NIHR HTA Programme

16 November 2012

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639

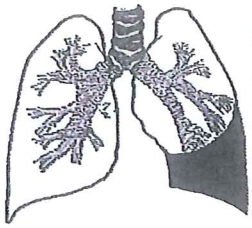
email: hta@hta.ac.uk
web: www.hta.ac.uk

NHS Lothian

THE UNIVERSITY OF EDINBURGH

Imperial College London

Royal Brompton & Harefield NHS Biomedical Research Unit NHS Trust



Oxford Respirator Trials Unit

PREDICT

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

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

ISRCTN number:	ISRCTN90464927
HTA Application Number:	08/56/02
Rec Reference Number:	09/H0708/33
Protocol:	Version 7.0
Date:	04/04/2012

Authorised by:

Name: Prof Mary Morrell

Signature:

M J Morrell

Role: Chief Investigator

Date: 04/04/2012

Name: Dr Renata Riha

Signature:

Role: Chief Investigator

Date: 04/04/2012

CHE Centre For Health Economics

MRC Clinical Trials Unit

UKCRN UK Clinical Research Network

General Information

This document describes the PREDICT trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Clinical problems relating to this study should be referred to the relevant local Principle Investigators, who can be contacted at the Academic Unit of Sleep and Breathing, Royal Brompton Hospital, Sydney Street, London SW3 6NP, Tel: 0207 352 8121 ext 4023, m.morrell@imperial.ac.uk, or Department of Sleep Medicine, Royal Infirmary Edinburgh, 51 Little France Crescent, Little France, Scotland EH16 4SA, Tel: 0131 242 3882, rriha1@staffmail.ed.ac.uk. Enquiries can also be directed to the Oxford Respiratory Trials Unit on 01865 225205.

Compliance

The trial will be conducted in compliance with the Protocol, Research Governance Framework, Data Protection Act and other guidelines as appropriate.

Main Contacts

Prof MJ Morrell (Chief Investigator)
Professor of Sleep and Respiratory Physiology
National Heat and Lung Institute, Imperial College London
Academic Unit of Sleep and Breathing
Royal Brompton Hospital
Sydney Street
London SW3 6NP
Tel: 0207 352 8121 ext 4023
Email: m.morrell@imperial.ac.uk

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

Research Fellow (Clinical Coordinator): Dr Alison McMillan (PI)
National Heat and Lung Institute, Imperial College London
Clinical and Academic Unit of Sleep and Breathing, Royal Brompton Hospital
Sydney Street
London SW3 6NP
Tel: 02073528121 ext 4182
Email: a.mcmillan@imperial.ac.uk

Trial Team

Clinical Trials Unit (Trial's Advisor): Professor RJO Davies (until Nov 2010)
Reader and Consultant in Respiratory Medicine
UKCRC Oxford Respiratory Trials Unit
Oxford Centre for Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford, OX3 7LE
Tel: 01865 225205
Fax: 01865 857109
E-mail: rtu@orh.nhs.uk

Clinical Trials Administration: Magda Laskawiec-Szkonter & Emma Hedley
UKCRC Oxford Respiratory Trials Unit
Oxford Centre for Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford, OX3 7LE
Tel: 01865 225205
Fax: 01865 857109
E-mail: rtu@orh.nhs.uk

Trial statistician

Senior Statistician: Professor Andrew Nunn, Head Other Diseases Group
MRC Clinical Trials Unit
Aviation House, 125 Kingsway
London, WC2B 6NH
Tel: 0207 6704710
Fax:02076704815

Sponsor

Imperial College is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance Manager:

Gary Roper
Clinical Research Governance Office
G02 Sir Alexander Fleming Building
Imperial College
Exhibition Road
London SW7 2AZ

Tel: 020 7594 1188
E-mail: gary.roper@imperial.ac.uk

RANDOMISATIONS

(Mon - Fri, 09:00 - 17:00) **MRC Tel: 0207 670 4711 / MRC Fax: 0207 670 4814**
Oxford Tel: 01865 225205 / Oxford Fax: 01865 857109

Contents **Page**

List of Tables

List of Figures

Abbreviations

AE	Adverse Events
AF	Atrial fibrillation
AHI	Apnoea/Hypopnoea Index
BMU	Biomedical Research Unit
BP	Blood pressure
BSC	Best Supportive Care
CPAP	Continuous positive airways pressure
CRF	Case Report Form
EQ-5D	EuroQol
ERC	Endpoint/Adverse Event Review Committee
ESS	Epworth Sleepiness Score
FEV_1	Forced expiratory volume in one second
GBP	Pound Sterling
GCP	Good Clinical Practice
HADS	Hospital anxiety and depression scale
HGV	Heavy Goods Vehicle
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
MOSAIC	Multi-Centre Obstructive Sleep Apnoea Interventional Cardiovascular Trial
MRC CTU	Medical Research Council Clinical Trial Unit
NHS	National Health Service
NICE	National Institute of Clinical Excellence
ORTU	Oxford Respiratory Trials Unit
OSAHS	Obstructive sleep apnoea hypopnoea syndrome
OSLER	Oxford Sleep Resistance Test
p.a.	per annum
PREDICT	Positive Airway Pressure in Older People: A Randomised Controlled Trial
PSV	Public Service Vehicle
QALY	Quality adjusted life years
REC	Research Ethics Committee
SAQLI	Sleep Apnoea Quality of Life Index
SAR	Serious Adverse Reaction
SUSARs	Suspected Unexpected Serious Adverse Reactions
SF-36	Short Form-36
SF-6	Short Form-6
SIGN	Scottish Intercollegiate Guidelines Network
TDS	Townsend Disability Scale
TIA	Transient ischemic attack
TMG	Trial Management Group
TNF-α	Tumour necrosis factor alpha
TSC	Trial Steering Committee
TVCLRN	Thames Valley Comprehensive Local Research Network
UK	United Kingdom
WTE	Whole time equivalent

1. SUMMARY

1.1 Lay summary

Obstructive sleep apnoea hypopnoea syndrome (OSAHS) is the name given to breathing difficulties during sleep as a result of repetitive closure of the throat. This causes difficulties in breathing that lead to sleep disruption, sometimes severe daytime sleepiness, high blood pressure and a possible increased risk of heart attacks, stroke and memory problems. OSAHS is the third most common respiratory disorder, after asthma and chronic obstructive pulmonary disease. In its severe form it affects 2 - 4% of middle-aged people. In older people, the prevalence is almost 10 times greater, with up to 20% of older people having OSAHS.

OSAHS can be treated with continuous positive airway pressure (CPAP), which helps breathing and stops the throat closing during sleep. A recent report by The National Institute for Clinical Excellence concluded that CPAP is an extremely cost-effective treatment for OSAHS in middle-aged people. Unfortunately, the beneficial effects of CPAP cannot be presumed to be replicable in older people because the causes and consequences of the disease change with age. Older patients with sleep apnoea seem to feel less sleepy, and receive less benefit from its treatment than the middle aged. They also have many other causes for sleepiness. This makes the interpretation of possible OSAHS symptoms more difficult in older patients. Very little information is available for doctors and health care professionals regarding the best way to treat OSAHS in older people. Even less information is available on how any treatment impacts on quality of life and economic measures in this age group.

This study will measure the effect of treating OSAHS with CPAP and a Best Supportive Care Package on sleepiness in a group of patients over 65 years of age. Particular attention will be paid to the use of health care facilities, and how much the patients use the CPAP machine, ('treatment compliance'). This information will be used to determine the cost effectiveness of CPAP treatment in older people. We will also measure the impact of CPAP on other factors; these will be the patient's quality of life and activities of daily living such as mobility and the number of times they use the bathroom during the night. Additionally, other health-related factors such as heart function, mood and memory will be assessed. This information will be compared to that collected in another group of older patients in whom OSAHS will be treated with a Best Supportive Care Package only (control). Before patients agree to take part in the study it will be explained to them that they may be allocated to receive either CPAP with Best Supportive Care or Best Supportive Care only; this 'randomisation' is the best way to test the effectiveness of a treatment. Each group will be monitored for 12 months. Comparison of the data from the two groups will show whether CPAP improves the health of older people with OSAHS.

The UK population is ageing, thereby increasing the burden of disease. One of the best ways to reduce the costs to the community of this disease burden is to maintain the independence of older people. Treating OSAHS appropriately in older people is a potentially important way of reducing the dependency of ageing, which will in turn benefit both individual patients and lessen the economic burden of disease within the UK.

1.2 Abstract and summary of trial design

The recent NICE Technology Appraisal of the use of continuous positive airway pressure (CPAP) in obstructive sleep apnoea hypopnoea syndrome (OSAHS) concluded that CPAP was effective and cost efficient treatment for OSAHS in middle-aged people [2]. However it identified evidence gaps with a need for trials in other patient groups. One such group is older people.

Establishing the efficacy of treatment for all common diseases in older populations is a priority for health care planners and the Research Councils. The UK population is ageing, thereby increasing the individual and societal burden of disease. By 2030 the older population will increase from 16% to 23% and, by 2040 requirements for long-term care will have increased by 60% at an additional cost of approximately £4 billion p.a. One of the best ways to reduce these costs is to maintain the independence of older people.

OSAHS affects approximately 20% of older people, compared to 2-4% of middle-aged people. Its symptoms are similar to (and could be confused with) some of the functional impairments of ageing. Both OSAHS and ageing reduce independent functioning and cognitive function, as well as increasing cardiovascular morbidity. Reversing the OSAHS component of these impairments is therefore a potentially important therapeutic target that may reduce the dependency of ageing; producing benefits at both an individual and societal level.

Systematic literature searches reveal only one small trial of CPAP for OSAHS in older people. These patients were not typical older people as they also had dementia. In middle-aged moderate to severe OSAHS patients, CPAP therapy produces large therapeutic improvements, which are highly cost effective at $\leq$ £4000 per QALY gained; allowing for changes in sleepiness, quality of life, vascular risk, driving performance and CPAP costs. Unfortunately, these therapeutic and economic benefits cannot be presumed to be replicated in older people without appropriate data. Specifically, the disease phenotype and aetiology vary, patient compliance with CPAP is reduced, and patients experience different daytime functional consequences (e.g. daytime sleepiness) for a given level of OSAHS. This population also has many other causes of excessive daytime sleepiness to obscure the interpretation of possible daytime OSAHS symptoms. This requires randomised data to identify what proportion of these symptoms are truly responsive to treatment for OSAHS.

This project will provide evidence regarding CPAP efficacy for OSAHS in older people, thereby addressing the paucity of data described by NICE. We propose a randomised, parallel, single-blinded, trial comparing CPAP with Best Supportive Care (control) in older patients ($\geq$ 65 yrs) with OSAHS (disease severity defined as: > 7.5 obstructive apnoeas/hour and symptoms of daytime sleepiness). Since this is a device trial it is not possible to blind the patients; however, the investigator collecting the data will be blinded to which arm the patient has been randomised to. The co-primary endpoints will be the major therapeutic outcome of a change in sleepiness, plus the cost efficiency of CPAP therapy calculated through the impact of CPAP on health-related quality of life and health service utilisation. The key health economic outcome will be the cost per QALY gained over a patient's lifetime using CPAP compared with best supportive care. A lifetime cost will be estimated by combining data from the trial with other sources in a decision model to extrapolate beyond the timeframe of the trial. The team who led the recent NICE/HTA Technology Appraisal of CPAP for OSAHS at the Centre for Health Economics in York will carry out the economic analysis. Since CPAP is the treatment of choice for OSAHS, the results of this trial will directly inform clinical practice and health care planning at both national and international levels.

The primary endpoints will be:

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

Secondary endpoints will be a change from baseline, in the following parameters measured at 3 and 12 months, with the exception of the ESS:

1. **Subjective sleepiness:** The mean of the ESS scores measured at months 10, 11 & 12 will be used to answer the question ‘does CPAP work at 12 months?
2. **Objective sleepiness:** OSLER maintenance of wakefulness test
3. **Self reported health status (quality of life and mood):** Short Form 36 questionnaire (SF-36), and Sleep Apnoea Quality of Life Index (SAQLI; a disease specific sleep apnoea questionnaire which includes CPAP side effects), Hospital Anxiety & Depression Scale (HADS)
4. **Functional index of activities of daily living:** Townsend Disability Scale (TDS)
5. **Frequency of nocturia:** reported at the study visits

6. **Mobility:** Timed to up and go test
7. **Accidents:** Including self-reported road accidents, domestic and work accidents
8. **Cognitive function:** Mini-mental state, Trail making B time, the Digit Symbol Substitution test, simple and four-choice reaction time.
9. **Cardiovascular riskfactors:** Systolic and diastolic blood pressures, fasting glucose, fasting lipids, HbA1c.
10. **Adverse cardiovascular events:** Myocardial infarction, stroke, transient ischemic attack, new angina, new atrial fibrillation, new peripheral vascular disease

Tertiary endpoint will be:

1. **Treatment compliance:** Measured objectively by 'runtime' clocks built into the machines and downloaded at 3 and 12 month clinic visits.

