been chosen?

You have been asked to consider taking part in this study because you have OSA and you are over 65 years of age.

4. Do I have to take part?

No. Your participation in this study is voluntary. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. Should you wish to stop taking part at any stage of this study you are free to do so without giving a reason. If you do stop taking part, we ask you if we can keep the records relating to the treatment given to you up to this point, as this is still valuable information to the study. A decision to stop treatment at any time, or a decision not to take part, will not affect the quality of care you receive.

5. What will happen to me if I take part?

If you decide to take part, we will review your history, which includes questions about your general health, medications smoking, alcohol and caffeine intake. We will also ask you about your sleeping habits, memory, schooling and how much exercise you take. Other routine tests, such as measuring your blood pressure, heart rate, height, weight, collar size and waist will be performed. As part of the research study you will be asked to undergo a number of other tests including a detailed sleep study. This sleep study may also have been requested as part of your original diagnosis and will provide us with information about your OSA and your sleep. We will also complete a brain scan and memory tests. These tests are listed below and outlined in the chart at the end of the information sheet.

Treatment: Sometimes we don't know which way of treating patients is best. To find out, we need to make comparisons between the different treatments. To do this we put people into groups and give each group a different treatment; the results are compared to see if one is better. To make sure the groups on each treatment are similar to start with, each patient is put into a group by chance (randomly). The results are then compared. If you agree to take part you will be asked to sign a consent form and then put in one of two groups through a randomised process.

One group will be asked to use the CPAP whilst the other group will continue with their normal medical treatment; we call this best supportive care. Both groups will be asked to undergo follow-up visits and investigations.

Follow-up: Regardless of which group you are in the follow up will be the same. We will ask you to attend the hospital overnight for a detailed sleep study and a brain scan at the start of the study. At 1 week and 1 month we will call you by telephone to find out how you are getting on and offer advice or an additional visit if needed. At 6 months we will ask you to attend the hospital for reassessment including a repeat brain scan. This study will last for 6 months.

These are the tests required on your first visit.

Overnight sleep study in hospital

You will be attached to a monitor overnight. We will measure the stages of your sleep with two leads attached to your head and two leads which measure the tone in your muscles. These leads are attached with special skin glue which is removed the following morning. Two stretchy bands will be placed round your waist and chest to measure your breathing. A small device will be placed onto your finger to measure the oxygen in your blood, and some sticky discs to the skin on your chest wall and a sensor that fits just under your nose to measure the air flowing in and out. They will be attached to a recording box (about the size of a large match box).

Cognitive function tests

We will ask you to complete a series of puzzles. Some are simple questions like; what day is it? We will also assess how quickly you can react, how you process and remember information or complete simple puzzles such as coping shapes or completing a dot to dot. They only require basic reading do not require you to write. Each test will be fully explained and you will be given a practice until you feel comfortable at completing them. It will take approximately an hour in the morning.

Maintenance of wakefulness test

We will assess how sleepy you are by asking you to fill in a short questionnaire, and also by seeing how long you can stay awake. This involves you lying comfortably on a bed in a quiet, darkened warm room. You will be asked to respond to a small flashing light by touching a button. We will complete this test twice in the morning.

Magnetic resonance imaging (MRI) brain scan

An MRI brain scan is a 3 dimensional scan of the brain that will allow us to assess structural changes in the brain. The scan will be completed at one of the sites within the Imperial College Healthcare NHS Trust. You will be transported to and from the hospital via taxi. MRI scans do not involve X-rays or radiation but do rely on strong magnets. There are some conditions that prevent you having an MRI such as metal implants or pacemakers and so you would not be eligible to participate in the trial, this will be checked prior to you entering the trial. A second checklist will be double checked prior to your scan. You will be asked to lie on your back in the scanner and your head will be placed in a head holder for the scan to prevent small head movements. It will take approximately 45 minutes to complete. The MRI scan can be completed on the same day as the sleep study if convenient or within 2 weeks of their sleep study and prior to starting CPAP. The scan will be examined by a specialist unrelated to the trial. If there are any unexpected findings we will contact you and discuss the management with you. The scans will be examined in batches and hence the results will not be available immediately.

Questionnaires

We will ask you to fill in a number of questionnaires that assess your quality of life and mood. These questionnaires will take approximately 15 minutes.

Blood tests

10ml (2 teaspoons) of your fasting blood will be taken to check a number of factors such as cholesterol and glucose levels, kidney, liver, bone and thyroid function as well as a full blood count. These tests will be carried out as part of the standard care. All these samples will be taken at the same time in one go. The samples will not be tested for HIV or chronic infectious disease.

6. What do I have to do?

If you agree to take part in the study we will help you with arranging your visits to the hospital. The study doesn't require you to do anything different in terms of your usual lifestyle or diet and we would ask you to continue your usual medications. We would like to review your progress regularly by keeping in contact with you over the phone at 1 week and 1 month and see you at 6 months. We will reimburse any additional travel expenses incurred in taking part in this trial.

7. What is being tested?

In this study we are testing whether CPAP treatment changes brain structure and cognitive function in older people with OSA

8. What are the alternatives for treatment?

Participating in the study will not change your diagnosis. In younger sleepy people one of the treatments for OSA is CPAP; however in older people we do not know if this treatment is beneficial.

9. What are the unwanted side-effects of any treatment received when taking part?

CPAP is generally very well tolerated. Sometimes it can cause nasal dryness/discomfort, nasal discharge, a dry mouth (and dribbling), facial discomfort and, rarely, ulceration due to poor mask fitting. These effects can be minimised by the use of warmed air and careful mask fitting. All the nurses and doctors involved in this trial are experienced in using CPAP and minimising these unwanted side-effects.

If you do decide to take part in the study, please report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this sheet for you to phone if you become worried at any time.

10. What are other possible disadvantages and risks of taking part?

The main disadvantage of taking part in this study is the time commitment to attend hospital for the visits. There is the small discomfort of having blood samples taken. An MRI scans is a very safe test and are commonly performed. There are no known complications or side-effects from the magnetic field used during the scan. Some people feel uncomfortable or claustrophobic inside the scanner. If you are worried about this please talk to us beforehand. We will complete a checklist to make sure you are safe to have a scan prior to entry into the trial and this will be checked again independently prior to your scan. Some private medical insurers require to be notified of participation in clinical trials.

11. What are the possible benefits of taking part?

All people taking part will receive advice on managing their OSA with improved diet, exercise and regular sleep patterns. You will also have regular health assessments and contact with a specialist team. We may find during the tests that something needs further investigation or treatment that would not have otherwise been found. If this is the case then we will organise appropriate care in liaison with your GP. We hope it will improve the understanding of OSA and how it affects older people differently.

12. What happens when the research study stops?

At the end of the study you will be reviewed. If you have been allocated CPAP and want to continue CPAP treatment we will arrange for this to happen. If you did not receive CPAP treatment and would like a trial we will also arrange this. You will then be followed up by your GP and / or hospital clinicians as usual.

13. What if there is a problem?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim

compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator Dr Alison McMillan, Academic Unit of Sleep and Ventilation, Royal Brompton Hospital, Fulham Road, London, SW3 6NP Tel: 02073528121 (ext 4182), a.mcmillan@imperial.ac.uk

The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

This completes Part 1 of the Information Sheet. If this has interested you and you are considering participation, please continue to read the additional information that follows before making any decision. Part 2 provides more information about how we run the study.

PART 2

14. What if new information becomes available during the study?

Sometimes during the course of a study, new information becomes available on the condition being studied. If this happens, the study team will review the information and let you know if it affects the study. If the study changes as a result and you decide to continue in it, you will be asked to sign an updated consent form.

15. What will happen if I don't want to carry on with the study?

You are free to withdraw entirely from this study at any stage. If you withdraw from the study, you can ask us to destroy all your identifiable samples, but we would seek your permission to keep and use information and samples collected up to your withdrawal. If you have registered with the NHS Central Register (NHSCR), we would also seek your permission to continue this.

16. Will my taking part in this study be kept confidential?

If you consent to join the study, your medical records may be looked at by representatives of the Sponsor (Imperial College London), the coordinating trials office, and Regulatory Authorities for the purposes of checking the study is being carried out correctly. All of these individuals will have a duty of confidentiality to you as a research participant.

As part of your participation in the study, information will be collected about you for analysis by the Sponsor's trial team and other collaborators involved in the study. This will include information about your health and other details such as your date of birth and gender. You will be allocated a study number to identify you, which means that you will not be identifiable from the study database.

In accordance with sponsor's guidelines, at the end of the study, your identifiable data will be securely stored for a minimum of 10 years. Arrangements for confidential destruction will then be made.

Finally, the information held by the NHS and records maintained by the NHS Information Centre may be used by the Sponsor's trial team to keep in touch with you and follow up your health status.

The information collected about you may also be shown to authorised people from the UK Regulatory Authorities and Sponsor (Imperial College London). This is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

17. Informing your General Practitioner (GP) and other clinicians.

We will ask your permission to inform your GP, other medical practitioners and carers involved in your care that you are participating in this study. Where it is appropriate, we will liaise with your family, GP and any relevant carers in completing the information for the study.

18. What will happen to any samples I give?

If you consent to take part in this study, blood samples will be taken specifically for the study and will also be used for the standard management of your condition. There will be no duplication of tests. The samples will be processed and stored as standard practice for all NHS samples

19. What will happen to the results of this study?

Once all the data has been collected and analysed, it will be written up as a scientific paper and made available through presentation in scientific journals and conferences. In all instances the data will be anonymous and none of the patients involved in the study will be identified in any report or publication.

20. Who is organising and funding this clinical trial?

Imperial College London is organising the research and the study is being funded by the NHS National Institute for Health Research Health Technology Appraisal Programme and the NIHR Respiratory Disease Biomedical Research unit at the Royal Brompton and Harefield NHS Foundation Trust. ResMed UK are supplying the CPAP machines; this company is not involved in running the study. No payment will be made to any of the doctors or nurses taking part in this trial.

21. Who has reviewed the study?

This study was given favourable ethical opinion for conduct in the NHS. Several doctors and scientists who are experienced in designing, setting up and running research projects have also reviewed this study.

22. Contact for further information

You are encouraged to ask any questions you wish, before, during or after your participation in the study. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the procedures involved. If you wish to see more detailed background to the study, we are happy to provide a copy of the full study protocol.

If you require any further information or have any concerns while taking part in the study, please contact:

Professor Mary Morrell PhD, Reader in Respiratory Physiology, Academic Unit of Sleep and Ventilation, Royal Brompton Hospital, Fulham Road, London, SW3 6NP. Tel: +44 (0) 20 7352 8121 (ext 4023), m.morrell@imperial.ac.uk

23. Consent

If you decide you would like to take part, please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes and one will be filed with the study records. You can have more time to think this over if you are at all unsure. Thank you for taking the time to read this information sheet and considering our study.

Study Outline

First contact

You have been diagnosed with Obstructive Sleep Apnoea and have been invited to take part in this study. We will complete the consent form before completing any tests.

⇩

Enrolment visit

You will be asked to arrive for your first hospital visit by 5pm. You will be free to leave at around 12.30pm the following morning. We will offer you dinner and breakfast and pay your travel costs.

Evening tests

Baseline measurements include height, weight, neck and waist circumference, blood pressure and lung function tests if needed.

We will ask about your medical history and current medication, smoking, alcohol and caffeine intake, and how much you exercise.

We will ask you to fill in questionnaires to measure your quality of life and mood

MRI scan and overnight sleep study.

⇩

Follow up: 1 week and 1 month (Telephone)

We will call and ask you how you are getting on and if you are experiencing any difficulties. You will be offered an additional clinic visit if needed

⇩

Follow up and trial exit: 6 months (Visit)

This will be similar to the first visit except no overnight sleep study.

PREDICT: GP Letter

A randomised controlled trial of continuous positive airway pressure treatment in older people with obstructive sleep apnoea / hypopnoea syndrome (PREDICT)

Ethics Ref: 09/H0708/33

ISRCTN No: 90464927

Dear Dr _____

Your patient, _____ (date of birth ____/____/____), has been entered into the above trial. This is currently a six centre study (Oxford, Royal Brompton Hospital, Edinburgh, Newport, Leeds and Taunton, but further UK centres may be joining us). The aim of this trial is to evaluate whether the use of nasal continuous positive airway pressure (CPAP) treatment improves sleepiness and is cost effective in treating older patients (>65 years) with OSA.

Nasal CPAP is currently the treatment of choice for younger patients with OSA who have significant symptoms that require treatment. However, there is inconclusive evidence that nasal CPAP is an effective treatment in older people with OSA.

