BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015836
Article Type:	Protocol
Date Submitted by the Author:	03-Jan-2017
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	SLEEP MEDICINE, Obstructive Sleep Apnoea, Continuous positive airway pressure

Combination of obstructive sleep apnoea and Insomnia treated by Continuous Positive Airway Pressure with the SensAwake™ pressure relief technology to assist sleep: a randomised cross-over trial

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Word Count: Main text 2117 words, plus 1 box and 1 table

Abstract

Introduction: Obstructive Sleep Apnoea (OSA) is a common sleep breathing disorder affecting around 5% of the middle-aged population. Continuous Positive Airway Pressure (CPAP) is the primary treatment for patients with OSA, but acceptance and adherence to therapy is sub-optimal in specific subgroups including the frequent combination of OSA and insomnia (40 – 80% of OSA patients). Pressure intolerance, particularly during periods of wakefulness, inhibiting sleep onset or return to sleep, is one reason for this poor CPAP adherence. AutoCPAPs continually monitor airflow changes and only increase the pressure when the upper airway requires it. Reducing the pressure during wakefulness-sleep transition and wakefulness-after-sleep-onset (WASO) may improve therapy comfort and potentially adherence without compromising therapy efficacy. We hypothesise that SensAwake™, a pressure relief function that reduces the CPAP pressure on the transition from sleep to wakefulness and on WASO, may improve objective sleep quality.

Methods and analysis: This is a multicentre, randomized double-blind cross-over clinical trial on patients with both OSA and insomnia. Insomnia is defined as an Insomnia Severity Index (ISI) > 15 at screening. Baseline data, including actigraphy, are collected for one week prior to randomisation (1:1) to either conventional AutoCPAP or AutoCPAP with SensAwake for 4 weeks. After an evaluation visit, patients are switched to the other treatment arm for a further 4 weeks. Allowing for 20% dropout, 48 patients are required. Repeated measures ANOVA will be used to assess differences in WASO measured by actigraphy (primary outcome) and other actigraphy measures, AutoCPAP compliance, subjective questionnaire (ISI, ESS, PSQI, and SF-12) scores and 24-hr blood pressure (secondary outcomes).

Ethics and Dissemination: This study was approved by the regional Ethics Committee (CPP Sud-Est –V, IRB N°6705) on 09/12/2015 and is registered on ClincalTrials.gov

(NCT02721329). It started in June 2016 with expected publication of primary outcome results in 2018.

Strengths and Limitations of the study

- A multicentre randomised controlled trial in a well-defined phenotype of obstructive sleep apnoea (OSA) combined with insomnia.
- An important clinical trial which will change practice in a common OSA subgroup having a high rate of CPAP non-compliance
- Objective sleep indices are the primary outcome measures, patient-centred outcomes and 24 hour blood pressure are the secondary outcome measures assessed.
- Multicentre and multidisciplinary input will improve generalization and dissemination of results to the fields of both insomnia and OSA.
- Only relevant to patients with this specific OSA phenotype

INTRODUCTION

Obstructive Sleep Aponea (OSA) is a common sleep breathing disorder affecting around 5% of the middle aged population[1] and is characterized by periodic collapse of the upper airway during sleep. Continuous Positive Airway Pressure (CPAP) is the primary treatment for patients with OSA.[2,3] Despite the effectiveness of CPAP in abolishing upper airway obstruction, acceptance of and adherence to therapy is often sub-optimal particularly in specific phenotypes, including the combination of OSA and insomnia.[4,5]

Pressure intolerance is one possible reason for this lack of adherence. Conventional CPAP generally delivers higher pressure than necessary for much of the night as the needed CPAP pressure is selected based either on one night's titration (in a sleep laboratory) or during several nights at home and pressure requirements can vary considerably with sleeping posture, sleep stage and environmental influences such as alcohol and sedative use.[6,7] AutoCPAPs address this problem by continually monitoring airflow changes and only increasing the pressure when the upper airway requires it. Research suggests that AutoCPAP generally delivers an overall lower mean treatment pressure than conventional CPAP.[8-14] Despite this, there is limited evidence to suggest that AutoCPAP therapy can considerably improve CPAP adherence and acceptance in an unselected population, but this might be different in OSA patients with concurrent insomnia.[8,12,15-21]

Conceptually, a patient's awareness of pressure occurs only during wakefulness. Thus reducing the pressure during wakefulness may improve therapy comfort and potentially adherence without compromising therapy efficacy. SensAwake™ (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) is a pressure relief technology that accurately detects irregularity in the flow signal indicative of the transition from sleep to wake.[22] When the transition from sleep to wake is detected, the device promptly reduces the pressure to help

facilitate a return to sleep. CPAP/Auto CPAP with SensAwake has been used in the general OSA population and has been shown to provide the same treatment efficacy at a lower overall pressure as CPAP/Auto CPAP without SensAwake[23,24] and patients have judged it to be more comfortable and preferred it to CPAP without SensAwake.[25]