Adverse events will also be closely monitored.

1.2.1 Type of design

A randomised, parallel, single-blinded (the investigator is blinded to the treatment arm the patient has been randomised to), comparison trial of CPAP therapy with Best Supportive Care in older patients (≥ 65 years) with OSAHS (>7.5 oxygen desaturation events/hour and symptoms of daytime sleepiness). The trial will define whether CPAP plus Best Supportive Care is superior to Best Supportive Care alone in improving sleepiness and is cost efficient. It will also describe compliance in this population. The trial will be delivered in two stages. *Stage 1* will establish feasibility. Transition from *Stage 1* to *Stage 2*, will occur when target recruitment rates have been established (see Section 3). The trial will generate the first substantial and detailed randomised data set (in any population) directly describing the health economic consequences of CPAP therapy in OSAHS.

1.2.2 Disease / patients studied

Patients will be identified from sleep and respiratory clinics in the recruiting centres (see Section 4.3). Screening criteria are based on normal clinical practice and consecutive eligible patients will be offered trial entry. The diagnosis of OSAHS will be based on sleep studies performed in the recruiting centres that are staffed and run by physicians appropriately trained in respiratory sleep medicine. The Principal Investigator from each centre or a nominated member of staff will approach participants who fulfil the criteria for inclusion in the trial. Screening logs will be kept.

1.2.3 Trial treatments: intervention / control

Patients will be randomly assigned (1:1) to CPAP therapy with Best Supportive Care; or Best Supportive Care alone. Patients assigned to CPAP will then be established on auto-adjusting CPAP (AutoSet™®, ResMed (UK) Ltd) delivered either by nasal or full-face masks using the standard clinical systems in the recruiting centres.

Allocation to the trial treatments will be through the MRC Clinical Trials Unit (CTU) randomisation service.

Allocation is by minimisation with a random component; the minimisation factors are:

- Subjective daytime sleepiness (Epworth Sleepiness Scale > 13 v ≤ 13)
- Functionality (Townsend Disability Scale > 1 v ≤ 1)
- Recruitment centre

Minimisation by recruitment centre will ensure that inter-centre differences in patient characteristics, methods for instituting CPAP therapy do not produce imbalances between the trial groups.

1.2.4 Outcome measures

Primary endpoints

1. Subjective Daytime Sleepiness assessed using the Epworth Sleepiness Scale

The primary outcome is the change from baseline in the mean of the Epworth Sleepiness Scale (ESS) scores measured at the end of months 3 and 4, answering the question 'does CPAP work at 3 months?' The ESS is a robust index widely used in both clinical practice and clinical trials. A change of 1 point on the ESS is the smallest detectable shift in the score (which is a categorical scale with one point increments) and is the minimum clinically significant change since it is indicative of one symptom state shift on one domain of the score. This trial is powered to detect a mean change of this magnitude.

2. Health Economic Analysis

The trial will collect information on health related quality of life using the SF-36 questionnaire at baseline, 3 and 12 months and measurements of EQ-5D measured at baseline, and monthly throughout the trial. The primary outcome for the cost-effectiveness analysis, the cost per QALY gained, will be based on utility scores calculated using the UK general population tariffs for the EQ-5D. A sensitivity analysis will be conducted using utility scores calculated using the UK general population tariff for the SF-6D, which is formed from a subset of questions included in the SF-36.

The trial will also collect information on health care resource utilisation. The average utilisation patterns for each resource item will be compared between groups. The unit costs of inpatient visits, outpatient visits, attendances at accident and emergency departments and general practitioner consultations will be based on published cost data relevant to the NHS [3]. The cost of a diagnostic sleep study will be determined, incorporating nurse and/or specialist time and any equipment and facilities used. The unit costs of the CPAP (including masks and sundries) will be based on published price lists relevant to the UK. The unit costs of medication will be obtained from published pricing lists [4].

A decision model will be used to extrapolate the trial results in order to calculate QALYs and health care costs over a lifetime horizon. In addition to reducing daytime sleepiness, CPAP may also improve cardiovascular risk factors such as blood pressure, thus reducing the risk of patients experiencing cardiovascular events. OSAHS has been linked to an increased risk of road traffic accidents, and the benefits of CPAP may extend to reducing the risk of road traffic accidents as a consequence of the reduction in daytime sleepiness. In secondary analyses the decision model will be expanded to incorporate cardiovascular events and road traffic accidents. Utility values for these other events considered in the decision analytic model will be derived from published studies. The costs of cardiovascular events and road traffic accidents will be derived from the published literature. The increase in health care utilisation costs associated with patients who have experienced a non-fatal cardiovascular event will also be derived from the published literature. Costs will be expressed in current year GBP. The Health Service Cost Index will be used to adjust costs to the current price year where necessary [3]. A discount rate of 3.5% per annum will be applied to both costs and QALYs in line with NICE guidance [5].

The strategies of CPAP versus no CPAP therapy will be evaluated using standard cost-effectiveness analysis. If one strategy is not found to be dominant (i.e. less costly and more effective) in comparison to the other, then an incremental cost-effectiveness ratio (ICER) will be determined. The ICER compares the cost per additional unit of outcome gained by selecting a more costly and more effective intervention. This can be compared to a cost-effectiveness threshold that describes the maximum amount that the health care payer would pay for an additional unit of health outcome. Stochastic analysis will be conducted using cost-effectiveness acceptability curves to describe the uncertainty around cost-effectiveness based on mean costs and outcomes. That is, the uncertainty in the inputs to the decision model, including the results of the trial in terms of health related quality of life and costs, will be fully characterised and propagated through to the model results. The estimated decision uncertainty will be expressed in terms of the probability that CPAP is cost-effective for a given cost-effectiveness threshold.

Secondary endpoints will be a change from baseline, in the following parameters measured at 3 and 12 months, with the exception of the ESS:

1. **Subjective sleepiness:** The mean of the ESS scores measured at months 10, 11 & 12 will be used to answer the question 'does CPAP work at 12 months?
2. **Objective sleepiness:** OSLER maintenance of wakefulness test
3. **Self reported health status - quality of life and mood:** Short Form 36 questionnaire (SF-36), and Sleep Apnoea Quality of Life Index (SAQLI; a disease specific sleep apnoea questionnaire inc. CPAP side effects), Hospital Anxiety & Depression Scale (HADS)
4. **Functional index of activities of daily living:** Townsend Disability Scale (TDS)
5. **Frequency of nocturia:** reported at the study visits
6. **Mobility:** Timed up and go test
7. **Accidents:** Including self-reported road, domestic and work accidents
8. **Cognitive function:** Mini-mental state, Trail making B time, the Digit Symbol Substitution test, simple and four-choice reaction time.
9. **Cardiovascular risk factors:** Systolic and diastolic blood pressures, fasting glucose, fasting lipids, HbA1c. .
10. **Adverse cardiovascular events:** Myocardial infarction, stroke, transient ischemic attack, new angina, new atrial fibrillation, new peripheral vascular disease

Tertiary endpoint

2. **Treatment compliance:** Measured objectively by 'runtime' clocks built into the machines and downloaded at 3 and 12 month clinic visits.

1.2.5 Duration of follow-up

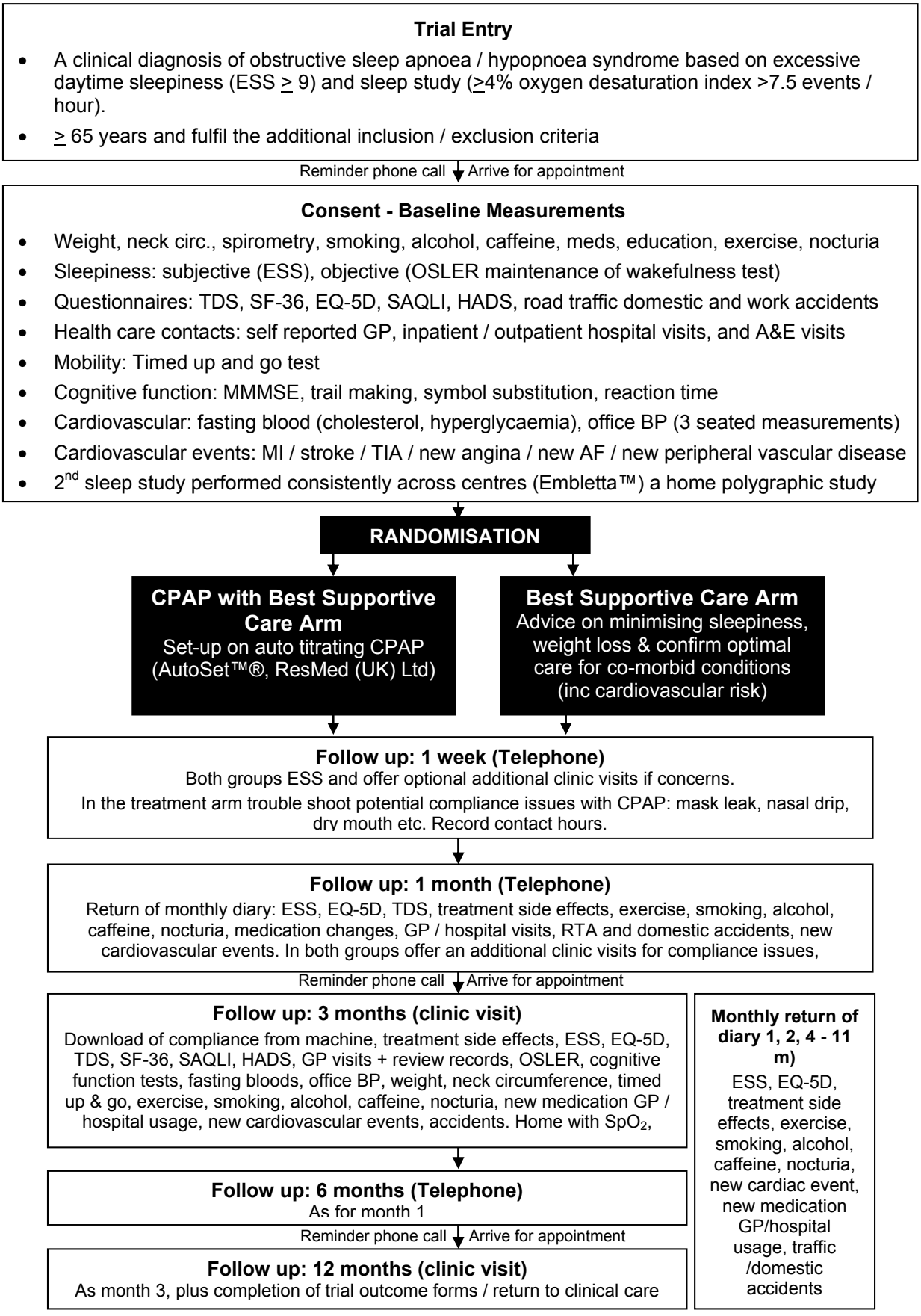
The study follow-up is 12 months from randomisation. Patients will be reviewed at 1 week, and at 1, 3, 6 and 12 months. Telephone follow-up will occur at 1 week (with an optional clinic visit for those experiencing difficulty with treatment compliance), 1 and 6 months. There will be further optional follow-ups for those experiencing difficulty with treatment compliance. Clinic follow-up will occur at 3 and 12 months. All trial follow-up phone calls and visits will be carried out by the investigator (or a research nurse). In addition, ESS and EQ-5D will be recorded monthly by the patient and mailed back to the Oxford Respiratory Trials Unit.

Treatment compliance will be a tertiary outcome in this trial. Compliance with CPAP in older patients with OSAHS may be reduced (see Section 2.1, and Figure 2). Although this factor may reduce the efficacy of CPAP in older people [6], it is also one of the reasons why the trial is required.

1.2.6 Data recorded directly on CRF

Data will be recorded on case report forms (CRF). The type of data to be recorded is detailed in Section 7 (Assessments and Procedures).

1.3 Flowchart: Figure 1



2. BACKGROUND

2.1 Introduction

Optimising health-care strategies in older people is a way of maintaining personal independence and quality of life, while minimising social care costs. The UK population is ageing and this is increasing the individual and societal burden of disease. By 2030 the proportion of people aged >64 years will increase from 16% to 23% [7], and by 2040 the requirement for long-term care will have increased by 60% at an additional cost of approximately £4 billion p.a. [8].

Obstructive Sleep Apnoea Hypopnoea Syndrome (OSAHS)

Treatment of OSAHS in older people may substantially improve health at an individual and thereby at a societal level. OSAHS occurs due to a sleep-related loss of pharyngeal dilator muscle tone; resulting in collapse of the pharyngeal airway, and cessation of breathing (apnoea) [9]. Each event causes hypoxia and is more often than that not terminated by a brief arousal from sleep, which in turn leads to excessive daytime sleepiness (due to sleep fragmentation) [10] and acute surges in blood pressure [11, 12].