A copy of the Patient Information Sheet is enclosed.

The study involves randomisation to nasal CPAP with best supportive care, or best supportive care with no nasal CPAP for a period of 12 months. Your patient will of course know which treatment they have been randomised to. No side effects are anticipated. If any clinically useful information relevant to your patient is uncovered we will contact you.

We will carry out:

- Monthly measurements of subjective sleepiness
- Analysis of the cost efficiency of nasal CPAP calculated through its impact on health related quality of life and health service utilisation.
- Measurements of secondary endpoints at 3 and 12 months: objective sleepiness, rate of accidents (including traffic accidents), disease specific quality of life, mood, functional index of daily living, mobility, exercise, nocturia, cognitive function, change in cardiovascular risk factors and new cardiovascular events.

We realise that you get many requests for information concerning your patients, but we would be very appreciative if we could contact your practice and obtain information regarding accurate health care utilisation, past medical history and start dates of medication. This is a key part of our trial. I enclose a signed patient consent form.

If you have any concerns, comments or would like any further information about the study please contact me on the above number.

Yours sincerely,

Kind regards,

Dr Mary Morrell

Reader in Respiratory Physiology

Brain MRI: GP Letter

Brain morphology and cognitive function in older people with obstructive sleep apnoea after continuous positive airway pressure treatment

Ethics Ref: 10/H0711/101

Dear Dr _____

Your patient, _____ (date of birth ____/____/____), has been entered into the above study. The aim of the study is to examine the effect of 6 months of continuous positive airway pressure (CPAP) treatment on brain structure and cognitive function in older people with obstructive sleep apnoea (OSA).

CPAP is currently the treatment of choice for younger patients with OSA who have significant symptoms that require treatment. However, there is inconclusive evidence that CPAP is an effective treatment in older people with OSA. ***A copy of the Patient Information Sheet is enclosed.***

The study involves your patient being randomised to best supportive care, or best supportive care with CPAP for a period of 6 months. Your patient will of course know which treatment they have been randomised to. No side effects are anticipated. If any clinically useful information relevant to your patient is uncovered we will contact you.

We will carry out:

- An overnight sleep study
- A medical assessment including anthropometric measurements and cardiovascular risk profile
- Measurements of subjective and objective sleepiness
- Questionnaires on their quality of life and mood
- A series of cognitive tests
- MRI scans of the brain at baseline and at 6 months.

At the end of the study all patients will be reassessed and offered CPAP if appropriate.

If you have any concerns, comments or would like any further information about the study please do not hesitate to contact me.

Yours sincerely,

Dr Alison McMillan Clinical Research Fellow

PREDICT: Consent Form

A randomised controlled trial of continuous positive airway pressure treatment in older people with obstructive sleep apnoea / hypopnoea syndrome (PREDICT)

Centre No: 1.0

Ethics Ref: 09/H0708/33

ISRCTN No: 90464927

(Please initial box to agree)

1	I confirm that I have read and understand the information sheet dated 21/04/2011 (version 5.0) for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that sections of my medical notes may be looked at by responsible individuals involved in the running of the trial, or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4	I understand that **information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.**	☐
5	I give permission for my trial data some of which may identify me, to be transported from my hospital site to the trial co-ordinating centre for the purposes of analysis, monitoring and follow-up.	☐
6	I understand that samples of my blood taken for the trial will be stored and genetic analysis will be performed on the samples.	☐
7	I confirm that samples of my blood may be used for other research in the future and I give my permission to the members of the PREDICT trial team to pursue this research. I regard these blood samples as a 'gift' to the research team.	☐
8	I would like my GP (Dr.....) to be notified about my participation in this trial and I give permission for you to contact him/her and obtain further medical information from my GP held notes.	☐
9	If you would like to know the results of this study, please tick the box and we will write to you when the study is completed.	☐
10	I agree to take part in the above study. All handling, storage and destruction of data are in accordance with the Data Protection Act 1998.	☐

Name of Patient	Date	Signature
_____	_____	_____

Name of Person Taking Consent	Date	Signature
_____	_____	_____

Brain MRI: Consent Form

Brain morphology and cognitive function in older people with obstructive sleep apnoea after continuous positive airway pressure treatment.

CI: Professor Mary Morrell

Ethics Ref: 10/H0711/101

(Please initial box to agree)

1 I confirm that I have read and understand the information sheet (version 1.0 September 2010) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3 I understand that relevant sections of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities, Imperial College London or from the NHS trust were it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4 I understand that **information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.** ☐

5 I give permission for my study data which will be anonymised, to be transported from one hospital site to another for the purposes of analysis. ☐

6 I agree to my blood being taken for the study and a MRI scan being completed. ☐

7 I agree to my GP (Dr.....) being informed of my participation in the study. I give permission to contact him/her and obtain further medical information from my GP held notes if needed. ☐

8 I understand that should I withdraw from the study my anonymous data will be included in the analysis unless I request that it be removed. ☐

9 If you would like to know the results of this study, please tick the box and we will write to you when the study is completed. ☐

10 I agree to take part in the above study. All handling, storage and destruction of data are in accordance with the Data Protection Act 1998. ☐

Name of Patient	Date	Signature
_____	_____	_____
Name of Person Taking Consent	Date	Signature
_____	_____	_____

MRI Consent Form

It is ESSENTIAL for your SAFETY that you answer ALL questions correctly

PATIENTS SURNAME FIRST NAME:……..

DATE OF BIRTH: WEIGHT:…….HEIGHT……

PLEASE ASK IF YOU ARE UNSURE ABOUT *ANY* OF THE QUESTIONS	Yes	No	For MRI staff only
1. Do you have a heart **pacemaker** or **pacing wires**?	☐	☐	
2. Do you have **aneurysm clips** in your head (from a surgical procedure)?	☐	☐	
3. Do you have an **artificial heart valve** or **coronary stent**?	☐	☐	
4. Do you have any **metal implants** e.g. joint replacements, pins, wires?	☐	☐	
5. Do you have a **cochlear implant**?	☐	☐	
6. Do you have a **programmable shunt (e.g. for hydrocephalus), deep brain stimulator** or **neurostimulator**?	☐	☐	
7. Do you have an **artificial limb**, **calliper** or **surgical corset**?	☐	☐	
8. Do you have any **shrapnel** or **metal fragments** in your body or eyes?	☐	☐	
9. Have you ever worked with **metal** (e.g. welding or lathe operation)?	☐	☐	
10. Do you wear **dentures**, **plate** or a **hearing aid**?	☐	☐	
11. Have you ever had a **fit/blackout**, or suffered from **epilepsy/diabetes**?	☐	☐	
12. Are you wearing a medicinal **patch**?	☐	☐	
13. Do you have an **intrauterine contraceptive device** fitted?	☐	☐	
14. Is it at all possible that you could be **pregnant**?	☐	☐	
15. Are you breastfeeding?	☐	☐	
16. I confirm that I have nothing metal within or about my body.	☐	☐	

SIGNATURE: …… **DATE**:……

NAME OF PERSON FILLING FORM (if not patient) ……..

RELATIONSHIP to PATIENT ……

DO NOT take removable metal objects into the examination room. This includes: **Keys, Coins, Watches, Jewellery, Hair clips, Hearing aids**. Please store these and other valuables in the lockers provided.

For your information:

Loose metal objects:	Can fly into the magnet like missiles.
Pacemakers:	May not work properly in the MRI room.
Travel/bank cards	May be erased if brought into the MRI room.
Watches	May be damaged in the magnet

CHECKED BY MRI staff only.

NAME …….…….. SIGNATURE……..……..…DATE……..…

Appendix 2:

Central record forms, questionnaires and standard operating procedures

PREDICT: Central Record Form

Enrolment Form

Recruiting Centre:		Enrolment Date: D D / M O N / 2 0 1 Y

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

1. Diagnostic sleep study Data - Date: D D / M O N / 2 0 1 Y

Type (please tick one)**:** Oximetry ☐ Respiratory Study ☐ Full PSG ☐

≥ 4% ODI		Wake SpO_2 on room air		%
Apnoea/hypopnoea index		Time SpO_2 <90%	mins	%
Sleep study data backed up	Yes ☐ Not possible ☐			

2. Baseline fasting blood tests

(If patient not fasted, ask them to fast on the morning that they return the Embletta and take bloods then) Blood samples taken at enrolment visit? Yes ☐ No ☐

	Sample Taken
Biochemistry tube(s): U & E, Creatinine, LFT, Cholesterol, HDL/LDL, Triglycerides, TSH, Glucose	Yes ☐ No ☐
EDTA tube: FBC	Yes ☐ No ☐
EDTA tube: HbA1c	Yes ☐ No ☐
2 x EDTA tube: Genetic tests (to be posted to Oxford RTU)	Yes ☐ No ☐

3a. What time (please use 24 hour clock) does the patient normally:

Go to bed (enter the range, If bedtime is always the same, enter the same time in both boxes)

☐☐:☐☐ to ☐☐:☐☐

Get up in the morning

☐☐:☐☐ to ☐☐:☐☐

Does the patient usually sleep on their own? Yes ☐ No ☐

(ie no other person sleeping in the same bed or the same room)

3b. Does the patient suffer from any of the following sleep related problems?

Snoring Yes ☐ No ☐ Unknown ☐

Nocturnal Choking Episodes Yes ☐ No ☐ Unknown ☐

Witnessed Apnoeas Yes ☐ No ☐ Unknown ☐

3c. Does the patient have a daytime nap? Yes ☐ No ☐

If Yes, please enter the estimated number of naps in the last week ☐

Please enter the average duration of each nap _____ minutes

4a Home Accident History

In the last month, has the patient had any accidents at home, such as a fall? Yes ☐ No ☐

If 'Yes', please answer the following questions:

	Yes	No
Required any form of treatment e.g. at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

4b. Nocturia symptoms

How many times do you usually get up to pass urine in the night? _____ times

(Please try to determine a single value which occurs on **most** nights e.g. 2 times. If not possible, enter a range typical of **most** nights e.g. 2-3 times)

In the last month, have you fallen when getting up in the night? Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____times

Have you have leaked urine (been incontinent of urine) while you were sleeping in the past month?

Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____times

5. Driving History

Which driving licence(s) does the patient hold? Car ☐ Motorbike ☐ None ☐

Does the patient drive? Yes ☐ No ☐

If Yes, please ask them to complete the Driving questionnaire and place in the envelope

Driving questionnaire completed? Yes ☐ No ☐ Not applicable ☐

6. Health Care Usage Questions

During the past <u>month</u>, how <u>many times</u> has the patient:

	Number of times
Visited a GP? (Please do not include contacts for repeat prescriptions)	☐
Been seen at home by a GP?	☐
Visited a nurse?	☐
Been seen at home by a nurse?	☐
Contacted general practice for telephone advice?	☐
Contacted NHS Direct for telephone advice?	☐
Had an ambulance called for themselves?	☐
Visited an Accident and Emergency department?	☐
Attended an out-patient clinic?	☐

Hospital Admissions (not including any admission for diagnostic sleep study)

In the past month, has the patient been in hospital overnight? Yes ☐ No ☐

If Yes: How many overnight hospital admissions have you had this month? ☐

How many times were you were admitted as an emergency? ☐

Please enter the total number of nights spent in hospital this month ☐

7. Please list below all medications, including sleeping pills and inhalers, which the patient is taking at time of enrolment:

Name of medicine	Total Daily Dose	Units
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

8. Smoking History

Have you ever smoked? Yes ☐ No ☐

Do you smoke now? Yes ☐ No ☐

9. Caffeinated and alcoholic drinks

How many cups of the following, do you drink **each day?**	Number:
Tea	
Coffee	
Caffeinated drinks (coca cola, lucozade etc.)	

How many of the following beverages do you drink **each week?**	Number:
Beer (pints)	
Wine (glasses)	
Spirits (measure)	
Sherry/port (glasses)	

10. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes, what form did it take?

	Yes	N
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls etc.)		
Attend a gym (aerobics, Pilates, yoga etc.)		

	Ye	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

11. Please ask the patient which ethic group describes how they see themselves.

This is a mixture of culture, religion, skin colour, language and origins. It is not the same as nationality. This information will be treated in the strictest confidence and will not be passed on to other parties.

A White		**D** Black Other		**G** Bangladeshi	
B Black Caribbean		**E** Indian		**H** Chinese	
C Black African		**F** Pakistani		**J** Other	

12. Please go through the following vascular questionnaire

Have you been diagnosed with, or had, any of the following?