The long-term consequences of severe OSAHS in middle-aged patients are considerable. Daytime sleepiness impairs social function, reduces employability and increases accident risk. Middle-aged OSAHS patients are 2 to 4 times more likely to have a road traffic accident as a result of reduced alertness while driving [13, 14]. These patients also have a very high cardiovascular risk [15-18]. Epidemiological studies show that OSAHS carries a 3-fold increased likelihood of developing hypertension over 4 years, independent of other risk factors [17], and randomised trial data shows that middle-aged patients with severe OSAHS experience a reduction in blood pressure sufficient to reduce vascular risk perhaps by as much as 20% following initiation of CPAP therapy [16, 19]. The 10-year predicted occurrence of stroke for OSAHS patients is 14%, and 23% for myocardial infarction [20].

Improvement in the symptoms of OSAHS in older people is likely to be beneficial, though the magnitude of such benefits cannot be simply inferred from younger populations. Reducing sleepiness may have added value in older people, as improved attentional capacity could offset age-related cognitive dysfunction. Alternatively, it may be less important in people who are retired from work, drive less frequently, and regard daytime naps as enjoyable. The prevalence of non-respiratory causes of sleepiness is also high in older people, with reduced sleep quality [21-23] and co-morbid disease responsible for sleep disturbance such Parkinson's disease, rheumatoid arthritis, diabetes and heart failure [24-27]. The use of medications also increases with age, which may confound sleep disturbances [28]. Thus, it is likely that substantial daytime sleepiness in the elderly is not due to OSAHS (and hence will not be OSAHS treatment responsive).

Vascular risk benefits may be larger in older people, since their event rate implies that more events could be prevented per unit change in risk. On the other hand the actual magnitude of risk reduction may be less in older people [29]. For example, CPAP does NOT reduce blood pressure in middle-aged OSAHS patients who are not sleepy [2, 30]; and older patients with OSAHS have less sleepiness than younger patients (see below) and so may not experience benefits in this outcome. They also have a reduced acute blood pressure response to each arousal from sleep [31]. This may be a protective response; alternatively it may suggest a survival bias [32]. If OSAHS is associated with increased mortality, then the older people with OSAHS will either be those who have survived, or those who have developed OSAHS later in life. Recent data suggest that acute repetitive transient hypoxic events associated with OSAHS may lead to the up-regulation of cellular and hormonal mechanisms that protect against major ischaemic events; so-called ischemic preconditioning. Thus, development of OSAHS in older people may be an adaptive response to possible future fatal or sub-fatal cardiac and cerebrovascular events [33]. If this is the case we may find that CPAP is not beneficial in this population.

The cost efficiency of CPAP therapy in older OSAHS patients is also probably different from the younger patients. Differential perceptions of health related quality of life will influence calculated utility scores, as will differential employment and driving. Changes in vascular risks (as outlined above and covered in more detail below) will also influence health economic model outcomes. Additionally, life

expectancy changes the results of a cost utility analysis for a lifetime horizon. Indeed there is some data to suggest that older people with OSAHS do not have an increased risk of mortality [34].

The complexity of these arguments requires that primary randomised data be generated in this age group in order to clarify the magnitudes of any treatment benefits in this population.

OSAHS is highly prevalent in older people

OSAHS presents a credible treatment target to improve the burden of disease in the elderly population. Moreover, the potential health-care costs are such that a secure evidence base is mandatory for resource planning. In middle-aged and younger populations OSAHS is the third most common respiratory disorder, after asthma and chronic obstructive pulmonary disease. In a working population of relatively young people (30 – 39 years) OSAHS defined as an AHI $\geq$ 15 events/hr and symptoms of daytime sleepiness, is present in 2% of women and 4% of men [35]. Its prevalence rises at least ten fold in older people, with estimates ranging between 13% and 32% [29, 36-40]. The sex distribution of OSAHS also changes with age. In younger people, OSAHS is a predominantly male disease (1:2) [39], whereas, in older people the proportion of females is increased. In a typical cohort, ageing resulted in the prevalence of sleep apnoea increasing from 4% to 32% in females and 22% to 42% in males [41]. The majority of randomised CPAP trial data has been collected in males only [15, 42, 43] and is not therefore transferable to women who have different health expectations and outcomes [44].

The economic implications of OSAHS treatment in older people

The recent NICE/HTA Technology Appraisal of CPAP for OSAHS [2] advocates treatment for all patients (including the elderly) with moderate or severe disease, though the need for specific evidence regarding efficacy in older people was identified. This report calculated that the health-care expenditure required to treat OSAHS warranted approximately £40 million of research spending to define the evidence base to guide CPAP therapy [2].

As preparatory work for this trial we have calculated the costs of treating older patients with OSAHS. Based on a conservative prevalence measure - 10% OSAHS in older people [45], and the costs of CPAP therapy derived in the NICE review [2], we estimate the costs of treating this age group would have been > £191m for the year 2006, and over £2 billion for treatment over the expected lifetime of the UK population aged > 65, (based on population figures for 2006). This would be largely new health care expenditure since over 95% of elderly care doctors do not currently investigate for OSAHS in older patients presenting with sleep complaints [46]. Thus the majority of older people with OSAHS are not currently treated. Indeed, a recently published survey of 13,507 US nursing home residents revealed virtually no sleep apnoea was diagnosed (0.5% [95% CI 0.4 to 0.6%]) [47].

The aetiology and phenotype of OSAHS in older people

The increased prevalence of OSAHS in older people is associated with complex changes in disease aetiology and phenotype. The reasons for this are not yet fully understood, but research to date suggests that OSAHS in older people is different to that in young/middle-aged populations [48, 49].

In middle-aged populations, obesity is the main predictor of the development of OSAHS [39, 50, 51] in addition to characteristic anatomical changes [52, 53]. In older populations different aetiological factors become important such that at any given level of obesity, the pharyngeal airway is more likely to collapse in older compared to younger OSAHS patients [54]. Physiological studies suggest this is likely to be due to an age-related decline in neuromuscular activity [55-57] and an increase in airway compliance [58]. Ageing also leads to structural changes in the upper airway that can predispose to collapse [59, 60], and an age-related preferential distribution of fat around the upper airway [55]. Ageing also produces disturbances in the stability of central regulatory breathing control [56]. This is likely to be due to destabilising sleep stage shifts [61] and a decreased arousal threshold [62] producing disruption of the respiratory phasic output to the upper airway and thoracic respiratory muscles [63]. Moreover, there is an increasing prevalence of cerebrovascular disease and heart failure in older people and both these disease predispose to sleep-related respiratory disturbances [27, 64]; specifically central sleep

apnoea, which is caused by a reduction or absence in efferent respiratory drive [65]. Taken together, these factors mean that the aetiology and therefore potentially the consequences of OSAHS in older patients are likely to differ from those in younger and middle-aged populations. Thus, it cannot be assumed that therapeutic benefits from OSAHS treatment seen in these populations are generalisable to older groups.

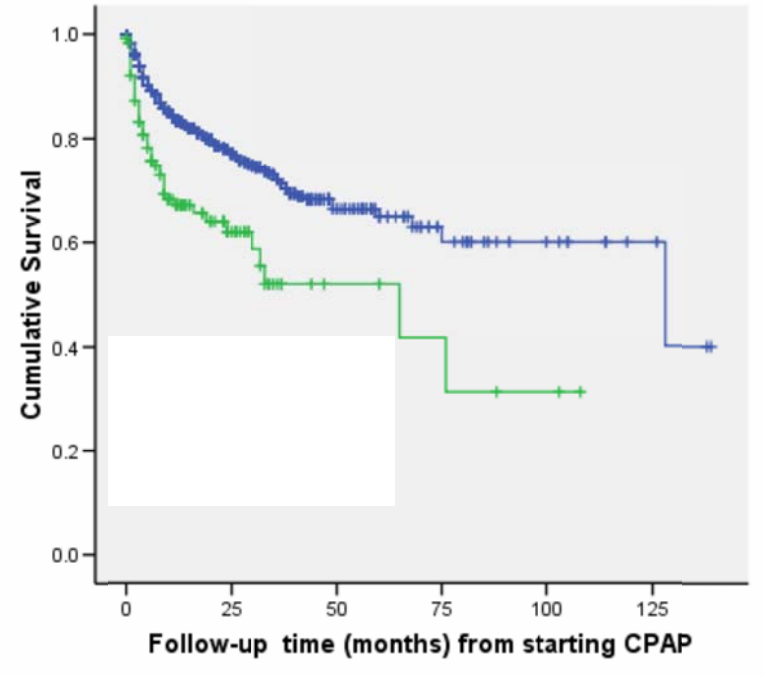
The symptoms of OSAHS in older people

The symptoms of OSAHS in older people are similar to (and could be confused with) some of the functional impairments of ageing. Both OSAHS and ageing led to poor sleep, sleepiness, fatigue, unintentional napping, impaired driving skills, cognitive dysfunction, nocturia, snoring and increased cardiovascular morbidity. These factors are discussed in more detail below.

Sleepiness in older people with OSAHS

Excessive daytime sleepiness appears to be less pronounced and less responsive to CPAP therapy in older people with OSAHS in most [66-69] but not all studies [70, 71]. These lower levels of sleepiness may reflect the differential aetiology of OSAHS in older people, or differences in patient perception of the symptomatic importance of daytime sleepiness; for example older people may have more time to nap, and thus be less aware of their sleepiness, or they may attribute their lack of sleepiness to a co-morbidity such as heart failure [72]. Another confounding effect may be the well documented age-related increase in sleep fragmentation [61] and reduction in total sleep time, leading to a reduction in sleep quality [73, 74].

As preparatory work for this trial, we have explored the severity of sleepiness and its treatment responsiveness in groups of older OSAHS patients started on CPAP in the Edinburgh and Oxford centres. In the Oxford centre 157 sequential older OSAHS patients were compared to 132 randomly selected middle-aged controls, matched for apnoea severity. The older patients reported symptomatically lower levels of sleepiness pre-treatment (Older patients: ESS 13 [sd 4.5] v middle-aged: 15 [sd 4.6], diff 1.9; 95% CI 0.9 to 3.1, p <0.02). The older patients also experienced smaller therapeutic responses to CPAP (older: ESS improvement 5.0 [sd 4.1] v middle-aged 7.1 [sd 4.3], diff 2.1; 95% CI 1.1 to 3.0, p<0.02). The older patients had lower treatment compliance, with 93/157 (59%) of older patients having a CPAP use time of > 0 hours, compared to 111/132 (84%) of middle-aged (p<0.01). These results are consistent with a reanalysis that we have carried out on previously published CPAP compliance data from the Edinburgh CPAP cohort (n=823) [1]. The reanalysis stratified the cohort at 65 years. The severity of OSAHS was greater in patients aged ≥65 years (older, apnoea/hypopnoea index (AHI): 48 [sd 55] events/hour) vs. younger patients (AHI: 40 [sd 33] evens/hour), but this was associated with milder sleepiness (older ESS: 11 [sd 5]; middle-aged: 12 [sd 5], mean difference 1.5, 95% CI 0.3 to 2.7, p=0.014). These findings corroborate the notion that for a given OSAHS severity older patients are less sleepy. Long-term follow-up data indicates a significant fall in treatment compliance over time in the older cohort (p<0.0001). A survival analysis of patients continuing to use CPAP therapy (i.e. compliance > 0 hour) is shown in Figure 2. Patients dying or lost to follow up were censored.



Health related quality of Life in older OSAHS patients

The literature regarding the quality of life consequences of OSAHS in older people is sparse, making it difficult to draw robust conclusions [75, 76]. In the middle-aged, OSAHS is associated with significant reductions in quality of life, with poor general health perceptions, vitality, physical and social functioning [77, 78]. CPAP therapy improves these symptoms in some, but not all randomised trials [79-81]. In older people with OSAHS there is only one randomised trial of CPAP therapy in patients with dementia and no measurements of quality of life were made [82] (see below).

In preparatory work for this trial we have found that older OSAHS patients report better quality of life scores than middle-aged patients closely matched for disease severity [83]. This may be because overall older people have poor general health perceptions and physical functioning, which can be confused with the symptoms of OSAHS. For example both ageing and OSAHS are associated with nocturia, yet CPAP therapy appears to reduce nocturia and improve quality of life [84]. The proposed trial will provide a large randomised data set to clarify this area, which is of fundamental importance for health economic analysis.

Cognitive dysfunction

Cognitive dysfunction is a major health problem of ageing [85], and treating OSAHS with CPAP improves many aspects of cognitive function in middle aged patients [86-90]. It is therefore an engaging hypothesis that treating OSAHS might moderate some of the cognitive impairments of ageing. Unfortunately there is currently little data to explore this hypothesis. Cognitive dysfunction does track the severity of OSAHS in older people [91-93], but given the strong association between ageing *per se* and cognitive impairment, and the high prevalence of depression in OSAHS patients [94] these data are insufficient. The only randomised trial of CPAP in older OSAHS patients focused on people who also had dementia [82]. There is one small non-randomised prospective study of CPAP therapy in 12 OSAHS patients > 55 years which used changes in cognitive function as an outcome variable [95]. The biggest responses were improved motor speed and executive function. A randomised controlled study is required to verify these findings.

Executive function is of importance in OSA patients, as driving related outcomes are a predictor of the increased likelihood of road traffic accidents [13, 14]. Reaction time is noted as an important driving related outcome measure in the SIGN guidelines (section 6.3; [96]) and a significant predictor of mortality in older adults [97]. CPAP therapy for OSAHS improves driving simulator function [14, 98] and

reaction time [99] in middle-aged patients, but again there is no data on older people. Given the societal importance of cognitive dysfunction in older people, exploration of the cognitive effects of CPAP therapy into this population is warranted.

Cardiovascular Risk in older OSAHS patients

In middle-aged populations, OSAHS is an independent risk factor for diurnal hypertension. Epidemiologically it has been implicated as a risk factor for stroke (OR 1.6) [100], and 'all cause' cardiovascular events (OR 2.87 – 3.17) [101]. In patients with severe OSAHS, randomised trial data shows clinically significant blood pressure reductions with CPAP therapy that are sufficient to reduce cardiovascular risk by approximately 20% [2, 16, 19]. To date, these effects have not been confirmed in patients who are not sleepy, even if they have substantial numbers of nocturnal apnoeic events [2, 30]. It is unclear whether the blood pressure lowering benefit of CPAP will be reproduced in the older age group since all but one of the randomised trials have been conducted in much younger patients. If CPAP is found to reduce blood pressure in non-sleepy patients, the high vascular event rate of old age would make this factor particularly important.

In Summary

A series of systematic reviews [96, 102-104] most recently and thoroughly by the NICE/HTA Technology Assessment [2] have reached consistent conclusions regarding OSAHS treatment. They have found that in middle-aged patients with moderate to severe disease (AHI ≥15 events/hour, and excessive daytime sleepiness; ESS > 9), CPAP therapy produces large and cost-efficient improvements in daytime sleepiness. Allowing for changes in sleepiness, quality of life, vascular risk, and road traffic accidents; and considering the costs of CPAP therapy, treatment is highly cost effective at <£4500 per QALY gained [2]. Even when the benefits are limited to the reduction in sleepiness and improvement in health related quality of life, the use of CPAP is cost-effective at <£10,000 per QALY. However, sensitivity analysis indicates that the cost per QALY gained with CPAP may fall in older patients (Table 6.26, p140 [2]). Unfortunately the trials that have informed these reviews are almost entirely performed in middle-aged patients.

As preparatory work for this trial we have reviewed the characteristics of the study groups in the three largest published trials contained in the Technology Assessment [15, 42, 105]. Only 5% of the OSAHS patients in these trials were aged >70 yrs, and they included only 5 (1.8%) female patients. The only CPAP trial specifically performed on older people is a small (underpowered) comparison of CPAP and sub-therapeutic (sham) CPAP in 39 patients with dementia [82].

Since the aetiology, clinical features, CPAP therapy responsiveness, and CPAP therapy compliance differ between older and younger patients, there is a need for high-quality randomised trial data, which is specifically applicable to this large and rapidly expanding age group. The proposed randomised trial will provide the specific evidence required to fill this deficit. The data produced will enable the role of CPAP therapy in older OSAHS patients to be defined.

2.1.1 Population

Inclusion criteria

1. Age ≥65 years
2. A clinical diagnosis of OSAHS: ≥ 4% Oxygen desaturation index > 7.5 events/hour and an Epworth sleepiness scale ≥ 9
3. Ability to give written informed consent

Exclusion criteria

1. Previous exposure to CPAP therapy
2. Arterial oxygen saturation <90% on room air
3. FEV_1 / FVC <60%
4. Substantial problems with sleepiness driving (in those who are still driving)
5. Currently using HGV or PSV driving licence (where applicable - annual application is required for drivers > 65 years)
6. Shift work
7. Any very severe complication of OSAHS such that CPAP therapy is mandatory
8. Inability to give informed consent or comply with the protocol e.g. the patient must be able to see to be able to participate in the wakefulness test

2.1.2 Investigational intervention

- Auto-adjusting CPAP combined with Best Supportive Care (see sections 6.1.2 and 6.2).
- Best Supportive Care only (see section 6.1.2)

2.2 Rationale and objectives

This trial will evaluate the efficacy of CPAP therapy combined with Best Supportive Care in older patients with OSAHS in improving daytime sleepiness. The cost-effectiveness analysis will provide an estimate of the cost per QALY gained by providing older patients with CPAP in comparison to Best Supportive Care only. The secondary outcomes will assess benefits on health related quality of life, vascular risk and cognitive function, mood and disability scores. Treatment compliance will be included as a tertiary outcome measure.

Relevant studies / trials

The background literature is reviewed above - Section 2: Introduction

3. SELECTION OF CENTRES / CLINICIANS

Recruitment will take place over 18 months of this 39-month study in at least six centres. All centers will have an active sleep service and be familiar with the delivery of a research protocol.

4. SELECTION OF PATIENTS

This trial will study patients with OSAHS and will be inclusive of all patients able to complete the protocol and not excluded by the specific exclusion criteria. This will ensure that the study result is generalisable to ordinary practice. It is recognised that this strategy will result in the inclusion of some patients with a proportion of central/mixed respiratory events, related partly to the presence of co-morbidity with cerebrovascular and cardiac disease. This is appropriate since these disorders are expected in the elderly population (and their presence is one of the reasons for a specific trial in this group). This is precisely why this trial is needed: to better define optimal treatment strategies. We will

capture changes in functional activities of daily living using a disability scale, measures of mobility, accidents, memory and mood.

4.1 Inclusion criteria

1. Age ≥65 years
2. A clinical diagnosis of OSAHS: ≥ 4% Oxygen desaturation index > 7.5 events/hour and an Epworth sleepiness scale ≥ 9
3. Ability to give written informed consent

4.2 Exclusion criteria

1. Previous exposure to CPAP therapy
2. Arterial oxygen saturation <90% on room air
3. FEV_1 / FVC <60%
4. Substantial problems with sleepiness driving (in those who are still driving)
5. Currently using HGV or PSV driving licence (where applicable - annual application is required for drivers > 65 years)
6. Shift work
7. Any very severe complication of OSAHS such that CPAP therapy is mandatory
8. Inability to give informed consent or comply with the protocol e.g. the patient must be able to see to be able to participate in the wakefulness test

4.3 Number and source of patients

For participant numbers see section 9.3.

Three centres (Edinburgh, London and Oxford) see approximately 100 patients who would fulfil the entry criteria for this trial each year.. Thus, establishing at least six recruitment centres should ensure achievement of the recruitment target since it requires centres to recruit 50% of eligible patients. Our previous experience shows that this recruitment rate is realistic as a substantial number of patients decline trial entry (usually for reasons of geographical inconvenience). Four of our centres are currently achieving the recruitment rate proposed for this trial in the MOSAIC trial in another subset of sleep apnoea patients.

In six of the recruiting centres a dedicated investigator (or a research nurse) will perform case finding, recruitment, and trial delivery. Diagnostic sleep studies will be performed as part of routine care; auto-titrating CPAP therapy will be established using the units' usual clinical systems wherever possible.

4.4 Screening procedure

All participants fulfilling the inclusion / exclusion criteria are eligible for the trial. Screening logs will be kept, documenting reasons for non inclusion. Diagnosis of OSAHS will be made using the clinical sleep study protocol at each centre. Following enrolment a standardised polygraphic home sleep study (Embletta™) will be carried out (see Section 7.1). If the Embletta Gold test is part of the patient's diagnosis before entering the trial, the results of the test done up to 3 months before randomisation will be acceptable, provided there has been no other clinical change requiring a repeat study.

These studies will be analysed centrally (Edinburgh) to minimise inter-scorer variability in AHI.

5. RANDOMISATION AND ENROLMENT PROCEDURE

Participants will be screened using the eligibility and ineligibility criteria (sections 2.1.1). The recruiting local Principle Investigator or dedicated members of staff will explain the trial to the patient. Participants will then be given the patient information sheet and consent form. Once the participant has given written consent to the trial, the trial team will complete an enrolment form and enter the patient into the trial using the telephone computerised randomisation service of the MRC CTU. Minimisation criteria will be: subjective day time sleepiness (Epworth sleepiness score > 13 v ≤ 13), functionality using the Townsend disability score >1 v ≤1 and recruitment centre.

Advice and support regarding recruitment/trial entry is available from the ORTU (tel: **01865 225205**).

6. TREATMENT OF PATIENTS

6.1 Trial treatment

6.1.1. Treatment arm - continuous positive airway pressure

Obstructive sleep apnoea will be diagnosed using the routine clinical sleep study at each participating centre. After trial entry, OSAHS will be characterised from an overnight sleep study (Embletta™ Embla Systems) common to all centres, carried out in the patient's own home. Patients assigned to CPAP therapy will be started on auto-adjusting CPAP therapy (AutoSet™®, ResMed (UK) Ltd). This therapy automatically adjusts airway pressure to be sufficient to prevent snoring and sleep apnoea without being excessive. The initiation of this therapy will be in keeping with the recruiting centres normal clinical practice (and minimisation by centre at trial entry will ensure that patients with slightly varying CPAP initiation protocols are evenly distributed among the trial groups). At months 3 and 12 of trial follow-up the stored memory of the CPAP machines will be interrogated to define treatment efficiency over multiple nights. This will define how well OSAHS has been controlled over time in the intervention group. Overnight arterial pulse oximetry recording will be performed to quantify sleep apnoea control on one night in both trial groups at 3 and 12 months.

The active treatment arm will also receive the Best Supportive Care package (see section 6.1.2).

6.1.2 Control arm – Best Supportive Care

Best Supportive Care package will consist of:

1. Advice on minimising daytime sleepiness through sleep hygiene and advice about using a nap/caffeine sleepiness management strategy.
2. Advice on weight loss strategies.
3. A general medical review to confirm optimal healthcare for any co-morbid conditions.
4. Modifiable cardiovascular risk factors identified will be highlighted to their General Practitioner to assess and intervene were appropriate to minimise vascular risk, consistent with national guidelines.

The same person who carries out the CPAP set-up will administer this package. All the recruiting centres have established clinical expertise in these areas.

In order to maintain blinding of the investigator to the treatment arm as far as possible centres will manage CPAP care through their normal clinical service. Any NHS service costs associated with this could be offset either by the trial nurse making some contribution to clinical care in other ways, or through local comprehensive local research network funding.

6.2 Trial Product(s)

The CPAP machine used for this trial will consist of a self-adjusting automatic system (the AutoSet™®, ResMed (UK) Ltd). This will be combined with optimal modern CPAP masking, tailored to the individual

patient's facial shape. Humidification will be used to minimise CPAP adverse events (nasal blockage/streaming etc) as required. All the recruiting centres have established clinical expertise in these areas.

6.3 Dispensing

Pharmaceutical dispensing is not applicable to this device trial. CPAP machines will be stored within recruiting centres in keeping with normal clinical practice.

6.4 Randomisation codes / blinding

A copy of the randomisation code will be held by the trial statistician, and systems analyst, and access to this code for a patient before the completion of the trial will only be permitted in exceptional circumstances, such as the necessity to determine the best acute medical care for a patient, and only after discussion with the Chief Investigators and the ORTU. In normal office hours, this access is by contacting the ORTU. Any regulatory body, which requests unblinded data during the course of the trial may approach the IDMC who will provide such data as requested directly to the regulatory body. Such a request will be given appropriate priority prior to trial completion. Access to the unblinded trial data set will only be available to the IDMC

Despite these systems, since this is a physical device trial, the treatment assignment for individual patients cannot be concealed. The recent NICE/HTA meta-analysis of randomised trials of sleep treatment for OSAHS (in middle-aged patients) has shown that the results of trials that used Best Supportive Care as a comparator (as does this study) produced results essentially identical to those from trials using subtherapeutic CPAP therapy as a comparator, where some further degree of patient blinding can be maintained, (though residual snoring while using subtherapeutic CPAP does risk unblinding even in this trial design).

In PREDICT, the use of Best Supportive Care as a comparator is helpful since it allows collection of 12-month health economic outcome data (which is a primary aim of the trial), and improves the simplicity of trial delivery, which is advantageous in a multi-centre recruitment design. To maintain single-blinding, the investigator monitoring the trial outcomes, will be unaware of the treatment arm the patient has been randomised to receive. Moreover, centres will manage CPAP care and clinical monitoring through their normal clinical service as far as possible.