1. Angina?	Yes ☐ No ☐
2. Hypertension?	Yes ☐ No ☐
3. Myocardial infarction/heart attack?	Yes ☐ No ☐
4. Diabetes Mellitus/sugar diabetes?	Yes ☐ No ☐
If 'no' go to q 8	
<u>Treatment</u>	
5. Diet	Yes ☐ No ☐
6. Tablets	Yes ☐ No ☐
7. Insulin	Yes ☐ No ☐
8. Intermittent claudication/artery narrowing to the legs?	Yes ☐ No ☐
9. Atrial fibrillation/irregular heart beat?	Yes ☐ No ☐
If 'no' go to q 14	
<u>Treatment</u>	
10. None	Yes ☐ No ☐
11. Tablets	Yes ☐ No ☐
12. Cardioversion	Yes ☐ No ☐
13. Pacemaker	Yes ☐ No ☐
14. Cardiac failure/heart failure?	Yes ☐ No ☐
15. Transient ischaemic attack/mini-stroke?	Yes ☐ No ☐
16. Full stroke?	Yes ☐ No ☐
17. Angioplasty/heart artery dilation?	Yes ☐ No ☐
18. Coronary stent/heart artery stent?	Yes ☐ No ☐
19. Coronary artery bypass surgery/heart bypass?	Yes ☐ No ☐
20. Endarterectomy/arterial surgery to artery to brain?	Yes ☐ No ☐
21. Peripheral vascular intervention/leg artery bypass or stent or amputation?	Yes ☐ No ☐
22. Aortic aneurysm/swelling of the main artery in your chest or abdomen?	Yes ☐ No ☐

13. Completed years of education (to the nearest full time whole year) ☐☐

14. Has the patient completed the Cognitive Function Tests?

Reaction Time Test	Yes	☐	No	☐
Mini Mental State Exam	Yes	☐	No	☐
Trail making Test	Yes	☐	No	☐
Digit Symbol Substitution Test	Yes	☐	No	☐

15. Please take 3 Blood Pressures with the patient seated

Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	

Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	

Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	

16. Anthropometry

Gender	Male: ☐	Female: ☐

Height (cms)	☐☐☐.☐	Weight (kg)	☐☐☐.☐

Neck circumference (cms)	☐☐.☐

Waist circumference (cms)	☐☐☐.☐	Hip circumference (cms)	☐☐☐.☐

17. Spirometry Yes ☐ No ☐

Date recorded: D D / M O N / 2 0 1 Y

Lung Volume	Measured Value	Predicted Value	% Predicted Value
FEV_1 (litres)			
FVC (litres)			
FEV_1/ FVC (%)			

18. Does the patient suffer from:

Asthma	Yes	☐	No	☐
COPD	Yes	☐	No	☐
Other Chronic Lung Disease	Yes	☐	No	☐

19. Timed 'UP AND GO TEST' Seconds

Tick box if participant physically unable to complete this test ☐

20. OSLER Test Results

Test	Start Time (24 hour clock)	Test Duration (mins)
1		
2		

- **Please ensure the patient has completed questionnaires A to F (pages 8 – 17)**

Please complete the randomisation form and randomise

(If you will be the researcher at future study visits, who does not know which treatment the patient has been randomised to, please ask a colleague to perform randomisation and provide Best Supportive Care package or CPAP)

After Randomisation:

- Provide patient with folder containing contact details, Best Supportive Care information sheet and Monthly Sleep diaries
- If randomised to CPAP, complete or arrange the set up
- Explain and give Embletta to the patient
- Please arrange a time for a 1 week telephone follow up call

Date for telephone call: D D / M O N / 2 0 1 Y **Morning** ☐ **Afternoon** ☐ **Evening** ☐

Blood sample for genetic tests posted to Oxford RTU: D D / M O N / 2 0 1 Y

Please send the top copy of this CRF & the questionnaires to the Oxford Respiratory Trials Unit:

UKCRC Oxford Respiratory Trials Unit

Oxford Centre for Respiratory Medicine

Churchill Hospital

Old Road, Headington

Oxford, OX3 7LE

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Randomisation Form

Recruiting Centre:		Randomisation Date: D D / M O N / 2 0 1 Y

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Inclusion Criteria	
Age ≥ 65 years	Yes ○ No ☹
A clinical diagnosis of OSAHS: ≥ 4% Oxygen desaturation index > 7.5 events/hour and an Epworth sleepiness scale ≥ 9	Yes ○ No ☹
Ability to give written informed consent	Yes ○ No ☹

Exclusion Criteria	
Previous exposure to CPAP therapy	Yes ☹ No ○
Arterial oxygen saturation <90% on room air	Yes ☹ No ○
FEV_1 / FVC <60% predicted, or FEV_1 <65% predicted	Yes ☹ No ○
Substantial problems with sleepiness during driving (in those who are still driving)	Yes ☹ No ○
Current Heavy Goods Vehicle or Public Service Vehicle driver.	Yes ☹ No ○
Shift work	Yes ☹ No ○
Any very severe complication of OSAHS (such as hypercapnia) such that CPAP therapy is mandatory	Yes ☹ No ○
Inability to give informed consent or comply with the protocol	Yes ☹ No ○

Does the patient agree to take part in the study?	Yes ○ No ☹
Is the patient eligible to take part in the study?	Yes ○ No ☹

Minimisation Criteria: **Epworth Sleepiness Scale:** _____

Townsend Scale Score: _____

Has the participant signed the consent form? **Yes ○ No ☹**

Please telephone MRC Clinical Trials Unit (0207 670 4711) to randomise the patient

Patient randomised to (please tick):

1. CPAP with Best supported Care ☐
2. Best supportive Care ☐

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Enrolment Cognitive Function Test Results

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Date Cognitive Function Tests Completed: D D / M O N / 2 0 1 Y

Cognitive test	**Score**
Simple and four-choice reaction time	**Save to database**
Mini Mental State Score	Out of 30
Trail making B time	(seconds)
Digit Symbol Substitution test (No. of correct answers in 90 seconds)	

Please send the top copy of this CRF to:

UKCRC Oxford Respiratory Trials Unit,

Oxford Centre for Respiratory Medicine,

Churchill Hospital,

Old Road, Headington,

Oxford, OX3 7LE

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Embletta and Blood Test Results

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

1. PREDICT Embletta sleep study date: D D / M O N / 2 0 1 Y

Is the Embletta study technically adequate? Yes ☐ No ☐

Embletta file backed up and sent to Edinburgh? Yes ☐ No ☐

2. Baseline blood tests

Blood samples taken on day Embletta returned Yes ☐ No ☐

(only required if not taken on enrolment visit)

If yes, was the patient fasted? Yes ☐ No ☐

	Sample Taken?
Biochemistry tube(s): U & E, Creatinine, LFT, Cholesterol, HDL/LDL, Triglycerides, TSH, Glucose	Yes ☐ No ☐
	Yes ☐ No ☐
EDTA tube: HbA1c	Yes ☐ No ☐
2 x EDTA tube: Genetic tests (to be posted to Oxford RTU)	Yes ☐ No ☐

3. Blood Test Results

	Value	Units
Haemoglobin		
MCV		
WBC		
Platelets		
Sodium		
Potassium		
Urea		
Creatinine		
TSH		
Glucose		
HBA1C		

	Value	Units
Total Cholesterol		
HDL Cholesterol		
LDL Cholesterol		
Triglycerides		
Total Protein		
Albumin		
ALT		
GGT		
Bilirubin		

Researcher's Name:	Signature:	Date D D / M O N / 2 0 1 Y

One Week Telephone Follow Up

Date of Phone Call: DD/MON/201Y	Trial No:					Patient's Initials:				Date of Birth: DD/MON/19YY

SECTION 1: This part of the interview must be completed by a researcher who does not know which treatment the patient has been randomised to.

1. Please complete the **Epworth Sleepiness Scale** with the patient during this phone call:

Thinking back over the last week, how likely are you to doze off or fall asleep in the situations described in the box below, in contrast to feeling just tired?

This refers to your usual way of life in the last week. Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

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

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

Researcher's Name:	Signature:	Date: DD/MON/201Y

Date of Phone Call: D D / M O N / 2 0 1 Y	Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

SECTION 2: To be completed by a researcher who knows which treatment the patient has been randomised to.

2. Has the patient suffered any adverse events possibly attributable to the study, since enrolment? Yes☐ No ☐

Diagnosis or Symptoms	Duration (Number of days)	Resolved?
		Yes ☐ No ☐
		Yes ☐ No ☐

If an event satisfies the criteria for a Serious Adverse Event/Reaction, please complete the appropriate form

2. Has the patient been randomised to CPAP treatment? **Yes** ☐ **No** ☐

If Yes, for patients who are on CPAP:

Are they using the CPAP?

Yes ☐ (approximate number of hours/night: _____No ☐ **Date stopped:** D D / M O N / 2 0 1 Y

Is the patient prepared to continue using CPAP? Yes ☐ No ☐

If No, reason for stopping CPAP:

4a. Does the patient need an additional appointment? Yes ☐ No ☐

4b. Is this related to CPAP usage? Yes ☐ No ☐

Additional appointment date (if needed): D D / M O N / 2 0 1 Y Time:_____:_____

- **Please remind patient to complete the monthly sleep diary three weeks from now**
- **Please arrange time for 1 month telephone call**

Date D D / M O N / 2 0 1 Y **Morning**☐ **Afternoon** ☐ **Evening** ☐

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Please send the top copies of Section 1 and 2 to the UKCRC Oxford Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE.

Please file the bottom copy of Section 2 in the Non Blinded Researcher CRF folder

One Month Telephone Follow Up

Date of Phone Call: D D / M O N / 2 0 1 Y	Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

SECTION 1: This part of the interview must be completed by a researcher who does not know which treatment the patient has been randomised to.

1a. Home Accident History

In the last month, has the patient had any accidents at home, such as a fall? Yes ☐ No ☐

If 'Yes', please answer the following questions:

	Yes	No
Required any form of treatment eg at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

1b. Nocturia symptoms

How many times do you usually get up to pass urine in the night? _____times

(Please try to determine a single value which occurs on **most** nights e.g. 2 times. If not possible, enter a range typical of **most** nights e.g. 2-3 times)

In the last month, have you fallen when getting up in the night? Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____times

Have you have leaked urine (been incontinent of urine) while you were sleeping in the past month?

Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____times

2. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes what form did it take? (please tick relevant boxes)

	Yes	No
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls etc)		
Attend a gym (aerobics, Pilates, yoga etc)		

	Yes	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

3. Has the patient smoked in the last month? Yes ☐ No ☐

This is the end of Section 1

Researcher's Name:	Signature:	Date: DD/MON/201Y

Date of Phone Call: D D / M O N / 2 0 1 Y	Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

SECTION 2: To be completed by a researcher who knows which treatment the patient has been randomised to.

4. Has the patient completed and posted their 1 month sleep diary? Yes ☐ No ☐

If necessary, please help the patient to complete their diary during this phone call

5. Has the patient suffered any adverse events possibly attributable to the study, since the 1 week phone call? Yes ☐ No ☐

Diagnosis or Symptoms	Duration (Number of days)	Resolved?
		Yes ☐ No ☐
		Yes ☐ No ☐
		Yes ☐ No ☐

If an event satisfies the criteria for a Serious Adverse Event/Reaction, please complete the appropriate form

6. Has the patient been randomised to CPAP treatment? Yes ☐ No ☐

If Yes, for patients who are on CPAP:

Are they using the CPAP? Yes ☐ No ☐ **Date stopped:** D D / M O N / 2 0 1 Y

Average usage (please ask patient to read from S9): _____ hours

(press *info* button, rotate *dial* one click to right. If necessary, change time period by depressing *dial* and rotating right until display reads '1 month')

Is the patient prepared to continue using CPAP? Yes ☐ No ☐

If No, reason for stopping CPAP:

7a. Does the patient need an additional appointment? Yes ☐ No ☐

7b. Is this related to CPAP usage? Yes ☐ No ☐

Additional appointment date (if needed): D D / M O N / 2 0 1 Y Time:_____:_____

- **Remind patient to complete their sleep diary again at 2 months**
- **Arrange date for 3 month visit and send appointment letter**
- **Three month visit appointment date:** D D / M O N / 2 0 1 Y Time:_____:_____

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Please send the top copies of Section 1 and 2 to the UKCRC Oxford Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE.Please file the bottom copy of Section 2 in the Non Blinded Researcher CRF folder

3 Month Follow-up Visit

Date of Visit: D D / M O N / 2 0 1 Y	Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

SECTION 1: This part of the interview must be completed by a researcher who does not know which treatment the patient has been randomised to.