6.5 Modification of trial treatment

Following a serious adverse event (SAE) by regulatory criteria (see Section 11) treatment may be interrupted at the discretion of the local Principal Investigator and restarted if clinically appropriate to complete the proposed treatment course.

Should a patient develop hypercapnic ventilatory failure with an arterial blood gas $paCO_2$ >6.5 Kpa, a patient may stop CPAP treatment for the initiation of bi-level ventilation. If this is necessary, patients on bi-level ventilation will be followed-up through the normal trial systems. CPAP treatment may be reintroduced at the discretion of the local Principal Investigator at a recruiting centre if clinically appropriate.

Details of interrupted therapy should be notified to the trial team on the routine trial case report forms.

6.6 Accountability

The CPAP machines and ancillary equipment required for this trial will be manufactured by ResMed (UK) Ltd, to appropriate regulatory standards for medical equipment. Equipment maintenance will be supervised through the normal management systems of the recruiting units.

6.7 Measures of compliance / adherence

Compliance with CPAP therapy will be monitored from the built-in "face on runtime" timing clocks within the CPAP machines. These clocks record periods for which the machine is on and being used. They provide the gold standard method for monitoring CPAP compliance.

At 3- and 12-month reviews, the memory banks of the CPAP machines will be interrogated to download overnight apnoea-hypopnoea index levels, which is an accurate way of confirming the accuracy of disease control over multiple nights.

6.8 Treatment data collection

Detailed compliance data will be recorded on the case report forms at 3 and 12 months and average usage (hrs/night) will be collected at telephone follow-up contacts at one and 6 months.

6.9 Non-trial treatment

6.9.1 Other therapies permitted

With the exception of therapies targeted at the treatment of OSAHS, patients may receive any other therapy that is clinically indicated (as would be normal under "Best Supportive Care").

6.9.2 Other therapies not permitted

Participants may not receive any therapy aimed at treating OSAHS other than CPAP. Where patients develop hypercapnic ventilatory failure, or any other life-threatening complication (in either trial arm) judged to be due to OSAHS, the patient will not be withdrawn from the trial for initiation of appropriate treatment. Any such patients will be retained within the trial follow-up systems.

6.9.3 Data on concomitant medications

Records of concomitant medications and any changes in medication will be recorded regularly under trial follow-up on the case report forms.

6.10 Co-enrolment guidelines

Patients may not be recruited into any other trial for the 12 months duration of follow-up unless the study is observational, and by prior agreement by the CI(s).
Nested sub-studies are allowed in any of the trial centres. Any planned nested sub-studies must be approved by the Trial Steering Committee, with the explicit proviso that they do not threaten the success of the overall trial.

7. ASSESSMENTS AND PROCEDURES

7.1 Flow chart / Schedule for follow up - Table 1

Trial entry	Randomisation	Intervention	1 month	3 month	6 months	12 months
Inclusion criteria satisfied **Informed consent** **Baseline measurements** • Polygraphic home sleep study (Embletta™) • Epworth sleepiness scale • Weight, Spirometry, neck circumference, smoking, alcohol, caffeine, drug, exercise, education, meds Cardiovascular events (one month prior to enrolment) • Townsend disability scale • SF-36, EQ-5D, SAQLI, HADS, nocturia, road,domestic and work accidents • OSLER test (x 2 times) • Office BP (x3 seated measurements) • Timed up and go test • Health care contacts: hospital and GP usage – self reported, plus review patients' hospital records and GP records • Cognitive function tests • Fasting bloods (Haemoglobin, Total Cholesterol, MCV, HDL Cholesterol, WBC, LDL Cholesterol, Platelets, Triglycerides, Sodium, Potassium, Total Protein, Urea, Albumin, Creatinine, ALT, TSH, GGT, Glucose, Bilirubin, HBA1C; genetics sample – posted to ORTU)	**Complete randomisation forms** **Allocated to one of the intervention regimes minimising by** 1. Epworth sleepiness scale 2. Townsend disability scale 3. Centre of recruitment	**ACTIVE TRIAL ARM** **CPAP Therapy with Best Supportive Care** • Set-up on autotitrating CPAP • Best supportive care (see below) **1 week: telephone follow-up with the option of an additional visit** **CONTROL TRIAL ARM** **Best Supportive Care** • Sleep Hygiene advice • Nap / caffeine advice • Weight loss advice • Cardiovascular risk advice **1 week: telephone follow-up with the option of an additional visit**	**Telephone follow-up to both groups** • Return of ESS, EQ-5D, TDS, diary • Return of side effects, hospital and GP usage smoking, alcohol caffeine, nocturia, road,domestic and work accidents, new medications, exercise, new cardiovascular events diary **Any patient finding compliance difficult will be offered addtional follow-ups**	**Clinic visit both groups** • Download of CPAP machine compliance • Overnight oximetry (to be returned next day by post) • Weight, neck circumference, BP • Return of ESS, EQ-5D, TDS, diary • Return of side effects, hospital and GP usage smoking, alcohol caffeine, nocturia, road, domestic and work accidents, new medications, exercise, new cardiovascular events diary • SF-36, SAQLI, HADS • OSLER test • Timed up and go test • Cognitive function tests • Fasting blood (as at enrolment apart from TSH and genetics)	**Telephone follow-up to both groups** • Return of ESS, EQ-5D, TDS, diary • Return of side effects, hospital and GP usage smoking, alcohol caffeine, nocturia, road, domestic and work accidents, new medications, exercise, new cardiovascular events diary	**Clinic visit for both groups Complete trial outcome forms** • Download of CPAP machine compliance • Overnight oximetry (post back next day) • Weight, neck circumference, BP • Return of ESS, EQ-5D, TDS, diary • Return of side effects, hospital and GP usage smoking, alcohol caffeine, nocturia, road, domestic and work accidents, new medications, exercise, new cardiovascular events diary • SF-36, SAQLI, HADS • OSLER test • Timed up and go test • Cognitive function tests • Fasting bloods (as at enrolment apart from TSH and genetics)
			Monthly return of diary (at 1, 2, 4 -11 m) ESS, EQ-5D, TDS, treatment side effects, exercise, smoking, alcohol, caffeine, nocturia, new cardiovascular events new medications GP / hospital usage, road/domestic accidents			

7.2 Procedure for Assessing Efficacy - Table 2

Enrolment	• Fulfil inclusion criteria
Baseline data collection and randomisation	• Establish AHI > 7.5 desaturation events/hours of sleep by carrying out an overnight sleep study • Complete patient history and measurements of weight, neck circumference, cognitive function, lung function • Fasting bloods (Haemoglobin, Total Cholesterol, MCV, HDL Cholesterol, WBC, LDL Cholesterol, Platelets, Triglycerides, Sodium, Potassium, Total Protein, Urea, Albumin, Creatinine, ALT, TSH, GGT, Glucose, Bilirubin, HBA1C; genetics sample – posted to ORTU) (*Recent blood test results are acceptable provided they were done not more than 1 month prior to the enrolment visit).* • Office BP (3 seated measurements), nocturia • Road, domestic and work accidents • Measures hospital and GP usage • Mobility: Timed up and go test • Subjective and objective measure of sleepiness • Questionnaires: Townsend Disability Score, EQ-5D, SF-36, SAQLI, HADS • Complete enrolment form • Mark-up of patients' records
Intervention	• Randomisation • Setup on AutoSet™® CPAP with administration of Best Supportive Care, or Best Supportive Care only • Carry out standardised sleep study Embletta™ • One week follow-up to by telephone with an option for an additional visit
At 1 month and 6 months follow-up	• Complete data collection: Return of self reported measures of sleepiness (completed monthly), hospital and GP usage, treatment side effects • Questionnaires: Townsend Disability Score, EQ-5D, medication changes, new cardiovascular events, road, domestic and work accidents
At 3 and 12 months follow-up	• Complete data collection: Return of self reported measures of sleepiness (completed monthly), hospital and GP usage, treatment side effects, medication changes, new cardiovascular events, road, domestic and work accidents • Treatment compliance, downloaded from the CPAP machine (CPAP arm), record of adherence to filling in questionnaires (Best Supportive Care– both arms) • Questionnaires: Townsend Disability Score, EQ-5D, SF-36, SAQLI, HADS • Weight, neck circumference, Timed up and go test • Office BP (3 seated measurements), nocturia • Objective measure of sleepiness and cognitive tests • Fasting bloods (as at enrolment apart from TSH and genetics) • Overnight oximetery • Review of patients records

The Townsend Disability Scale will be utilised [106] in the randomisation as a minimisation factor, since older patients are likely to have differing abilities, which are not necessarily correlated with chronological age. It is a self-report scale that evaluates nine tasks relating to Activities of Daily Living, including more complex instrumental activities of daily living items. Each activity can be scored with a 0 (no difficulty), 1 (can do but with difficulty) or 2 (not able to do) and then items are summed to give a total score. Since the scale exhibits hierarchical properties it is also possible to apply Item Response Theory to identify scale items most sensitive to change at different degrees of disability. The proportion of people with very significant disability, as measured by the Townsend scale, increases rapidly with age [107]. The Townsend scale is sensitive to changes in health, both mental and physical, but relatively impervious to the influence of social support either formal or informal [108]. It is strongly related to self-rated health in older people [109]. The availability of population-representative norms allows the characterization of samples.

Mobility will be assessed using the 'up and go' test. This is a quick, simple and practical test of daily movement which is sensitive to morbidity [110]. Community-dwelling older people (65-85 years) should be able to perform the test in 12 seconds or less.

Cognitive Tests will be used to assess cognitive dysfunction. *Mini Mental State Examination* (MMSE) will be used as a quick (10 min) way of screening for cognitive function; recognising that it will not detect subtle memory losses. MMSE is used in the MRC Cognitive Function and Ageing Study and has well defined normative data. *Simple and four-choice reaction time* will be used to assess speed and variability of simple information processing. The task is administered using simple stand-alone computer programme [111] and has been used in the Lothian Birth Cohort 1936 study [112] providing normative data (Starr: Co-director of the University of Edinburgh MRC Centre in Cognitive Ageing and Cognitive Epidemiology). Both the Digit Symbol Substitution test and Trailmaking B time have been shown to be impaired in middle aged patients with OSAHS and to improve with CPAP therapy use during a randomised controlled trial [94]. Both are tests of working memory and attention and as such will be influenced by sleepiness as well as other factors such as mood and intelligence; these factors will be monitored using ESS, HADS questionnaire and recording years of education, respectively. More detailed investigation of cognitive function capitalising on the trial infrastructure will be carried out as a nested sub-study in selected centres where appropriate (see Section 12).

7.3 Procedures for assessing safety

Details of adverse event and serious adverse event reporting are presented in Section 11. Any adverse events which have occurred since the previous follow-up visit **must** be reported at the next follow-up visit; there are both structured and 'free text' spaces on the case report forms (CRF) to document adverse events.

The case report forms will specifically record deaths, side-effects of CPAP therapy (particularly nasal stuffiness and obstruction, superficial nasal soreness or ulceration), cardiovascular events such as myocardial infarction or stoke, and accidents - including road accidents.

In the case of any serious adverse event (SAE) by regulatory criteria (Section 11.2), and subject to the specific adverse event recording criteria for this trial (Section 11), the recruiting centre local Principle Investigator will report the event to ORTU in keeping with regulatory reporting timelines. ORTU will manage such events in keeping with its established Standard Operating Procedures for serious adverse event assessment/management.

7.4 Other assessments

Participants will be asked to record information as stated in the flow chart (Section 7.1; Table 1). At enrolment patients will be given a folder with two Sleep Diaries with prepaid envelopes (to cover Month 1 & Month 2). At 3 month visit patients will be given a folder with 8 sleep diaries and prepaid envelopes. At the end of each month they will fill out one diary and send it back (with the exception

of the 3 and 12 months when they will be having a clinic visit). If the diaries are not received, the patient will be called as a reminder.

Questions about driving will be given to the patients by the investigator (or a research nurse) and returned directly to the ORTU. The ORTU will follow-up any incomplete or missing forms.

7.5 Loss to follow-up

Loss to follow-up will be minimised by diligent liaison of the co-ordinating centre with the Principal Investigators and the trial teams at recruiting centres with the patient, their respiratory consultant and general practitioner (GP). Every effort will be made to carry out a 12 month assessment, even in patients who have changed treatment arm, or have not attended earlier trial visits.

7.6 Trial closure

Trial closure will either be when the last patient completes follow-up or at the direction of the Trial Steering Committee (TSC) acting on the recommendation of the Independent Data Monitoring Committee (IDMC).

The IDMC will advise the TSC that the trial should be stopped if in their view there is proof beyond reasonable doubt that one of the trial treatments is clearly indicated or clearly contradicted in terms of a net difference in efficacy or safety. A difference of at least three standard errors in efficacy in an interim analysis would be needed to justify closing the study prematurely. If this criteria (Haybittle-Peto) is used the exact number of interim analyses is of little importance so no fixed schedule is proposed.

8. EARLY STOPPAGE OF TREATMENT OF PATIENTS

Patients have the right to stop treatment at any time without having to give a reason and this will not affect their future care.

a) Treatment stoppage of a participant from the trial should be under the guidance of the Principal Investigator (in liaison with the ORTU team as appropriate), details should be recorded on the relevant CRF.

b) Participants stopping treatment during this trial should continue normal trial follow up, unless consent for this follow up has been specifically withdrawn. Should a patient decide to stop follow-up, all efforts will be made to complete and report the observations as thoroughly as possible.

c) For participants moving from the area, every effort should be made for the participant to be followed up at another centre, or for follow up via GP.

d) Where patients wish to switch from Best Supportive Care to CPAP plus Best Supportive Care, this should not be encouraged and in particular not before the patient's 4 month data have been collected. For those who do switch to CPAP, follow-up in the trial will be maintained. Any proposed changes should be discussed first with the chief investigators, or the clinical trial coordinator and should be indicated on the CRF.

9. STATISTICAL CONSIDERATIONS

9.1 Method of randomisation

Participants will be allocated to the trial groups by randomisation with minimisation. This will be derived using the established randomisation systems of MRC CTU.

9.2 Outcome measures

9.2.1 Primary outcome measure

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

9.2.2 Secondary endpoints will be a change from baseline, in the following parameters at 3 and 12 months, with the exception of ESS:

1. **Subjective sleepiness:** the mean of the ESS scores measured at months 10, 11 & 12 will be used to answer the question 'does CPAP work at 12 months?
2. **Objective sleepiness:** OSLER maintenance of wakefulness test
3. **Self-reported health status (quality of life and mood):** Short Form 36 questionnaire (SF-36), and Sleep Apnoea Quality of Life Index (SAQLI; a disease specific sleep apnoea questionnaire which includes CPAP side effects), Hospital Anxiety & Depression Scale (HADS)
4. **Functional index of activities of daily living:** Townsend Disability Scale (TDS)
5. **Frequency of nocturia:** Self-reported using the patient monthly diary
6. **Mobility:** Timed up and go test (TUG)
7. **Accidents:** Including self-reported road, domestic and work accidents
8. **Cognitive function:** Mini Mental State examination, Trail making B, The Digit Symbol Substitution Test, Simple and Four-Choice Reaction Time.
9. **Cardiovascular risk factors:** Systolic and diastolic blood pressures, fasting glucose, fasting lipids, HbA1c.
10. **Adverse cardiovascular events:** Myocardial infarction, stroke, transient ischemic attack, new angina, new atrial fibrillation, new peripheral vascular disease

9.2.3 Tertiary endpoint will be:

1. **Treatment compliance:** Measured objectively by 'runtime' clocks built into the machines and downloaded at 3 and 12 month clinic visits.

9.3 Sample size and Power calculations

9.3.1 Subjective excessive daytime sleepiness (the Epworth Sleepiness Score)

The primary analysis will be a change in the mean Epworth Sleepiness Score (ESS) recorded monthly. In the recent NICE/HTA Technology Appraisal of CPAP for OSAHS in middle-aged patients [2], the difference in ESS for the treatment with CPAP of middle-aged patients with mild sleep apnoea was 1.07 (sd 2.4). The inclusion criterion for this trial lies in the range of "moderate" sleep apnoea by OSAHS severity, but since sleepiness is often less pronounced in older people,

power calculations are performed assuming a treatment response similar to that seen in mild disease in the middle-aged. A mean change of 1 point on the ESS is also the smallest detectable shift in the Epworth score (which is a categorical scale with one point increments), and the minimum clinically significant change since it is indicative of one symptom state shift on one domain of the score. To detect a one point change in Epworth score (sd of change 2.4), requires 244 patients randomised 1:1 (alpha=0.05, tails=2, power 90%)

In our previous randomised trials with a similar design we have found a loss to follow-up rate of 5%. Since this is a 12-month trial we have assumed the loss to follow-up rate will be 10%. Patients who cease CPAP therapy will be followed-up through the normal trial systems, with a compliance rate of zero hour being presumed. This policy is consistent with previous trials including those from which data has been used to inform these power calculations. Therefore, the sample size for this trial will be **270** patients in total randomised 1:1. A sample size table exploring other scenarios is presented in the table below.

Table 3: Sample size calculations for different mean ESS score results

Intervention Group CPAP	**Control Group Best Supportive Care**					
	90% power (alpha 0.05, 10% loss to FU)			80% power (alpha 0.05, 10% loss to FU)		
Change in mean ESS (SD)	**0.0 (2.4)**	**0.1 (2.4)**	**0.2 (2.4)**	**0.0 (2.4)**	**0.1 (2.4)**	**0.2 (2.4)**
1.2 (2.4)	188	224	**270**	140	168	**202**
1.1 (2.4)	224	**270**	334	168	**202**	250
1.0 (2.4)	**270**	334	422	**202**	250	314
0.9 (2.4)	334	422	550	250	314	412
0.8 (2.4)	422	550	748	314	412	560

9.3.2 Health economic analysis

The health economic analysis will involve the use of a decision model to extrapolate the trial results to a lifetime horizon. The resulting cost per QALY gained with auto-titrating CPAP with Best Supportive Care, compared to Best Supportive Care only, over a lifetime horizon will provide information to health care providers about the value of making auto-titrating CPAP available to older patients with OSAHS. The health economic analysis will be based on the difference in health related quality of life observed in the trial. A fully probabilistic analysis will be conducted such that the uncertainty in the difference in health related quality of life between CPAP and Best Supportive Care will be propagated through to the model results. This, in combination with the uncertainty in the other sources of data used to populate the decision model will allow the health economic analysis to provide an estimate of the decision uncertainty, expressed in terms of the probability that CPAP is cost-effective given a cost-effectiveness threshold of £20,000 per QALY gained.

A previous study of the effects of CPAP in patients (n=39) with diabetes and OSAHS [43] showed that CPAP may be associated with a mean improvement of 0.02 (se 0.51) in health related quality of life (which is measured on a scale between 1=full health and 0=death). The diabetic population identified by West *et al,* had not self-presented with OSAHS, which may explain why their improvement in health related quality of life was lower than the average improvement estimated for the previous analysis of CPAP middle-aged patients (mean 0.03; [2]). We can utilise the decision model from the previous cost-effectiveness analysis of CPAP in middle-aged patients [2], to extrapolate the expected improvement in health related quality of life to an improvement in QALYs. By adjusting the age of the hypothetical cohort in the model to reflect the greater age of the patient

population in this trial and adjusting the standard error of the improvement in quality of life to reflect the size of the trial, we can get an indication of the decision uncertainty that would result from this trial for a range of effect sizes. The estimates are only indicative, as the other elements of the existing decision model, such as the improvement in cardiovascular risk, may not be considered to be generalisable to an older population. The use of the effect size and standard error from the West *et al.* trial may be considered conservative as this was a very small trial in patients for whom the symptoms of OSAHS were not severe enough to cause them to seek treatment.

This trial will also provide information on any improvement in cardiovascular risk factors. The previously published trials did not provide any information as to whether use of CPAP is associated with a reduction in other health care resource utilisation. If the results of this trial indicate that the health benefits from CPAP translate to a reduction in other health care resource use, CPAP will appear more cost-effective and the decision uncertainty would be further reduced.

9.4 Interim monitoring and analyses

An Independent Data Monitoring Committee (IDMC) will monitor safety and efficacy. The IDMC will consult with the Trial Steering Committee at the start of the trial to agree its terms of reference and to set out a formal charter. The IDMC will review the trial outcomes and adverse events after each 100 patients randomised. The trial statistician will liaise with the IDMC following any Unanticipated Adverse Device Effects (UADEs) and will review the need for an extra IDMC meeting in response to such events. No interim efficacy analyses are planned by the steering committee, though the IDMC will monitor efficacy data.

9.5 Analysis plan

The Trial Management Group will develop a detailed analysis plan before treatment codes are broken.

10. DATA VERIFICATION AND SITE MONITORING

10.1 In house monitoring and Quality Control

The data will be stored in a trial database which will be developed and maintained by MRC CTU and subject to duplicate and range checks. Data stored (in line with GCP standards) in the database will be accessed from the coordinating centre at the ORTU and checked for missing or unusual values (range checks) and for consistency within participants over time. If any such problems are identified, a copy of the problematic CRF(s) will be returned to investigators for checking and confirmation or correction, as appropriate. One copy of the amended CRF(s) will be filed at the participating site and another copy will be sent to the ORTU for data entry.

10.2 Clinical Site Monitoring

The MRC Clinical Trials Unit will be responsible for monitoring the ORTU and the ORTU will monitor all other recruiting sites as per Monitoring Plan. Primary source data checks of a subset of information will be performed in a subset of patients according to the Monitoring Plan based on the trial Risk Assessment developed by ORTU.

10.3 Direct Access to Data

Principal Investigators at the recruiting centres will facilitate access to trial records for the purpose of monitoring, audits and ethic committee reviews. We will obtain participants' consent for this at the time of randomisation.

10.4 Confidentiality

Full medical confidentiality will be preserved. The WMA Helsinki Declaration (Amended October 2008) is accepted as the basis for conducting this trial.

Investigators at the recruiting centre will sign an agreement agreeing to adhere to this protocol and stating their responsibilities. Participants' personal identification will not be disclosed. Patients involved in this trial will be identified by initials and trial number on all CRFs. Stored specimens at Oxford will only identify patients by trial number. Patients will not be individually identified in any results publications.

10.5 Quality Assurance

Quality Assurance: This will be a randomised, controlled trial. All appropriate ethical approvals will be obtained. A register of screened patients will be kept. Randomisation (with minimisation) will be by central computer derived allocation. A Trial Steering Committee with an independent Chair and additional independent members will have oversight of the study. The Trial Steering Committee and IDMC will review the final report. Safety data will be reviewed by the IDMC. The protocol will be submitted to the MRC Clinical Trials Unit Protocol Review Committee.

Quality Control: Data validation of primary data will include at least confirmation of patient identity, informed consent, eligibility criteria, treatment compliance, and primary outcome data. Protocol delivery will be managed according to Standard Operating Procedures governing the performance of the Clinical Trials Units.

11. ADVERSE EVENTS AND REACTIONS

CPAP therapy for OSAHS has been extensively used in the middle-aged population and therefore its adverse event profile is generally well known. Description of this treatment's tolerability and adverse event profile in the elderly population is an important aim of this study, and there are reasons to believe older people may suffer more adverse events than middle-aged populations. For example, manual dexterity allowing comfortable mask adjustment may be reduced, and there may be increased facial skin fragility affected by the mask. Nonetheless, it is not expected that novel (unexpected) adverse device effects will be encountered, and the adverse event profile is expected to be modest. Therefore, the pattern of adverse event reporting is tailored to the needs of this study and is restricted compared to the general ICH E2A description.

11.1 Adverse Event (AE)

An AE or adverse event is any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

11.1.1 Serious Adverse Event (SAE):

A Serious Adverse Event (SAE) is an adverse event that:

- ♣ Led to death
- ♣ Led to foetal distress, foetal death or congenital abnormality or birth defect
- ♣ Led to serious deterioration in the health of the subject that

- Resulted in a life-threatening illness or injury
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Resulted in a permanent impairment of a body structure or a body function
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events*
  *Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "*serious*" and "*severe*", which are not synonymous, the following note of clarification is provided:

The term "*severe*" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

This is not the same as "*serious*," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.2 Adverse Device Effect (ADE)

Adverse Device Effects (ADEs) are all untoward and unintended responses to a medical device.
The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
All cases judged by either a medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as a device effect.
This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

11.2.1 Expected Adverse Device Effects

CPAP therapy is generally very well tolerated. The main expected adverse device effects on CPAP therapy are:

- nasal dryness/discomfort
- nasal discharge
- mouth drying and dribbling
- facial soreness/discomfort
- occasional facial ulceration due to poor mask fitting

These adverse device effects can be minimised by the use of humidification and careful mask fitting. All the centres recruiting to this trial have established experienced clinical services with the necessary skill set to minimise these side-effects. The frequency of these adverse device effects will be recorded on the case report forms (CRFs).

11.2.3 Serious Adverse Device Effects (SADE)

A Serious Adverse Device Effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or lead to the characteristics of a Serious Adverse Event.
SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. SADE will be documented on an SAE form.

11.2.4 Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is any Serious Adverse Device Effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if it was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application). It can also be any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

Unexpected Adverse Device Effects will be documented on an SAE form. The probability of Unexpected Adverse Device Effect is low.