1. Three month blood tests:

Fasted? Yes ☐ No ☐ (If patient not fasted, can bloods be rearranged?)

	Sample Taken
Biochemistry tube(s): U & E, Creatinine, LFT, Cholesterol, HDL/LDL, Triglycerides, TSH, Glucose	Yes ☐ No ☐
EDTA tube: FBC	Yes ☐ No ☐
EDTA tube: HbA1c	Yes ☐ No ☐

2a. In the last month, what time (please use 24 hour clock) does the patient normally:

Go to bed (enter the range) ☐☐:☐☐ to ☐☐:☐☐

(If bedtime is always the same, enter the same time in both boxes)

Get up in the morning (enter the range) ☐☐:☐☐ to ☐☐:☐

(If getting up time is always the same, enter the same time in both boxes)

Does the patient usually sleep on their own? Yes ☐ No ☐

(ie no other person sleeping in the same bed or the same room)

2b. Does the patient have a daytime nap? Yes ☐ No ☐

If Yes, please enter the estimated number of naps in the last week ☐

Please enter the average duration of each nap _____minutes

3a. Nocturia symptoms

How many times do you usually get up to pass urine in the night? _____ times

(Please try to determine a single value which occurs on **most** nights e.g. 2 times. If not possible, enter a range typical of **most** nights e.g. 2-3 times)

In the last month, have you fallen when getting up in the night? Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened?_____ times

Have you have leaked urine (been incontinent of urine) while you were sleeping in the past month?

Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____times

3b. Home Accident History

In the last month, has the patient had any accidents at home, such as a fall? Yes ☐ No ☐

If 'Yes', answer the following questions:

	Yes	No
Required any form of treatment e.g. at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

4. Has the patient driven in the past 3 months? Yes ☐ No ☐

If Yes, please ask them to complete the 3 month Driving questionnaire and seal in envelope

3 Month Driving questionnaire completed? Yes ☐ No ☐ Not applicable ☐

5. Does the patient currently smoke? Yes ☐ No ☐

6. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes, what form did it take? (please tick relevant boxes)

	Yes	No
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls)		
Attend a gym (class, aerobics, Pilates etc)		

	Yes	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

7. New Vascular Events Questionnaire

Please go through the following vascular questionnaire asking if the patient has been <u>newly diagnosed</u> with, or had any of the following since the enrolment visit.

1. Angina?	Yes ☐ No ☐
2. Hypertension?	Yes ☐ No ☐
3. Myocardial infarction/heart attack?	Yes ☐ No ☐
4. Diabetes Mellitus/sugar diabetes? If 'no' go to q 8 <u>Treatment</u>	Yes ☐ No ☐
5. Diet	Yes ☐ No ☐
6. Tablets	Yes ☐ No ☐
7. Insulin	Yes ☐ No ☐
8. Intermittent claudication/artery narrowing to the legs?	Yes ☐ No ☐
9. Atrial fibrillation/irregular heart beat? If 'no' go to q 14 <u>Treatment</u>	Yes ☐ No ☐
10. None	Yes ☐ No ☐
11. Tablets	Yes ☐ No ☐
12. Cardioversion	Yes ☐ No ☐
13. Pacemaker	Yes ☐ No ☐
14. Cardiac failure/heart failure?	Yes ☐ No ☐
15. Transient ischaemic attack/mini-stroke?	Yes ☐ No ☐
16. Full stroke?	Yes ☐ No ☐
17. Angioplasty/heart artery dilation?	Yes ☐ No ☐
18. Coronary stent/heart artery stent?	Yes ☐ No ☐
19. Coronary artery bypass surgery/heart bypass?	Yes ☐ No ☐
20. Endarterectomy/arterial surgery to artery to brain?	Yes ☐ No ☐
21. Peripheral vascular intervention/leg artery bypass or stent or amputation?	Yes ☐ No ☐
22. Aortic aneurysm/swelling of the main artery in your chest or abdomen?	Yes ☐ No ☐

8. Please take 3 Blood Pressures with the patient seated

Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	

9. Anthropometry

Weight (kg)	☐☐☐.☐
Neck circumference (cms)	☐☐.☐

Waist circumference (cms)	☐☐☐.☐	Hip circumference (cms)	☐☐☐.☐

10. Timed 'UP AND GO TEST'
(to the nearest whole second)

seconds

Tick box if participant physically unable to complete this test ☐

11. Has the patient completed the Cognitive Function Tests?

Reaction Time Test	Yes	☐	No	☐
Mini Mental State Exam	Yes	☐	No	☐
Trail making B	Yes	☐	No	☐
Digit Symbol Substitution	Yes	☐	No	☐

12. OSLER Test results

Test	Start Time (24 hour clock)	Test Duration (mins)
1		
2		

- **Please ensure the patient has been provided with the 3 month sleep diary and questionnaires A to C (pages 6 -11) to be completed at a convenient time during the morning, before moving on to section 2**
- **Provide pulse oximeter for one night home oximetry study (can be returned by post)**
- **Please arrange date for 6 month phone call and provide more monthly sleep diaries**

Date D D / M O N / 2 0 1 Y Morning ☐ Afternoon ☐ Evening ☐

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Trial No:					Pt's Initials:				DOB::D D / M O N / 1 9 Y Y

SECTION 2: To be completed by a researcher who knows which treatment the patient has been randomised to.

Please check the 3 month sleep diary and questionnaires have been fully completed

13. Has the patient suffered any adverse events possibly attributable to the study, since the one month phone call? Yes ☐ No ☐

Symptoms	Duration (Number of days)	Resolved?
		Yes ☐ No ☐
		Yes ☐ No ☐

If an event satisfies the criteria for a Serious Adverse Event/Reaction, please complete the appropriate form

14. CPAP adherence/efficacy data:

CPAP Downloaded: ☐ Download not possible: ☐ Not on CPAP: ☐

For 3 month data, please use the interval from the date CPAP started to the 3 month visit date. For last month data please enter data for 1 month preceding the 3 month visit date Please enter the dates used for each of these intervals.

	3 month data (from: D D / M O N / 2 0 Y Y To D D / M O N / 2 0 Y Y)	**Last month data** (from: D D / M O N / 2 0 Y Y To: D D / M O N / 2 0 Y Y)
Total days	Days	Days
Days not used	Days	Days
Total Hours	Hours	Hours
Used days ≥ 4 hours	Days	Days
Used days < 4 hours	Days	Days
Mean daily usage	Hours	Hours
Median daily usage	Hours	Hours
Pressure 95th percentile	cmH2O	cmH2O
Leak 95th percentile	l/sec	l/sec
AHI	Events/hour	Events/hour

15. Has the patient stopped CPAP? Yes ☐ (date stopped: D D / M O N / 2 0 Y Y) No ☐

If Yes, reason for stopping CPAP: _____

16. Has additional time been needed (today or in the last 3 months) to deal with CPAP problems or adherence issues? Yes ☐ No ☐ Not on CPAP ☐

If Yes, please enter the total additional time over the past 3 months _____mins

(Please remember to check the contact sheet in the patient CRF file for details of additional time spent with the patient)

Researcher's Name:	Signature:	Date: DD/MON/201Y

3 Month Cognitive Function Test Results

Trial No:				

Patient's Initials:			

Date of Birth: D D / M O N / 1 9 Y Y

Date Cognitive Function Tests Completed: D D / M O N / 2 0 1 Y

Cognitive test	**Score**
Simple and four-choice reaction time	**Save to database**
Mini Mental State Score	Out of 30
Trail making B time	(seconds)
Digit Symbol Substitution test (No. of correct answers in 90 seconds)	

Please send the top copy of this CRF to:

UKCRC Oxford Respiratory Trials Unit,

Oxford Centre for Respiratory Medicine,

Churchill Hospital,

Old Road, Headington,

Oxford,

OX3 7LE

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

3 Month Pulse Oximetry and Blood Test Results

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Pulse Oximeter returned and oximetry downloaded: **Y**es ☐ No ☐

Date of oximetry: D D / M O N / 2 0 1 Y

Technically adequate? Yes ☐ No ☐

≥ 4% ODI	Dips per hour

Time SpO_2 <90%	mins	%

3 Month visit blood test results

	Value	Units
Haemoglobin		
MCV		
WBC		
Platelets		
Sodium		
Potassium		
Urea		
Creatinine		
Glucose		
HBA1C		

	Value	Units
Total Cholesterol		
HDL Cholesterol		
LDL Cholesterol		
Triglycerides		
Total Protein		
Albumin		
ALT		
GGT		
Bilirubin		

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Please send top copy of this CRF to: UKCRC Oxford Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE

6 Month Telephone Follow Up

Date of Phone Call: DD/MON/201Y	Trial No:					Patient's Initials:				Date of Birth: DD/MON/19YY

SECTION 1: This part of the interview must be completed by a researcher who does not know which treatment the patient has been randomised to.

1a. Home Accident History

In the last month, has the patient had any accidents at home, such as a fall? Yes ☐ No ☐

If 'Yes', please answer the following questions:

	Yes	No
Required any form of treatment e.g. at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

1b. Nocturia symptoms

How many times do you usually get up to pass urine in the night? _____times

(Please try to determine a single value which occurs on **most** nights e.g. 2 times. If not possible, enter a range typical of **most** nights e.g. 2-3 times)

In the last month, have you fallen when getting up in the night? Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____ times

Have you have leaked urine (been incontinent of urine) while you were sleeping in the past month?

Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____ times

2. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes what form did it take? (Please tick relevant boxes)

	Yes	No
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls etc)		
Attend a gym (aerobics, Pilates, yoga etc)		

	Yes	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

3. Has the patient smoked in the last month? Yes ☐ No ☐

This is the end of Section 1

Researcher's Name:	Signature:	Date: DD/MON/201Y

Date of Phone Call: DD/MON/201Y	Trial No:					Patient's Initials:				Date of Birth: DD/MON/19YY

SECTION 2: To be completed by a researcher who knows which treatment the patient has been randomised to.

4. Has the patient completed and posted their 3 month sleep diary? Yes ☐ No ☐

If necessary, please help the patient to complete their diary during this phone call

5. Has the patient suffered any adverse events possibly attributable to the study, since their 3 month visit ? Yes ☐ No ☐

Diagnosis or Symptoms	Duration (Number of days)	Resolved?
		Yes ☐ No ☐
		Yes ☐ No ☐

If an event satisfies the criteria for a Serious Adverse Event/Reaction, please complete the appropriate form

6. Has the patient been randomised to CPAP treatment? Yes ☐ No ☐

7a. Does the patient need an additional appointment? Yes ☐ No ☐

7b. Is this related to CPAP usage? Yes ☐ No ☐

Additional appointment date (if needed): DD/MON/201Y Time:_____:____

Researcher's Name:	Signature:	Date: DD/MON/201Y

Please send the top copies of Section 1 and 2 to the UKCRC Oxford Respiratory Trials Unit, Oxford Centre for

If Yes, for patients who are on CPAP:

Are they using the CPAP?Yes ☐ No ☐ **Date stopped:** DD/MON/201Y

Average usage (please ask patient to read from S9): _____ hours

(press *info* button, rotate *dial* one click to right. If necessary, change time period by depressing *dial* and rotating right until display reads '1 month')

Is the patient prepared to continue using CPAP? Yes ☐ No ☐

If No, reason for stopping CPAP:

Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE.Please file the bottom copy of Section 2 in the Non Blinded Researcher CRF folder

12 Month Follow-up Visit

Date of Visit: D D / M O N / 2 0 1 Y	Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

SECTION 1: This part of the interview must be completed by a researcher who does not know which treatment the patient has been randomised to.

1. Twelve month blood tests:

Fasted? Yes ☐ No ☐ (If patient not fasted, can bloods be rearranged?)

	Sample Taken
Biochemistry tube(s): U & E, Creatinine, LFT, Cholesterol, HDL/LDL, Triglycerides, TSH, Glucose	Yes ☐ No ☐
EDTA tube: FBC	Yes ☐ No ☐
EDTA tube: HbA1c	Yes ☐ No ☐

2a. In the last month, what time (please use 24 hour clock) does the patient normally:

Go to bed (enter the range) ☐☐:☐☐ to ☐☐:☐☐

(If bedtime is always the same, enter the same time in both boxes)

Get up in the morning (enter the range) ☐☐:☐☐ to ☐☐:☐☐

(If getting up time is always the same, enter the same time in both boxes)

Does the patient usually sleep on their own? Yes ☐ No ☐

(ie no other person sleeping in the same bed or the same room)

2b. Does the patient have a daytime nap? Yes ☐ No ☐

If Yes, please enter the estimated number of naps in the last week ☐

Please enter the average duration of each nap _____minutes

3a. Nocturia symptoms

How many times do you usually get up to pass urine in the night? _____times

(Please try to determine a single value which occurs on **most** nights e.g. 2 times. If not possible, enter a range typical of **most** nights e.g. 2-3 times)

In the last month, have you fallen when getting up in the night? Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened?_____times

Have you have leaked urine (been incontinent of urine) while you were sleeping in the past month?

Yes ☐ No ☐

If the answer is 'Yes', how many times has this happened? _____ times

3b. Home Accident History

In the last month, has the patient had any accidents at home, such as a fall? Yes ☐ No ☐

If 'Yes', answer the following questions:

	Yes	No
Required any form of treatment e.g. at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

4. Has the patient driven in the past 3 months? Yes ☐ No ☐

If Yes, please ask them to complete the 12 month Driving questionnaire and seal in envelope

12 Month Driving questionnaire completed? Yes ☐ No ☐ Not applicable ☐

5. Does the patient currently smoke? Yes ☐ No ☐

6. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes, what form did it take? (please tick relevant boxes)

	Yes	No
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls)		
Attend a gym (class, aerobics, Pilates etc)		

	Yes	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

7. New Vascular Events Questionnaire

Please go through the following vascular questionnaire asking if the patient has been **<u>newly diagnosed</u>** with, or had any of the following **since the 3 month visit.**

1. Angina?	Yes ☐ No ☐
2. Hypertension?	Yes ☐ No ☐
3. Myocardial infarction/heart attack?	Yes ☐ No ☐
4. Diabetes Mellitus/sugar diabetes? If 'no' go to q 8 <u>Treatment</u>	Yes ☐ No ☐
5. Diet	Yes ☐ No ☐
6. Tablets	Yes ☐ No ☐
7. Insulin	Yes ☐ No ☐
8. Intermittent claudication/artery narrowing to the legs?	Yes ☐ No ☐
9. Atrial fibrillation/irregular heart beat? If 'no' go to q 14 <u>Treatment</u>	Yes ☐ No ☐
10. None	Yes ☐ No ☐
11. Tablets	Yes ☐ No ☐
12. Cardioversion	Yes ☐ No ☐
13. Pacemaker	Yes ☐ No ☐
14. Cardiac failure/heart failure?	Yes ☐ No ☐
15. Transient ischaemic attack/mini-stroke?	Yes ☐ No ☐
16. Full stroke?	Yes ☐ No ☐
17. Angioplasty/heart artery dilation?	Yes ☐ No ☐
18. Coronary stent/heart artery stent?	Yes ☐ No ☐
19. Coronary artery bypass surgery/heart bypass?	Yes ☐ No ☐
20. Endarterectomy/arterial surgery to artery to brain?	Yes ☐ No ☐
21. Peripheral vascular intervention/leg artery bypass or stent or amputation?	Yes ☐ No ☐
22. Aortic aneurysm/swelling of the main artery in your chest or abdomen?	Yes ☐ No ☐

8. Please take 3 Blood Pressures with the patient seated

Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting Heart rate (bpm)	

9. Anthropometry

Weight (kg)	☐☐☐.☐
Neck circumference (cms)	☐☐.☐

Waist circumference (cms)	☐☐☐.☐	Hip circumference (cms)	☐☐☐.☐

10. Timed 'UP AND GO TEST'
(to the nearest whole second)

seconds

Tick box if participant physically unable to complete this test ☐

11. Has the patient completed the Cognitive Function Tests?

Reaction Time Test	Yes	☐	No	☐
Mini Mental State Exam	Yes	☐	No	☐
Trail making B	Yes	☐	No	☐
Digit Symbol Substitution	Yes	☐	No	☐

12. OSLER Test results

Test	Start Time (24 hour clock)	Test Duration (mins)
1		
2		

- **Please ensure the patient has been provided with the 12 month sleep diary and questionnaires A to C (pages 6 -11) to be completed at a convenient time during the morning, before moving on to section 2**
- **Please provide pulse oximeter for one night home oximetry study (can be returned by post)**

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Trial No:					Pt's Initials:				DOB: D D / M O N / 1 9 Y Y

SECTION 2: To be completed by researcher aware of treatment allocated

Please check the 12 month sleep diary and questionnaires have been fully completed

13. Has the patient suffered any adverse events possibly attributable to the study, since the 6 month telephone call?

Yes ☐ No ☐

Symptoms	Duration (Number of days)	Resolved?
		Yes ☐ No ☐
		Yes ☐ No ☐

If an event satisfies the criteria for a Serious Adverse Event/Reaction, please complete the appropriate form

14. CPAP adherence/efficacy data:

CPAP Downloaded: ☐ Download not possible: ☐ Not on CPAP: ☐

For 12 month data, please use the interval from the date CPAP started to the 12 month visit date. For last 3 month data please enter data for 3 months preceding the 12 month visit date Please enter the dates used for each of these intervals.

	12 month data (from: D D / M O N / 2 0 Y Y To D D / M O N / 2 0 Y Y)	**Last 3 months data** (from: D D / M O N / 2 0 Y Y To: D D / M O N / 2 0 Y Y)
Total days	Days	Days
Days not used	Days	Days
Total Hours	Hours	Hours
Used days ≥ 4 hours	Days	Days
Used days < 4 hours	Days	Days
Mean daily usage	Hours	Hours
Median daily usage	Hours	Hours
Pressure 95th percentile	cmH2O	cmH2O
Leak 95th percentile	l/sec	l/sec
AHI	Events/hour	Events/hour

15. Has the patient stopped CPAP? Yes ☐ (date stopped: D D / M O N / 2 0 Y Y) No ☐

If Yes, reason for stopping CPAP: _____

16. Has additional time (either today or in the last 9 months) been spent with the patient, to deal with CPAP problems or compliance issues? Yes ☐ No ☐ Not on CPAP ☐

If Yes, please enter the total additional time over the past 9 months _____mins

(Please remember to check the contact sheet in the patient CRF file for details of additional time spent with the patient)

Final Disposition:

Patient returned to care of clinical team Yes ☐ No ☐

If on CPAP, does patient wish to continue CPAP? Yes ☐ No ☐

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Please send the top copy of this CRF with the 12 month sleep diary and questionnaires, to the Oxford Respiratory Trials Unit

12 Month Cognitive Function Test Results

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Date Cognitive Function Tests Completed: D D / M O N / 2 0 1 Y

Cognitive test	**Score**
Simple and four-choice reaction time	**Save to database**
Mini Mental State Score	Out of 30
Trail making B time	(seconds)
Digit Symbol Substitution test	(No. of correct answers in 90 seconds)

Please send the top copy of this CRF to:

UKCRC Oxford Respiratory Trials Unit,

Oxford Centre for Respiratory Medicine,

Churchill Hospital,

Old Road, Headington,

Oxford, OX3 7LE

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

12 Month Pulse Oximetry and Blood Test Results

Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Pulse Oximeter returned and oximetry downloaded: Yes ☐ No ☐

Date of oximetry: D D / M O N / 2 0 1 Y

Technically adequate? Yes ☐ No ☐

≥ 4% ODI	Dips per hour

Time SpO_2 <90%	mins	%

12 Month visit blood Test Results

	Value	Units
Haemoglobin		
MCV		
WBC		
Platelets		
Sodium		
Potassium		
Urea		
Creatinine		
Glucose		
HBA1C		

	Value	Units
Total Cholesterol		
HDL Cholesterol		
LDL Cholesterol		
Triglycerides		
Total Protein		
Albumin		
ALT		
GGT		
Bilirubin		

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

Please send top copy of this CRF to: UKCRC Oxford Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE.

Driving Questionnaire

Recruiting Centre:		Trial No:					Patient's Initials:				Date of Birth: D D / M O N / 1 9 Y Y

Please tick box to indicate visit Enrolment ☐ 3 month ☐ 12 month ☐	Date of visit: D D / M O N / 2 0 1 Y

All answers to this questionnaire will be treated confidentially

Please think about your driving over the last 3 months, when answering these questions

On average, how many hours do you spend driving in a week? _____hours

Have you nodded off whilst driving in the last 3 months? Yes ☐ No ☐

Have you pulled off the road because of sleepiness in the last 3 months? Yes ☐ No ☐

Please answer the following questions *(tick one box)*

	More than once per week	A few times each month	Less than once a month
How often do you drive short, local journeys (less than 1 hour)?			
How often do you drive long motorway journeys (more than 1 hour)?			

	Never	Rarely	Occasionally	Frequently	Always
How often do you feel sleepy on short journeys (less than 1 hour)?					
How often do you feel sleepy on long journeys (more than 1 hour)?					

Please tell us about any incidents you have experienced whilst driving a vehicle, during the last 3 months. Please fill in each box with the number of events:

	Number caused by sleepiness	Number unrelated to sleepiness
Near-miss accidents (e.g. veering out of lane, running a red traffic light or failing to give way at a junction)		
Collisions		

Please complete the following questions only if you were the driver of a vehicle involved in a collision in the last 3 months:

Were there any injuries to you? Yes ☐ No ☐

Was anyone else injured? Yes ☐ No ☐

If you were injured in the collision, please tell us how it affected you by ticking the appropriate boxes below:

	Yes	No
Required any form of treatment e.g. at a hospital, or from GP, nurse, physiotherapist etc.		
Required advice from a doctor, nurse, therapist, NHS direct or other health care professional		
Required a home visit from a doctor, nurse, therapist or other health care professional		
Required an emergency ambulance to be called for yourself		
Required a hospital visit		
Required a stay in hospital		
Resulted in broken bones		
Resulted in bruising		

Thank you for completing this questionnaire.

Please check all questions have been answered and seal it in the envelope provided.

Brain MRI: Central Record Form

Enrolment form

Enrolment Date: D D / M O N / 2 0 1 Y

1. Diagnostic sleep study Data - Date: D D / M O N / 2 0 1 Y

Type (please tick one)**:** Oximetry ☐ Respiratory Study ☐ NPSG ☐

≥ 4% ODI		Wake SpO_2 on room air	%	
Apnoea/hypopnoea index		Time SpO_2 <90%	mins	%
Sleep study data backed up	Yes ☐ Not possible ☐			

2. Fasted Baseline blood tests

	Sample Taken
Biochemistry tube(s): U & E, Creatinine, LFT, Cholesterol, HDL/LDL, Triglycerides, TSH, Glucose, Vit B12 and Folate	Yes ☐
EDTA tube: FBC	Yes ☐
EDTA tube: HbA1c	Yes ☐

3. Sleep Details

What time (please use 24 hour clock) does the patient normally:

Go to bed (enter the range) ☐☐ : ☐☐ to ☐☐ : ☐☐

Get up in the morning (enter the range) ☐☐ : ☐☐ to ☐☐ : ☐☐

Does the patient usually sleep on their own? Yes ☐ No ☐

Does the patient suffer from any of the following sleep related problems?

	Yes	No	Unknown
Snoring			
Nocturnal Choking Episodes			
Witnessed Apnoeas			

Brain MRI Study

Randomisation Form

Trial No:	A	M	C	M	0	2	3	5	P	0	0	

Patients Initials:				Date of Birth: D D / M O N / 2 0 1 Y

Inclusion Criteria	
Age ≥ 65 years	Yes ○ No ☹
A clinical diagnosis of OSA: ≥ 4% Oxygen desaturation index > 7.5 events/hour	Yes ○ No ☹
Exclusion Criteria	
Arterial oxygen saturation <90% on room air	Yes ☹ No ○
FEV_1 <65% predicted	Yes ☹ No ○
Substantial problems with sleepiness during driving (in those who are still driving)	Yes ☹ No ○
Current Heavy Goods Vehicle or Public Service Vehicle driver.	Yes ☹ No ○
Shift work	Yes ☹ No ○
Any very severe complication of OSAHS (such as hypercapnia) such that CPAP therapy is mandatory	Yes ☹ No ○
Contraindication to undergoing an MRI scan	Yes ☹ No ○
Previous or current psychiatric disorders (including alcohol or drug abuse)	Yes ☹ No ○
Psychotropic medications (including all sedating medications, anxiolytics, major tranquilizers, antipsychotics, hypnotics, anticonvulsants)	Yes ☹ No ○
Neurological disorders	Yes ☹ No ○
Previous head injury resulting in loss of consciousness or notable cognitive deficit	Yes ☹ No ○
Inability to give informed consent or comply with the protocol	Yes ☹ No ○

Does the patient agree to take part in the study?	Yes ○ No ☹
Is the patient eligible to take part in the study?	Yes ○ No ☹

Has the participant signed the consent form? Yes ○ No ☹

Patient randomised to (please tick): CPAP with Best supported Care ☐ Best supportive Care ☐

Researcher's Name:	Signature:	Date: D D / M O N / 2 0 1 Y

4. Medical History

1.
2.
3.
4.
5.