11.3 Recording of Adverse Events

CPAP therapy has been very extensively used in middle-aged patients. Its adverse event profile in that group is well described. The pattern/severity of the expected adverse events may differ in the study population in this trial, but novel (unexpected) adverse device effects are not likely.

For this trial, Adverse Events will be recorded systematically during the CPAP set-up and during the 12 months of the follow-up. Adverse Event recording will include any adverse event having a reasonable possibility of being attributable to the trial (that is an Adverse Device Effect) **and** any other Adverse Event considered to be of medical interest/importance by the local Principal Investigator. Adverse Events should be recorded on the routine CRFs.

All Adverse Reactions that result in a patient stopping treatment early, or are present at the end of the study should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an Adverse Event is of sufficient severity to require the patient's removal from the trial treatment. A patient may also voluntarily withdraw from treatment due to what they perceive an intolerable Adverse Device Effect.

If either of these occurs, the patient must be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. Every effort will be made to gather outcome data on these subjects through the trial follow-up systems, or general practitioner/hospital staff unless the patient has specifically withdrawn consent to such efforts.

The secondary adverse consequences of sleepiness (the correction of which is the primary reason for using CPAP therapy for OSAHS) are recorded as trial outcomes. This particularly applies to accidents, including road accidents.

11.4 Reporting of Serious Adverse Events

Subject to the specific reporting procedures for this trial, a Serious Adverse Event (SAE) occurring to a research participant should be reported to the main REC and the Sponsor (via the ORTU) where in the opinion of the Chief Investigators, in discussion with the ORTU, the event was:

1. 'Related' – that is, it resulted from administration of any of the research procedures (Serious Adverse Device Effect) **and**

2. 'Unexpected' – that is, the event is not expected from the known characteristics of the trial intervention or the patient's clinical situation

Serious Adverse Events (related and unexpected) should be reported to the ORTU by the Principal Investigator at a recruiting site within **one working day of awareness**. The ORTU will assess this event and report the event to the main REC and the Sponsor within 15 days of the CI becoming aware of the event. The following attributes are recorded by the investigator: description, date of onset and resolution date, severity, assessment of relatedness to study intervention, other suspect drug or device and action taken.

The ORTU assessment will consist of a review of the completed Serious Adverse Event form by a medical reviewer from within ORTU with specific expertise in respiratory disease. Where the study participant has been under the care of the PI (Oxford site only), this review will be by one of the Chief Investigators, or a consultant respiratory physician from the Oxford Centre for Respiratory Medicine working under the relevant ORTU SOP.

Other adverse events which are 'serious' by the criteria specified in section 11.1.1 but are unrelated to the CPAP treatment will be documented on the SAE forms but will not be reported to the REC or the Sponsor. Submission of these SAEs to ORTU is not subject to specific timelines.

A list of all Serious Adverse Events which have occurred during the study will be kept at ORTU and provided to the manufacturers of CPAP machines - ResMed (UK) Ltd within three months of the end of the study. It will be clearly stated whether SAEs, in the opinion of the local Principle Investigator, are related to the study treatment.

11.5 Status of Adverse Events

Adverse Events should be reported as either: resolved, persisting, worsening, or fatal.

11.6 Relationship to trial treatment

The relationship between the trial treatment and the adverse event will be reported as: definitely, probably, possibly, unlikely, not related.

11.7 Follow-up after Adverse Events

Adverse Events (serious or non-serious) which are considered to be related to the study intervention (Adverse Device Effects) are followed up until resolution, or the event is considered stable. After recovery these participants will be followed up in the normal trial follow-up sequence. The recruiting centre's Principal Investigator may be asked to provide follow-up information.

11.8 Annual reporting

In addition to the above reporting, a progress report will be submitted to the REC and R&D once a year throughout the trial.

12. ANCILLARY STUDIES

Nested sub-studies capitalising on the trial infrastructure will be planned. Such studies must first be approved by the Trial Steering Committee, which will specifically consider whether any sub-study can be performed without interfering with the primary aims of the trial.

OSAHS patients will be asked to contribute to a gene and blood sample "biobank" of sleep apnoea patients, and these samples will be used for the exploration of future hypotheses related to sleep

and breathing disorders. Collection and storage of these samples will be covered by specific consent during the trial entry process.

13. ETHICAL CONSIDERATIONS AND APPROVAL

13.1 Ethical considerations

Eligible patients will be given detailed information, in the form of a patient information sheet, and the opportunity to discuss the trial further with a member of the trial team. They will also have 24 hours 'thinking time' thereafter to consider enrolling in the trial where possible. It is recognised that clinical circumstances may sometimes make this impossible. Patients will be asked to consent to trial entry, the collection of information about their care, and collection of subsequent data sheets. All will be appropriately anonymised.

Some patients will receive Best Supportive Care only; this is explicitly explained in the patient information sheet and covered by specific consent.

The magnitude of treatment effects with CPAP for OSAHS in younger populations is large. There is a necessity (highlighted by NICE) for data defining the magnitude of treatment efficacy and older populations since it is not straightforward to generalise results from middle-aged populations to older populations. If the therapeutic advantages in older populations are as large as they are in middle-aged populations it is possible that the trial questions may be clearly answered prior to the completion of the full sample size. The IDMC will regularly (approx once a year, unless otherwise needed) review the trial data to assess if this has occurred.

13.2 Ethical approval

This protocol will have Research Ethics Committee (REC) approval before participants are entered. The participant's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

The right of the participant to refuse to participate in the trial without giving reasons is respected. After the participant has entered the trial, the patients' responsible clinicians are free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interests of the participant. However, the reason for doing so should be noted and discussed with the ORTU and Chief Investigators where possible (making contact via ORTU tel: 01865 225205). These participants will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment. These participants will remain within the trial for the purpose of follow-up unless the patient has specifically withdrawn consent for such follow-up.

13.3 Risks and benefits

Benefits: If CPAP and Best supportive care proves effective in older people, the therapeutic benefits both to older individuals with this disease, and at a societal level, may be substantial. Reduction in sleepiness and vascular risk may significantly contribute to independence, quality of life, and economic healthcare utility in older people. This issue is explored in detail in the background discussion above.

Risks: CPAP therapy is generally very well tolerated. The main expected adverse effects of CPAP therapy are nasal dryness/discomfort, nasal discharge, a dry mouth (and dribbling), facial discomfort, and rarely ulceration due to poor mask fitting. These adverse effects can be minimised

by the use of humidification and careful mask fitting. All the centres recruiting to this trial have established experienced clinical services with the necessary skill set to minimise these side-effects. The frequency of these adverse events will be recorded on the case report forms.

14. REGULATORY APPROVAL

This trial does not involve Investigational Medicinal Products and therefore does not need to be approved by MHRA. Management approval will be obtained from each host organisation prior to the start of the study at each participating site.

15. INDEMNITY

The NHS will have a duty of care to participants receiving conventional care irrespective of participation in the trial.

Imperial College London accepts protocol indemnity as Sponsors of the trial.

ResMed (UK) Ltd will provide indemnity against technical problems with the auto-titrating CPAP machinery (the trial intervention).

16. TRIAL COMMITTEES

The trial will have the following management committees and these will be consistent with GCP during the setup phase (following funding)

- **Trial Management Group (TMG)**

Professor Mary Morrell (CI), Dr Renata Riha (CI)

Marjorie Vennelle (Research Nurse)

Dr Alison McMillan (PI, Research Fellow)

Professor Andrew Nunn / Daniel Bratton / Dr Nicola Muirhead (MRC CTU)

Professor Robert Davies (PI, Clinical Director of ORTU) (*until Nov 2010*), Professor John Stradling (PI, Trial Advisor)

Magda Laskawiec (Trial Manager, ORTU) / Melissa Dobson (Director of Operations, ORTU)

- **Trial Steering Committee (TSC)**

Independent Chairman:	Professor Walter McNicholas
Chief Investigators	Professor Mary Morrell and Dr Renata Riha
UKCRC ORTU:	Professor Rob Davies (until Nov 2010)
Trial Statistician:	Professor Andrew Nunn (MRC CTU)
Key Investigators:	Professor John Stradling
Gerontologist:	Dr John Starr
Service Provider:	Dr Mark Elliott
Service Provider:	Dr Melissa Hack
Service Provider:	Dr Justin Pepperell
Service Provider:	Dr Anita Simonds
Health Economists	Professor Mark Sculpher / Dr Susan Griffin
Research Fellow	Dr Alison McMillan
Independent members:	Dr Ian Smith
	Professor Sir Neil Douglas (President, Royal College of Physicians of Edinburgh)
Patient representative:	Mr Frank Govan
Trial Manager	Magda Laskawiec-Szkonter

The TSC will meet once every 12 months, or more regularly if required.

- **Independent Data Monitoring Committee (IDMC)**

Chair:	Professor Tim Peto (Clinical Trialist)
Disease expert	Professor John Gibson
Independent Statistician	Professor David Wright

The IDMC will meet when recruitment reaches 100, and thereafter to be determined by the IDMC

- **Endpoint/Adverse Event Review Committee (ERC)** if needed (to be decided in the light of trial progress)

17. PUBLICATION

The preparation of a manuscript for timely publication will be the sole responsibility of the TSC, and the TSC and IDMC will have sight of the finished manuscript prior to submission. High priority will be given to this.

Authorship of the primary report will include (but not be limited to) the Chief Investigators, Trial Advisor, Trial Coordinator, Trial Administrator, Trial Statistician and Key Investigator(s).

18. PROTOCOL AMENDMENTS

1. Substantial Amendment SA01 (approved by the REC on 04/11/2009)

2. Substantial Amendment SA02 (approved by the REC on 02/12/2009)

3. Substantial Amendment SA03 (approved by the REC on 10/05/2010)

4. Non-substantial amendment NA04 (acknowledged by the REC on 14/05/2010)

5. Substantial Amendment SA05 (approved by the REC on 24/02/2011)
6. Substantial Amendment SA06 (approved by the REC on 20/06//2011)

5. 19. REFERENCES

[1] McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med. 1999;159:1108-14.

[2] McDaid C, Griffin S, Weatherly H. The Continuous Positive Airway Pressure for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis: Assessment report for the National Institute for Health and Clinical Excellence; 2008.

[3] Curtis L, Netten A. Unit costs of health and social care: Available from: http://www.pssru.ac.uk/uc/uc2006contents.htm; 2006.

[4] British National Formulary: BMJ Group and RPS Publishing. Available from: http://www.bnf.org 2008.

[5] NICE. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2004. Report No.: NO515.

[6] Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30:711-9.

[7] Shaw C. 2004 Based national population projections for the UK and constituent countries. Popul Trends. 2006;123:9-20.

[8] Karlsson M, Mayhew L, Plumb R, Rickayzan B. Future costs for long-term care: cost projections for long-term care for older people in the United Kingdom. Health Policy. 2006;75:187-213.

[9] Remmers J, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol. 1978;44:931-8.

[10] Stradling JR, Davies RJ. Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. Thorax. 2004;59:73-8.

[11] O'Driscoll DM, Meadows GE, Corfield DR, Simonds AK, Morrell MJ. Cardiovascular response to arousal from sleep under controlled conditions of central and peripheral chemoreceptor stimulation in humans. J Appl Physiol. 2004 Mar;96:865-70.

[12] Davies RJ, Stradling JR. Nocturnal ambulatory blood pressure measurement. BMJ. 1994;309(6953):543.

[13] George CF. Sleep. 5: Driving and automobile crashes in patients with obstructive sleep apnoea/hypopnoea syndrome. Thorax. 2004;59:804-7.

[14] George CF, Findley LJ, Hack MA, Douglas McEvoy R. Across-country viewpoints on sleepiness during driving. Am J Respir Crit Care Med. 2002;165:746-9.

[15] Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet. 1999;353:2100-5.

[16] Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med. 2001;163:344-8.

[17] Peppard P, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378-84.

[18] Nieto FJ, Young TB, Lind E, Shahar J, Samet S, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. JAMA. 2000;283:1829-36.

[19] Pepperell JC, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med. 2003;168:1109-14.

[20] Kiely J, McNicholas W. Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. Eur Respir J. 2000;16:128-33.

[21] Ancoli-Israel S, Kripke D, Mason W, Messin S. Sleep apnea and nocturnal myoclonus in a senior population. Sleep. 1981;4:349-58.