5. Medication

Name of medicine	Each Dose	Units	Frequency (times/day)
1.			
2.			
3.			
4.			
5.			

6. Smoking History

Have you ever smoked? Yes ☐ No ☐

Do you smoke now? Yes ☐ No ☐

7. Caffeinated and alcoholic drinks

How many cups of the following, do you drink **each day?**	Number:
Tea	
Coffee	
Caffeinated drinks (coca cola, lucozade etc)	

How many of the following beverages do you drink **each week?**	Number:
Beer (pints)	
Wine (glasses)	
Spirits (measure)	
Sherry/port (glasses)	

8. Exercise

	5 to 7 times a week	2 to 4 times a week	Once per week	1 to 3 times in the past month	None
In the past month, how often have you taken any exercise lasting more than 10 minutes?					

Of exercise which lasted over 10 minutes, what form did it take?

	Yes	No
Walking		
Running/Jogging		
Cycling		
Sport (e.g. Tennis, golf, bowls etc.)		
Attend a gym (aerobics, Pilates, yoga etc.)		

	Yes	No
Dancing		
Swimming		
Horse riding		
Gardening		
Other (please specify)		

9. Please ask the patient which ethic group describes how they see themselves. This is a mixture of culture, religion, skin colour, language and origins. It is not the same as nationality. This information will be treated in the strictest confidence and will not be passed on to other parties.

A White		**D** Black Other		**G** Bangladeshi	
B Black Caribbean		**E** Indian		**H** Chinese	
C Black African		**F** Pakistani		**J** Other	

10. Please go through the following vascular questionnaire

Have you been diagnosed with, or had, any of the following?

1. Angina?	Yes ☐ No ☐
2. Hypertension?	Yes ☐ No ☐
3. Myocardial infarction/heart attack?	Yes ☐ No ☐
4. Diabetes Mellitus/sugar diabetes? If 'no' go to q 8 <u>Treatment</u>	Yes ☐ No ☐
5. Diet	Yes ☐ No ☐
6. Tablets	Yes ☐ No ☐
7. Insulin	Yes ☐ No ☐
8. Intermittent claudication/artery narrowing to the legs?	Yes ☐ No ☐
9. Atrial fibrillation/irregular heart beat? If 'no' go to q 14 <u>Treatment</u>	Yes ☐ No ☐
10. None	Yes ☐ No ☐
11. Tablets	Yes ☐ No ☐
12. Cardioversion	Yes ☐ No ☐
13. Pacemaker	Yes ☐ No ☐
14. Cardiac failure/heart failure?	Yes ☐ No ☐
15. Transient ischaemic attack/mini-stroke?	Yes ☐ No ☐
16. Full stroke?	Yes ☐ No ☐
17. Angioplasty/heart artery dilation?	Yes ☐ No ☐
18. Coronary stent/heart artery stent?	Yes ☐ No ☐
19. Coronary artery bypass surgery/heart bypass?	Yes ☐ No ☐
20. Endarterectomy/arterial surgery to artery to brain?	Yes ☐ No ☐
21. Peripheral vascular intervention/leg artery bypass or stent or amputation?	Yes ☐ No ☐

11. Completed years of education ☐☐

12. Blood pressure

Systolic: (mmHg)		Diastolic:(mmHg)		Resting heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting heart rate (bpm)	
Systolic: (mmHg)		Diastolic:(mmHg)		Resting heart rate (bpm)	

13. Anthropometry

Gender	Male: ☐	Female: ☐	
Height (cms)	☐☐☐ . ☐	Weight (kg)	☐☐☐ . ☐
Neck circumference (cms)	☐☐ . ☐		
Waist circumference (cms)	☐☐☐ . ☐	Hip circumference (cms)	☐☐☐ . ☐

16. Spirometry Yes ☐ Not done ☐

Date recorded: D D / M O N / 2 0 1 Y

Lung Volume	Measured Value	Predicted Value	% Predicted Value
FEV_1 (litres)			
FVC (litres)			
FEV_1/ FVC (%)			

17 OSLER Test Results

Test	Start Time (24 hour clock)	Sleep Latency (mins)
1		
2		

Researcher's Name:	Signature:	Date:D D / M O N / 2 0 1 Y

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

Questionnaires and monthly diary

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

1. Health Care Usage Questions

In the past month, have you contacted a health care service? Yes ☐ No ☐

(Please do not include contacts for repeat prescriptions)

If yes, please tell us how **many times** during the past **month** you have:

	Number of times
Visited a GP?	☐
Been seen at home by a GP?	☐
Visited a nurse?	☐
Been seen at home by a nurse?	☐
Contacted general practice for telephone advice?	☐
Contacted NHS Direct for telephone advice?	☐
Had an ambulance called for yourself?	☐
Visited an Accident and Emergency department?	☐
Attended an out-patient clinic?	☐

Hospital Admissions

In the past month, have you had to stay in hospital overnight? Yes ☐ No ☐

If Yes:

How many overnight hospital admissions have you had this month? ☐

How many times were you were admitted as an emergency? ☐

Please enter the total number of nights spent in hospital this month ☐

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

2. Has your medication / inhalers changed since you last completed this diary ?	Yes ☐ No ☐

If yes, please list any changes below:

New Medication or medications with a change to the dose

	Strength of each dose	Number of times taken each day
1.....	.....	.....
2.....	.....	.....
3.....	.....	.....
4.....	.....	.....

Medication Stopped

1..... .....

2..... .....

3..... .....

4..... .....

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

3a. Over the last month, about how many cups of the following did you drink **each day?**

	Number:
Tea	
Coffee	
Caffeinated drinks (coca cola, lucozade etc)	

3b. Over the last month, about how many of the following did you drink **each week?**

	Number:
Beer (pints)	
Wine (glasses)	
Spirits (measure)	
Sherry/port (glasses)	

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

Please complete the following 3 questionnaires;

this should take you about 10 minutes

1. Epworth Sleepiness Scale

Thinking back over the last month:

How likely are you to doze off or fall asleep in the situations described in the box below, in contrast to feeling just tired?

This refers to your usual way of life in the last month.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

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

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

2. Townsends Disability Index

Please tell us if you are able to:

(Even if you haven't done some of these things recently try to work out how they would affect you)

Please tick one box on each line

	Yes, with no difficulty	*Yes, with some difficulty*	*No, need help*
Cut your own toe-nails?			
Wash all over or bathe?			
Get on a bus?			
Go up and down stairs?			
Do the heavy housework?			
Shop and carry heavy bags?			
Prepare and cook a hot meal?			
Reach an overhead shelf?			
Tie a good knot in a piece of string?			

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

3. EQ-5D Questionnaire

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

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

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

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

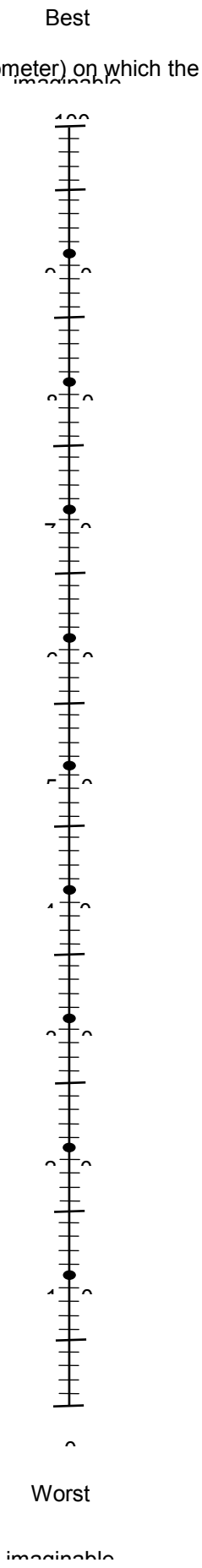
Trial Number: _____

Please add this number BEFORE the diary is given to the patient

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

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

Your own health state today



Trial Number: _____

Please add this number BEFORE the diary is given to the patient

Please answer this last questionnaire only if you have been asked to use CPAP:

We would like to know if you are experiencing any problems using CPAP. Please tick a box for each of the following problems to let us know how severe these problems are for you.

	Not a Problem	**Problem present, but not affecting CPAP use**	**Problem present, limiting CPAP use**	**Problem present, stopping CPAP use**
Nasal stuffiness / nose bleeds				
Dry throat				
Wake up with mask off				
Red or sore eyes				
Difficulty in falling asleep				
Frequent wakenings from sleep				
Stomach bloating or 'wind'				
Chest wheeze				
Difficulty in breathing out with mask				
Sore or rubbing mask				
Leaking of air from mask				

Trial Number: _____

Please add this number BEFORE the diary is given to the patient

Unpleasantly cold airstream				
Unpleasant appearance of CPAP				
Still snoring				
I find the CPAP machine too noisy				
My partner finds the machine too noisy				
Inconvenience is not worth bother				
Other (please specify any other problem and its severity)				

Thank you for answering these questions.

Please now answer questionnaires A to C on the following page

A) HOSPITAL ANXIETY AND DEPRESSION SCALE

This questionnaire is designed to let the doctor know how you feel. Read each item and place a tick in the box opposite the reply that comes closest to **how you have been feeling <u>in the past week.</u>** Do not take too long over your replies: your immediate reaction to each item will probably be more accurate.

I feel tense or wound up:		**I feel as if I am slowed down:**	
Most of the time	☐	Nearly all the time	☐
A lot of the time	☐	Very often	☐
Time to time, occasionally	☐	Sometimes	☐
Not at all	☐	Not at all	☐
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like "butterflies" in the stomach:**	
Definitely as much	☐	Not at all	☐
Not quite so much	☐	Occasionally	☐
Only a little	☐	Quite often	☐
Hardly at all	☐	Very often	☐
I get a sort of frightened feeling as if something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly	☐	Definitely	☐
Yes, but not too badly	☐	I don't take so much care as I should	☐
A little, but it doesn't worry me	☐	I may not take quite as much care	☐
Not at all	☐	I take just as much care as ever	☐
I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could	☐	Very much indeed	☐
Not quite so much now	☐	Quite a lot	☐
Definitely not so much now	☐	Not very much	☐
Not at all	☐	Not at all	☐
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time	☐	As much as I ever did	☐
A lot of the time	☐	Rather less than I used to	☐
From time to time bur not too often	☐	Definitely less than I used to	☐
Only occasionally	☐	Hardly at all	☐

I feel cheerful:		**I get sudden feelings of panic:**	
Not at all	☐	Very often indeed	☐
Not often	☐	Quite often	☐
Sometimes	☐	Not very often	☐
Most of the time	☐	Not at all	☐
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV programme:**	
Definitely	☐	Often	☐
Usually	☐	Sometimes	☐
Not often	☐	Not often	☐
Not at all	☐	Very seldom	☐

B) SHORT SAQLI

Instructions for completing this questionnaire: Please circle the number corresponding to your answer.

SECTION I

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

OVER THE PAST 4 WEEKS:

	not at all	a little	small to moderate amount	moderate amount	moderate to large amount	Large amount	Very large amount
How much have you had to push yourself to remain alert during a typical day (e.g. work, school, childcare, housework)?	7	6	5	4	3	2	1
How often have you had to use all your energy to accomplish your most important activity (e.g. work, school, childcare, housework)?	7	6	5	4	3	2	1
How much difficulty have you had finding the energy to do other activities (e.g. exercise, relaxing activities)?	7	6	5	4	3	2	1
How much difficulty have you had fighting to stay awake?	7	6	5	4	3	2	1
How much of a problem has it been to be told that your snoring is irritating?	7	6	5	4	3	2	1
How much of a problem have frequent conflicts or arguments been?	7	6	5	4	3	2	1
How often have you looked for excuses for being tired?	7	6	5	4	3	2	1

How often have you not wanted to do things with your family and/or friends?	7	6	5	4	3	2	1
How often have you felt depressed, down, or hopeless?	7	6	5	4	3	2	1
How often have you been impatient?	7	6	5	4	3	2	1
How much of a problem has it been to cope with everyday issues?	7	6	5	4	3	2	1
How much of a problem have you had with decreased energy?	7	6	5	4	3	2	1
How much of a problem have you had with fatigue?	7	6	5	4	3	2	1
How much of a problem have you had waking up feeling unrefreshed?	7	6	5	4	3	2	1

SECTION II – Patients on CPAP only.

(If you have **not** been using treatment for sleep apnoea in the past 4 weeks **DO NOT** complete this section)

We would like you to list up to **three side effects** which you have found most troubling as a result of **this treatment** – please write them in the spaces below. For each side effect please rate how much of a problem it has been for you in the **past 4 weeks**. Some side effects that people may experience include: nasal stuffiness, dry nose or throat, sore eyes, headache, sore throat, jaw pain, waking up frequently, stomach upset, increased saliva

15. Side effect 1: _____ How much of a problem have you had with this?

no problem	a small problem	a small to moderate problem	a moderate problem	a moderate to large problem	a large problem	a very large problem
7	6	5	4	3	2	1

16. Side effect 2: _____ How much of a problem have you had with this?

no problem	a small problem	a small to moderate problem	a moderate problem	a moderate to large problem	a large problem	a very large problem
7	6	5	4	3	2	1

17. Side effect 3: _____ How much of a problem have you had with this?

no problem	a small problem	a small to moderate problem	a moderate problem	a moderate to large problem	a large problem	a very large problem
7	6	5	4	3	2	1

18. Considering these **side effects** please choose the statement that best describes the trade off between side effects and benefits. Overall, compared with the benefits, would you say that the problems with side effects you listed in the questions 15-17 were (choose one):

no problem compared to the benefits	a small problem compared to the benefits	a small to moderate problem compared to the benefits	a moderate problem compared to the benefits	a moderate to large problem compared to the benefits	a large problem compared to the benefits	a very large problem compared to the benefits
0.25	0.50	0.75	1.00	1.00	1.00	1.00

C) The Short Form 36 Health Survey Questionnaire (SF-36)

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any questions, please give the best answer you can and make any of your own comments if you like. Do not spend too much time in answering as your immediate response is likely to be the most accurate:

1. <u>In general,</u> would you say your health is: (tick one box)

Excellent	
Very Good	
Good	
Fair	
Poor	

2. <u>Compared to one year ago,</u> how would you rate your health in general <u>now?</u> (tick one box)

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

3. Health and daily activities:

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

	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
b) Moderate activities, such as moving a table, pushing a vacuum, bowling or playing golf			
c) Lifting or carrying groceries			
d) Climbing several flights of stairs			
e) Climbing one flight of stairs			
f) Bending, kneeling or stooping			
g) Walking more than a mile			
h) Walking half a mile			
i) Walking 100 yard			
j) Bathing and dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Please answer yes or no)

	Yes	No
a) Cut down on the amount of time you spent on work or other activities	☐	☐
b) Accomplished less than you would like	☐	☐
c) Were limited in the kind of work or other activities	☐	☐
d) Had difficulty performing the work or other activities (e.g. it took more effort)	☐	☐

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Please answer yes or no)

	Yes	No
a) Cut down on the amount of time you spent on work or other activities	☐	☐
b) Accomplished less than you would like	☐	☐
c) Didn't do work or other activities as carefully as usual	☐	☐

6. During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? (Please tick one box)

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

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

None	☐
Very mild	☐
Mild	☐
Moderate	☐
Severe	☐
Very Severe	☐

8. During the <u>past 4 weeks</u> how much did pain interfere with your normal work (including work both outside the home and housework)? (Please tick one box)

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

9. These questions are about how you feel and how things have been with you <u>during the past month</u>. (For each question, please indicate the one answer that comes closest to the way you have been feeling). (Please tick one box on each line).

How much time during <u>the last month</u>:	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
b) Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c) Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f) Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐	☐
h) Have you been a happy person?	☐	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐	☐
j) Has your health limited your social activities (like visiting friends or close relatives)?	☐	☐	☐	☐	☐	☐

10. Please choose the answer that best describes how true or false each of the following statements is for you. (Please tick one box on each line).

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a) I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

This is the end of the questions.
Thank you for completing these questionnaires

Standard Operating Procedures

SOP - Epworth Sleepiness Scale (ESS)
Reference: PREDICT SOP/ESS/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 18/5/2010

Equipment

Epworth Sleepiness Scale in CRF, Also available online.

www.patient.co.uk/doctor/Epworth-Sleepiness-Scale.htm

www.britishsnoring.co.uk/sleep_apnoea/epworth_sleepiness_scale.php

Instructions to administer questionnaire

- This is a self administered questionnaire with 8 questions. It is essential that the words used in the ESS are not changed and the instructions to the respondents are used in a standardized way. The complete instruction can be found at the following website http://epworthsleepinessscale.com/about-epworth-sleepiness.

- Prior to the administering the questionnaire it is permissible for the researcher to check that the patient can see, read and understand the questions. Once this has been done the researcher should ask the patient to answer the questionnaire.
- Tell the patient that they will need to specify how likely they are to doze off or fall asleep in the situations described (rather than just feeling tired) - referring to their usual way of life in recent times. If they haven't done some of these things recently, ask them to try and work out how it would have affected them - so all questions have an answer; it is important that they answer each question as best they can.

- The researcher can answer enquires from the patient and help explain the questions but should not influence the patient's response.

- At the end of the questionnaire the researcher should check that all the questions have been answered, and that the answers can be scored e.g. no ticks instead of numbers.

- Please note that in the one week CRF the instructions refer to how the patient has felt 'in the last week' and not in "recent times". In addition, all the ESS questionnaires in the sleep diaries refer to how the patient has felt "in the last month".

Instructions how to score ESS

- The ESS is the sum of the 8 item score, if one score is missing the ESS is invalid.
- Scores are recorded as a number form 0-3 written in a single box for each question.
- If the patient cannot decide on whole number e.g. 1 ½ these scores should be added up including halves. If the total score is e.g. 6½ it should be rounded up to the next whole score.

IMPORTANT INFORMATION ABOUT THE USE OF SCORES

- For the patient to fulfill the inclusion criteria they must have an ESS of ≥ 9 at time of diagnosis. This score is to be recorded on the enrolment form (question 1b - the Enrolment form has now been changed to include the ESS at clinical diagnosis).
- If the ESS score completed during the enrolment visit is different or lower than that obtained during the clinical diagnosis the patients can still be enrolled and randomised. Note that the enrolment ESS score is only used for the minimization criteria and should be recorded on the randomisation form.
- It is permissible for the recruiting center to check if a patient fulfils the inclusion criteria by checking the ESS and then documenting this in the notes. This may be required if, for example, the referral letter is inaccurate or does not contain an ESS, or if there are several different ESS in the notes.

SOP: Reaction Time Task
Reference: PREDICT SOP/ESS/version 1.0
Author: DR Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 18/5/2010

Equipment

Laptop with Reaction Time software

Procedure

Sit the participant at a table with the laptop in front of them.

Tell the patient that you are going to measure how quickly they can react. The test is in two parts.

Start the programme enter the subject trial number in the space provided

1) Simple Reaction Time (SRT)

Click “Run SRT practice”. Confirm “Test Start” in the following dialogue box.

Explain to the patient

- First of all you will have a practice session.
- A cross will appear in the box on the screen 8 times and each time it appears you should press any button as quickly as you can. Don’t hold the key down, but press and release it when the cross appears. Use the index finger of your preferred hand to press the key throughout the test.
- When you are ready press any key to start.

At the end of the practice a message will read “Test Completed Thank You”. Wait a few moments for the screen to disappear.

Check the participant understands what to do.

As before Click “Run SRT Test”. Confirm “Test Start” in the following dialogue box.

Explain to the patient

- Now a cross will appear another 20 times again you should press any key as quickly as you can, as in the practice. When you are ready, press any key to start.
- At the end of the test a message will read “Test Completed Thank You.”. Wait a few moments for the screen to disappear.

You can abort the experiment at any time by hitting the “Escape” key on the Keyboard.

2) Four Choice Reaction Time (CRT)

Explain to the patient

- In this test there will be four boxes on the screen. A cross will appear in one of them and you have to press the correct key for that box as quickly as you can.

Click “Run CRT practice”. Confirm “Test Start” in the following dialogue box.

Explain to the patient

- When the cross appears in the box on the far left press the “z” key (point to each), when it appears in the box one from the left press the “x” key (point to each); when the cross appears in the box on the far right press the “full stop” key (point to each) and when it appears in the box one from the right press the “comma” key (point to each).
- Place the middle and index fingers of your left hand over the “z” and “x” keys like this (indicate which keys) and the index and middle fingers of your right hand over the “comma” and “full stop” keys like this (indicate which keys).
- As before you will have a practice of 8 crosses first. Remember, a cross can appear in any of the four boxes. When you are ready, press any key to start.

At the end of the practice a message will read “Test Completed Thank You” Wait a few moments for the screen to disappear.

Check the patient understands what to do. As before now run the test

Click “Run CRT Test”. Confirm “Test Start” in the following dialogue box.

At the end the results will be stored automatically

SOP: Digit symbol substitution test
Reference: PREDICT SOP/DSST/version 1.0
Author: Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 18/5/2010

Equipment

Digit symbol sheet provided

Pencil

Stop watch

Preparation

Have the participant sitting comfortably at a table or stable surface.

Instruction to Patient

This is a coding exercise with a key to the code at the top of the piece of paper (point). Each symbol corresponds to a single digit number. Write each code under each number, practice up to the thick line (if you observe the participant doing all the 2s first, for example, say – very clever but you must do them in the sequence they appear on the page to standardize results).

Well done – so now I want you to fill out as many boxes as you can in 90 seconds.

This test is designed to be unfinishable, if you get to the third line you are doing exceptionally well.

Instructor

Start test and ask the patient to stop at 90 seconds

Scoring

The number they get correct in 90 seconds is the total score. Record on the CRF

SOP: Mini mental state examination
Reference: PREDICT SOP/MMSE /version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 4/2/2010

Equipment

Mini-Mental State Examination (MMSE) questionnaire

Procedure

Follow the question sheet

Question number

1) Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?").
2) Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?"
   One point for each correct answer (0-10)
3) Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials record the number of trials. If the patient does not eventually learn all three, recall cannot be meaningfully tested.

   After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."
4) Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). One point for each correct answer (0-5)

   If the patient cannot perform the subtraction task, ask the patient to spell the word "world" backwards. One point for each letters in correct order (e.g., dlrow=5, dlorw=3).
5) Ask the patient if he or she can recall the three words you previously asked him or her to remember. One point for each correct answer (0-3)
6) Show the 2 simple objects i.e. a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct answer (0-2).
7) Ask the patient to repeat the phrase after you ("No ifs, ands, or buts."). Allow only one trial. One point for correct repetition
8) Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." One point for each part of the command correctly executed.
9) Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of

memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.

10) Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
11) Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

SOP: Trail making tests
Reference: PREDICT SOP/TMT /version 1.0
Author: Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

Pencil

Trail making sheet provided

Stop watch

Procedure

This is a dot to dot connecting circles distributed over a sheet of paper.

The circles include both numbers (1-13) and letters (A – L)

The participant should draw lines to connect the circles in an ascending pattern alternating between the numbers and letters (i.e. 1-A-2-B-3-C, etc.)

Demonstrate the test to the participant using the sample sheet

Instruction to participant

- Join up the consecutive numbers and letters as quickly as possible, without lifting the pen or pencil from the paper.

(If the patient makes an error, point it out immediately and allow the patient to correct it.)

Scoring

Time in seconds to complete task (rounding up or down to whole second)

Stop the test if not completed after 5minutes

SOP: Waist and hip circumference
Reference: PREDICT SOP/TMT /version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment
Tape measure

Procedure

1) **Waist circumference**

Ask the patient to stand with their feet together.
Find the top of the hip bone and the bottom of the ribs.
Breathe out naturally.
Place the tape measure midway between these points and wrap it around the waist

2) **Hip circumference**

Ask the patient to stand as above, with their arms at their side with palms of their hands facing inwards, breath out gently.
Position the measuring tape around the maximum circumference of the buttocks. For women this is usually at groin level. For men it is normally about 2 - 4 inches below the navel.

SOP: Blood pressure measurement
Reference: PREDICT SOP/BP/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

Omron M7 COMPACT Automatic Blood pressure Monitor and Cuff

Four AAA size batteries

Procedure

Measurements should be taking in a quiet place and should be in a relaxed seated position.

The patient should avoid eating, drinking alcohol, smoking or exercising for at least 30mins before taking a measurement.

Do not move or talk during the measurement.