[22] Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000;123:331-9.
[23] Vitiello MV, Larsen LH, Moe KE. Age-related sleep change: Gender and estrogen effects on the subjective-objective sleep quality relationships of healthy, noncomplaining older men and women. J Psychosom Res. 2004;56:503-10.
[24] Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology. 2002;59:585-9.
[25] Abad V, Sarinas P, Guilleminault C. Sleep and rheumatologic disorders. Sleep Med Rev. 2008;12:211-28.
[26] West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax. 2006;61:945-50.
[27] Vazir A, Hastings PC, Dayer M, McIntyre HF, Henein MY, Poole-Wilson PA, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail. 2007;9:243-50.
[28] Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. JAMA. 1994;272:292-6.
[29] Hass D, Foster G, Nieto J, Redline S, Resnick H, Robbins J, et al. Age-dependent associations between sleep disordered breathing and hypertension. Circulation. 2005;111:614-21.
[30] Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. Ann Intern Med. 2001;134:1015-23.
[31] Goff EA, O'Driscoll DM, Simmonds AK, Trinder J, Morrell MJ. The cardiovascular response to arousal from sleep decreases with age in healthy adults. Sleep. 2008;31:In Press.
[32] Ancoli-Israel S. Sleep apnea in older adults - is it real and should age be the determining factor in the treatment decision matrix? Sleep Med Rev. 2007;11:83-5.
[33] Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. Med Hypotheses. 2006;66:1069-73.
[34] Lavie P, Lavie L, Herer P. All-cause mortality in males with sleep apnoea syndrome: declining mortality rates with age. Eur Respir J. 2005;25:514-20.
[35] Young TD, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230 - 5.
[36] Hoch CC, Reynolds CF. Comparison of sleep-disordered breathing among healthy elderly in the seventh, eighth, and ninth decades of life. Sleep. 1990;6:502-11.
[37] Ancoli-Israel S, Klauber M, Stepnowsky C, Estline E, Chinn A, Fell R. Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med. 1995;152:1946-9.
[38] Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med. 1998;157:144-8.
[39] Young T, Shahar E, Nieto F, Redline S, Newman A, Gottlieb D, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162:893-900.
[40] Hader C, Schroeder A, Hinz M, Micklefield G, Rasche K. Sleep disordered breathing in the elderly: comparison of women and men. J Physiol Pharmacol. 2005;56:85-91.
[41] Redline S, Strohl K. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. Clin Chest Med. 1998;19:1-19.
[42] Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet. 2002;359:204-10.
[43] West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax. 2007;62:969-74.
[44] Kezirian E, Harrison S, Ancoli-Israel S, Redline S, Ensrud K, Claman D, et al. Behavioral correlates of sleep-disordered breathing in older women. Sleep. 2007;30:1181-8.

[45] Ancoli-Israel S, Kripke D, Klauber M, Manson W, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep. 1991;14:486-95.
[46] Haponik EF. Sleep disturbances of older persons: physicians' attitudes. Sleep. 1992;15:168-72.
[47] Resnick HE, Phillips B. Documentation of sleep apnea in nursing homes: United States 2004. J Am Med Dir Assoc. 2008;9:260-4.
[48] Lévy P, Pépin JL, Malauzat D, Emeriau JP, Léger JM. Is sleep apnea syndrome in the elderly a specific entity? Sleep. 1996;19:S29-38.
[49] Young T. Sleep-disordered breathing in older adults: is it a condition distinct from that in middle-aged adults? Sleep. 1996;19:529-30.
[50] Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. Thorax. 1992;47:101-5.
[51] Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA. 2004;291:2013-6.
[52] Haponik EF, Smith PL, Bohlman ME, Allen RP, Goldman SM, Bleecker ER. Computerized tomography in obstructive sleep apnea. Correlation of airway size with physiology during sleep and wakefulness. Am Rev Respir Dis. 1983;127:221-6.
[53] Schwab RJ, Pasirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med. 2003;168:522-30.
[54] Eikermann M, Jordan A, Chamberlin N, Gautam S, Wellman A, Lo Y, et al. The influence of aging on pharyngeal collapsibility during sleep. Chest. 2007;Epub ahead of print.
[55] Malhotra A, Huang Y, Fogel R, Lazic S, Pillar G, Jakab M, et al. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. Am J Med. 2006;119:72.e9-14.
[56] Browne HAK, Adams L, Simonds AK, Morrell MJ. Impact of age on breathing and resistive pressure in people with and without sleep apnea. J Appl Physiol. 2001;90:1074 - 82.
[57] Worsnop C, Kay A, Kim Y, Trinder J, Pierce R. Effect of age on sleep onset-related changes in respiratory pump and upper airway muscle function. J Appl Physiol. 2000;88:1831-9.
[58] Brown IG, Bradley TD, Phillipson EA, Zamel N, Hoffstein V. Pharyngeal compliance in snoring subjects with and without obstructive sleep apnea. Am Rev Respir Dis. 1985;132:211-5.
[59] Martin SE, Mathur R, Marshall I, Douglas NJ. The effect of age, sex, obesity and posture on upper airway size. Eur Respir J. 1997;10:2087-90.
[60] Maltais F, Carrier G, Cormier Y, Series F. Cephalometric measurements in snorers, non-snorers, and patients with sleep apnoea. Thorax. 1991;46:419-23.
[61] Mathur R, Douglas NJ. Frequency of EEG arousals from nocturnal sleep in normal subjects. Sleep. 1995;18:330-3.
[62] Zepelin H, McDonald CS, Zammit GK. Effects of age on auditory awakening thresholds. J Gerontol. 1984;39:294-300.
[63] Pack AI, Silage DA, Millman RP, Knight H, Shore ET, Chung DC. Spectral analysis of ventilation in elderly subjects awake and asleep. J Appl Physiol. 1986;64:533-44.
[64] Turkington P, Allgar V, Bamford J, Wanklyn P, Elliott M. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax. 2004;59:367-71.
[65] Dempsey J. Crossing the apnoeic threshold: causes and consequences. Exp Physiol. 2005;90:13-24.
[66] Roehrs T, Zorick F, Wittig R, Conway W, Roth T. Predictors of objective sleepiness in patients with sleep-related breathing disorders. Chest. 1989;95:1202-6.
[67] Phillips B, Berry DTR, Lipke-Molby TC. Sleep-disordered breathing in healthy, aged persons. Chest. 1996;110:654-8.
[68] Bixler EO, Vgontaz AN, Lin H-M, Calhoun A, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: The role of sleep apnea, age, obesity, diabetes and depression. J Clin Endocrinol Metab. 2006;90:4510-5.
[69] Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. Sleep Med Rev. 2007;11:99-111.

[70] Knight H, Millman R, Gur R, Saykin A, Doherty J, Pack A. Clinical significance of sleep apnea in the elderly. Am Rev Respir Dis. 1987;136:845-50.
[71] Valencia-Flores M, Campos R, Mendez J, Haro R, Schenkel E, Bliwise D, et al. Multiple sleep latency test (MSLT) and sleep apnea in aged women. Sleep. 1993;16:114-7.
[72] Hastings PC, Vazir A, O'Driscoll DM, Morrell MJ, Simonds AK. Symptom burden of sleep-disordered breathing in mild-to-moderate congestive heart failure patients. Eur Resp J. 2006;27:748-55.
[73] Unruh ML, Redline S, An MW, Buysse DJ, Nieto FJ, Yeh JL, et al. Subjective and Objective Sleep Quality and Aging in the Sleep Heart Health Study. J Am Geriatr Soc. 2008 Epub 2008 May 14.
[74] Bixler EO, Kales A, Jacoby JA, Soldatos CR, Vela-Bueno A. Nocturnal sleep and wakefulness: effects of age and sex in normal sleepers. Int J Neurosci. 1984;23:33-42.
[75] Moore P, Bardwell W, Ancoli-Israel S, Dimsdale J. Association between polysomnographic sleep measures and health-related quality of life in obstructive sleep apnea. J Sleep Res. 2001;10:303-8.
[76] Martinez-Garcia MA, Soler-Cataluna JJ, Roman-Sanchez P, Gonzalez V, Amoros C, Montserrat JM. Obstructive sleep apnea has little impact on quality of life in the elderly. Sleep Med. 2008 Jan 18.
[77] Finn L, Young T, Palta M, Fryback DG. Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. Sleep. 1998;21:701-6.
[78] Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. Sleep. 2001;24:96-105.
[79] Moyer C, Sonnad S, Garetz S, Helman J, Chervin R. Quality of life in obstructive sleep apnea: a systematic review of the literature. Sleep Med. 2001;2:477-91.
[80] Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. J Sleep Res. 1997;6:199-204.
[81] D'Ambrosio C, Bowman T, Mohsenin V. Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure-a prospective study. Chest. 1999;115:123-9.
[82] Ayalon L, Ancoli-Israel S, Stepnowsky C, Marler M, Palmer BW, Liu L, et al. Adherence to continuous positive airway pressure treatment in patients with Alzheimer's disease and obstructive sleep apnea. Am J Geriatr Psychiatry. 2006;14:176-80.
[83] Browne HAK, Adams L, Simonds AK, Morrell MJ. Sleep apnoea and daytime function in the elderly-what is the impact of arousal frequency? Respiratory Medicine. 2003;97:1102-8.
[84] Guilleminault C, Lin C, Gonçalves M, Ramos E. A prospective study of nocturia and the quality of life of elderly patients with obstructive sleep apnea or sleep onset insomnia. J Psychosom Res. 2004;56:511-5.
[85] Steffens DC, Otey E, Alexopoulos GS, Butters MA, Cuthbert B, Ganguli M, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. Arch Gen Psychiatry. 2006;63:130-8.
[86] Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med. 2002;165:773-80.
[87] Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull. 2003;61:87-92.
[88] Barnes M, McEvoy R, Banks S, Tarquinio N, Murray C, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med. 2004;170:656-64.
[89] Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. Am J Respir Crit Care Med. 1999;159:461-7.

[90] Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. Thorax. 1998;53:341-5.
[91] Cohen-Zion M, Stepnowsky C, Marler M, Shochat T, Kripke D, Ancoli-Israel S. Changes in cognitive function associated with sleep disordered breathing in older people. J Am Geriatr Soc. 2001;49:1622-7.
[92] Cohen-Zion M, Stepnowsky C, Johnson S, Marler M, Dimsdale JE, Ancoli-Israel S. Cognitive changes and sleep disordered breathing in elderly: differences in race. J Psychosom Res. 2004;56:549-53.
[93] Mathieu A, Mazza S, Decary A, Massicotte-Marquez J, Petit D, Gosselin N, et al. Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. Sleep Med. 2008;9:112-20.
[94] Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. Lancet. 1994;343:572-5.
[95] Aloia MS, Ilniczky N, Di Dio P, Perlis ML, Greenblatt DW, Giles DE. Neuropsychological changes and treatment compliance in older adults with sleep apnea. J Psychosom Res. 2003;54:71-6.
[96] SIGN. Management of Obstructive Apnoea/Hypopnoea Syndrome in Adults: Scottish Intercollegiate Guidelines Network; 2003. Report No.: 73.
[97] Deary IJ, Der G. Reaction time explains IQ's association with death. Psychol Sci. 2005;16:64-9.
[98] Hack M, Davies RJ, Mullins R, Choi SJ, Ramdassingh-Dow S, Jenkinson C, et al. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. Thorax. 2000;55:224-31.
[99] George CF, Boudreau AC, Smiley A. Effects of nasal CPAP on simulated driving performance in patients with obstructive sleep apnoea. Thorax. 1997;52:648-53.
[100] Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results from the sleep heart health study. A J Respir Crit Care Med. 2001;163:19-25.
[101] Marin J, Carrizo S, Vicente E, Agusti A. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046-53.
[102] Bazzano L, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension. 2007;50:417-23.
[103] Gay P, Weaver T, Loube D, Iber C. Positive Airway Pressure Task Force; Standards of Practice Committee; American Academy of Sleep Medicine; Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29:381-401.
[104] Giles T, Lasserson T, Smith B, White J, Wright J, Cates C. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev. 2006;19:CD003002.
[105] Montserrat JM, Ferrer M, Hernandez L, Farre R, Vilagut G, Navajas D, et al. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. Am J Respir Crit Care Med. 2001;164:608-13.
[106] Townsend P. Poverty in the United Kingdom. Harmondsworth: Penguin 1979.
[107] Brayne C, Matthews F, McGee M, Jagger C. Health and ill-health in the older population in England and Wales. The Medical Research Council Cognitive Function and Aging Study (MRC CFAS). Age & Ageing. 2001;30:53-62.
[108] Bowling A, Grundy E. Activities of daily living: changes in functional ability in three samples of elderly and very elderly people. Age & Ageing. 1997;26:107-14.
[109] Starr JM, Deary IJ, Macintyre S. Associations with successful ageing in the Healthy Old People in Edinburgh cohort: being well, fit and healthy. Aging Clinical & Experimental Research. 2003;15:336-42.

[110] Bischoff HA, Stahelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, et al. Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. Age Ageing. 2003;32:315-20.
[111] Cox B, Huppert F, Whichelow M. The health and lifestyle survey: seven years on. Aldershot: Dartmouth Press 1993.
[112] Deary I, Gow A, Taylor M, Corley J, Brett C, Wilson V, et al. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. BMC Geriatrics. 2007;7:28.