Make sure the patient is in correct position, sitting on a chair with straight back and feet flat on the floor. Remove tight fitting clothes from the upper arm, do not place the cuff over thick clothing and do not roll up the sleeve if it is too tight.

Place the arm on a table so that the cuff will be at the same level as the heart.

Use the same arm on each occasion.

Apply the cuff to the upper arm the blue arrow should be centered on the inside of the inner arm and point down (copy picture on cuff) the air tubing should run down the inside of the forearm and is in line with the middle finger. The bottom of the cuff should be 1-2cm above the elbow.

Secure the cuff using the fabric fastener.

Press the start button to record. When the measurement is complete the monitor displays the BP and Pulse and automatically deflates the cuff.

Wait 2-3mins before taking another reading

Measure 3 times and record on CRF

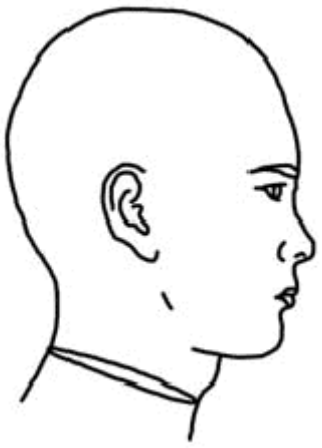
Reference

El Feghali RN, Topouchian JA, Pannier BM, El Assaad HA & Asmar RG. Validation of the Omron M7 (HEM0780-E) blood pressure measuring device in a population requiring large cuff use according to the International Protocol of the European Society of Hypertension. Blood Pressure Monitoring 2007, 12: 173-178.

SOP: Neck measurement
Reference: PREDICT SOP/neck/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment
Tape measure

Procedure
Stand patient upright with shoulders relaxed.
Measured in the midway of the neck, between midcervical spine and midanterior neck.
In men with a laryngeal prominence (Adam's apple), measured just below the prominence.



SOP: Oxford sleep resistance test (OSLSER)
Reference: PREDICT SOP/OSLER/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

Osler box**,** Handset**,** Cable, Power adaptor

Software which can be installed on laptop but the test can be run independently

Procedure

Make sure the patient is sitting comfortably, upright on a bed in a dimly lit quiet room.

The head can be supported to prevent the neck jerking if the patient drops off to sleep.

The study should be run twice in the morning for 40 minutes with approximately 2 hours between tests, preferably around 9.30 and 11.30am.

Set up Equipment

1) Connect the cable between the Osler and Handset
2) Switch on the hand unit first
3) Then switch on the Osler display unit symbol **Ø**

It should say Cable Mode DC

Press **X** to enter and exit the Check Mode

Instruction to Patient

- This is a test to measure you reaction time to a flashing light on the box by pressing a sensor on this hand box. The light will flash frequently and you should respond to each flash.

Show the patient how to hold the hand unit. Resting their index finger of their dominant hand over the button, then to briefly lift their finger off the button and replace it. Their arm and handset can rest on a pillow beside them on the bed.

Running the Osler Test

1) Press **>** Display reads - Osler 2 Run Mode
2) Press **>** again to enter Run Mode. Screen displays 30s delay to run, Opening file, Test in progress

3) Set the display unit approximately 1-2m in front of the patient and give them the hand unit.
4) When 7 consecutive illuminations are missed it is assumed that the patient has fallen asleep and the terminates.
5) The time in minutes and seconds appear on screen at the end of the test record on the CRF.

SOP: Oximetry
Reference: PREDICT SOP/neck/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

Oxygen Saturation Monitor Konica Minolta Pulsox-300i plus instruction manual
Finger clip probe Pulsox SR-5C
Laptop with DS -5 Data analysis Software
USB Adapter UA-300 main unit
UA cable
USB cable

Procedure

Check the battery is in correctly
Connect the finger probe
When the Pulsox is turned on, it runs a short self- test.
Check battery levels – 3 bars
About 10 second after the power is switched ON, measurements will be started and will record data at 1 second intervals.

Instruction to patient

Give the patients the prepared information sheet to take home

- To turn on press the light blue button and hold until the backlight is on.
- Attach the device to the wrist.
- To stop press the light blue button and hold until the backlight turns off

Patients can return the oximeters in person or via the prepaid envelopes provided

SOP: Storing and sending electronic information
Reference: PREDICT SOP/info/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

PREDICT laptop

Portable Hard drive (recommended)

CDs or network to NHS local drive

Procedure required for:-

Reaction time tests- baseline, 3 and 12 months

Embletta sleep study - baseline

Oximetry overnight studies – 3 and 12 months

Optional for Osler test

Procedure

All data should be stored with the Trial number as an Identifier.

Data from the tests should be automatically stored on the C drive of the PREDICT Laptop

A backup copy should be kept, either burn to the CD provided, save on portable hard drive or network to a NHS local drive.

For the Respiratory Polygrapy studies

1) Label CD-RW with PREDICT and Site name as an Identifier (or use CDs provided)
2) Copy one study at a time
3) Always save the data with the Trial number as an Identifier
4) Send one study at a time to (use envelopes and address labels provided)

Mrs. Marjorie Vennelle

Senior Research Manager

Department of Sleep Medicine,

Royal Infirmary Edinburgh

51 Little France Crescent,

Edinburgh EH16 4SA

5) Email m.vennelle@ed.ac.uk when study posted
6) You will receive a confirmatory email when the study has arrived
7) The CD will be cleared and returned to each site once study scored
8) The results will be sent via email to the centre and to the ORTU

SOP: Townsend disability scale (TDS)
Reference: PREDICT SOP/TDS/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment

Questionnaire provided in Central record form and monthly diary.

Instructions to patient

- *Ask "Are you able to…?" if "yes" ask "Do you have difficulty"*

Probing may be necessary to establish whether the patient would be able to undertake the activity in the absence of another person

Scoring

The first column "Yes, with no difficulty" scores zero for each answer.

The second column "Yes, with some difficulty" score one point for each answer.

The third column "No need help" scores 2 points for each answer.

Add up the score for each column and record the total score on the CRF

SOP: Timed up and go (TUG)
Reference: PREDICT SOP/TUG/version 1.0
Author: Dr Alison McMillan
Approved by: Dr Mary Morrell
Version : 1.0
Date: 23/01/2010

Equipment:

Chair with arms – the same one each time

Tape measure

Stop watch

Preparation

Place a piece of tape or other marker on the floor 3 meters away from the chair so it is easily seen.

The participant should wear their regular footwear and may use any gait aid that they normally use, but may not be assisted by another person.

They may stop and rest but not sit down.

There is no upper time limit.

The subject should be given a practice trial that is not timed.

Start the test with the subject sitting correctly in the chair. (Back should be resting on the back of the chair. The chair should be stable and positioned such that it will not move when the subject moves from sitting to standing).

Instruction to patient

- On the word *GO* you will stand up, walk to the marker on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace.

Scoring

Start timing on the word "*GO*" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.

Record the total time in seconds to complete test (round up or down to whole second) on the CRF

Appendix 3:

Ethical approvals

Royal Brompton & Harefield NHS
NHS Foundation Trust

Dr Mary Morrell
Reader in Respiratory Physiology
Clinical and Academic Unit of Sleep and Breathing
Royal Brompton Hospital
Sydney Street
London SW3 6NP

16 July 2009

Dear Dr Morrell,

A randomised controlled trial of continuous positive airway pressure treatment in older people with obstructive sleep apnoea/hypopnoea syndrome (PREDICT)

Project Reference: 2009LF006B

Thank you for registering your Research Project with the R&D office. The project details have been entered on our Research Management Database. Please ensure you keep the R&D office informed of the following:

- changes to the status of the project e.g. abandoned, completed etc
- changes to the funding arrangements
- changes to the original application e.g. change in personnel or amendments requiring ethical review

RESEARCH GOVERNANCE
Royal Brompton & Harefield NHS Trust manages all research in accordance with the requirements of the research governance framework. Whilst working as an employee of the Royal Brompton and Harefield NHS Trust, or holding an Honorary Contract to do research which involves NHS staff or patients, their organs tissue or data, you must comply with all reporting requirements, systems, and duties of action put in place by the Trust to deliver research governance. As such if you are acting as either Chief/Principal Investigator your responsibilities under this framework include:

- ensuring compliance with protocol and advising of any changes to the protocol
- reporting any adverse events whether related to research or not to clinical governance/ethics/R&D
- taking appropriate urgent safety measures
- ensuring adherence to the principles of ICH GCP
- ensuring researchers have necessary expertise
- ensuring compliance with the Data Protection Act
- ensure adequate monitoring arrangements are in place
- ensure compliance with the Human Tissue Act

The Trust routinely audits a minimum of 10% of its research activity. This is to ensure that research is progressing satisfactorily and to guard against research fraud. You are requested to maintain and retain appropriate records of your research, and assist the Trust as and when required should any such audit take place in your area.

CLINICAL TRIALS REGISTRATION
The majority of research journals will now only publish research that has been registered at a publicly accessible database before the enrolment of the first patient. Where research projects are sponsored by either the Trust or Imperial College it is recommended that the project is registered at www.ClinicalTrials.gov which is free of charge. For Trust sponsored projects please contact 020 7351 8736 and an account will be set-up for you to register your project. Similarly, please contact clinicalresearchoffice@imperial.ac.uk for an account to register Imperial College sponsored projects.

In receiving this letter you are agreeing to abide by the terms as outlined above. Please accept this letter as the Trust's authorisation to commence your research.

Yours sincerely

Wendy Hutchin
Head of Research & Development

NRES Committee London - Fulham
Charing Cross Hospital
Room 4W/12, 4th Floor
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Telephone: 02033117283

06 April 2011

Prof Mary Morrell
Reader Respiratory Physiology
Imperial College London
Sleep and Ventilation
Fulham Wing
Royal Brompton Hospital, London
SW36NP

Dear Prof Morrell

Study title:	**Brain morphology and cognitive function in older people with obstructive sleep apnoea after continuous positive airway pressure treatment.**
REC reference:	**10/H0711/101**

Thank you for your letter of 16 February 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

Appendix 4:

Memberships of committees and PREDICT Investigators

Trial steering committee - Prof Walter McNicholas (Chair), Prof Sir Neil Douglas and Dr Ian Smith (independent members) Daniel Bratton, Prof Robert Davies, Dr Mark Elliot, Mr Frank Govan, Dr Melissa Hack, Magda Laskawiec-Szkonter, Dr Alison McMillan, Prof Mary Morrell, Prof Andrew Nunn, Dr Justin Pepperell, Dr Renata Riha, Prof Mark Sculpher, Prof Anita Simonds, Prof John Stradling, Dr John Starr.

Independent data monitoring committee - Chair Prof. Tim Peto, Prof. John Gibson, and Prof. David Wright.

Trial management - Magda Laskawiec-Szkonter (ORTU)

Data entry - Jack Quaddy and Assunta Sabia (ORTU), Luxumi Sridharan and Lydia Paniccia (RBH)

PREDICT Investigators by centre

Birmingham (Heartlands Hospital): Dr Dev Banerjee, Kerryanne James, Sarah Manney and Matthew Nicholls.

Blackpool (Victoria Hospital): Dr Mohammed Paracha, Jules Chadwick, Kate O'Reilly, Judith Saba and Gemma Swarbrick.

Edinburgh (Royal Infirmary Edinburgh): Dr Renata Riha, Lizzie Hill, Donna Fairley and Marjorie Vennelle.

Leeds (St James' University Hospital): Dr Mark Elliott, Craig Armstrong, Clair Favager and Sue Watts.

Liverpool (Aintree Hospital): Dr John O'Reilly, Stephen Emegbo and Pam Parry.

London (Royal Brompton Hospital): Prof. Mary J Morrell, Prof. Anita Simonds, Dr Martin Glasser, Lydia Paniccia, Luxumi Sridharan, Dr Alison McMillan and Dr Neil Ward.

Newcastle (Freeman Hospital): Dr Sophie West, Peter Close, Lyndsay Rostron and Therese Small.

Newport (St Woolos Hospital): Dr Melissa Hack, Clare Acreman, Sarah Mitchell and Jeanette Richards

Oxford (Churchill Hospital): Prof John Stradling, Isabel Chabata, Nicky Crosthwaite, Tara Harris, Debby Nicoll and Barbara Winter.

Reading (Royal Berkshire Hospital): Dr Chris Davies and Jacqui Webb.

Stoke on Trent (City General Hospital): 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): Dr Justin Pepperell, Dawn Redwood and Tania Wainwright.

Wolverhampton (New Cross Hospital): Dr Lee Dowson, Jillian Andrew, Lucy Reynolds and Louise Spragg.