The prevalence of insomnia symptoms in OSA patients is estimated to be 40 – 80%,[26-30] and existence of insomnia has been shown to negatively affect CPAP compliance in some studies.[31,32] It is proposed that insomnia patients are preoccupied with external factors that may be perceived as a threat to sleep, which results in a higher wake-after-sleep-onset (WASO), and which may be further exacerbated by the presence of CPAP.[31] It is therefore hypothesized that the pressure relief that SensAwake provides during wakefulness may be of a greater benefit to patients with OSA and insomnia if it can facilitate the return to sleep. There is no known published data on the use of SensAwake in the OSA/Insomnia population.

Primary research objective

The primary objective is to compare the at-home objective sleep quality (WASO, as measured by actigraphy on AutoCPAP with SensAwake compared to AutoCPAP without SensAwake in patients with a diagnosis of OSA and insomnia.

Secondary Research Objectives

The secondary objectives of this trial are to compare AutoCPAP compliance, other measures of objective sleep quality (total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE) as measured by actigraphy), data from validated questionnaires evaluating daytime sleepiness (Epworth Sleepiness Scale [ESS]), subjective sleep quality (Pittsburgh Sleep Quality Index [PSQI], insomnia (Insomnia Severity Index [ISI]) and quality of life (Short Form 12 Health Survey [SF-12)]), and blood-pressure indices (measured by 24-hour ambulatory blood pressure monitoring).

METHODS AND ANALYSIS

Study Design

This is multicenter prospective 1:1 randomised, double-blind, crossover trial.

Patient entry and screening for insomnia

Out-patients diagnosed with OSA by Polysomnography (PSG) at one of the participating centres between June 6, 2016 and June 6, 2017, eligible for CPAP treatment under local requirements (AHI>30 with no more than 20% of central respiratory events) and meeting the study inclusion/non-inclusion criteria (including the HAD score) are asked to complete an Insomnia Severity Index (ISI) questionnaire to screen for insomnia. If they have an ISI score > 15, they are asked for their written informed consent and are enrolled into the study. The inclusion and non-inclusion criteria are shown in box 1.

Box 1

Inclusion criteria

- Age > 18 years.
- Diagnosed with OSA and eligible for CPAP treatment under local requirements (AHI>30 with no more than 20% of central respiratory events).
- Naïve to CPAP therapy, i.e. have not been prescribed, or used CPAP in the last 5 years.
- Fluent in spoken and written French

Non-inclusion criteria

- Significant uncontrolled cardiac disease, and/or Left Ventricular Ejection Fraction (LVEF) < 45%
- Co-existing severe lung disease
- Co-existing sleep disorder, such as predominant central sleep apnoea
- Previous or current diagnosis of sleep phase delay
- Pregnancy
- Patients who are unable or unwilling to give informed consent
- Patients receiving cognitive behavioural therapy or other intervention to treat insomnia. Subjects may be using hypnotics, but there shall be no change in hypnotic use during the protocol or during the 4 weeks preceding enrolment into the study.
- Diagnosed with clinical depression and/or currently using anti-depressants and/or anxiolytics within the last 6 months.
- Hospital Anxiety and Depression (HAD) score > 8
- Participating in another research study for the duration of participation in this study.
- Patient protected by the Law, under guardianship or curators,
- Patient not covered by a health insurance

Materials

Nighttime actigraphy is monitored using a wrist actimeter (wGT3X-BT monitor ActiGraph corporation, Pensacola, FL 32502 (USA)).

The AutoCPAP device used is the ICON^{TM}+ Auto (Fisher & Paykel Healthcare Ltd (Auckland, New Zealand)). This has an integrated heated humidification system and is intended for use on adult patients for the treatment of OSA at home or in a sleep laboratory. The ICON+ treats OSA by delivering a continuous flow of air at a pressure prescribed by the physician, to maintain the airway open. In AutoCPAP mode, the device auto-adjusts the therapeutic pressure between a set minimum and maximum in response to respiratory events (apnoea, hypopnoea and flow limitation). SensAwake responsive pressure relief technology is integrated in the ICON+ Auto device and can be switched on or off. The device records adherence, efficacy, and leak values.

The choice of CPAP mask is left to the patient, physician and/or home care provider and is the same as for usual care with CPAP.

24 hour ambulatory blood pressure monitors are those normally used by the centres and are fitted and collected by qualified clinical research assistants (CRA) blinded to the study arms during weeks 1, 5 and 9 of the study.

Answers to the validated French versions of the self-reported questionnaires, ISI, ESS, PSQI, and SF-12, will be analysed as recommended by the authors of the questionnaires.

Baseline data collection

All patients wear a wrist actimeter for 1 week to record baseline sleep data. Participants are issued with and trained in the use of the actimeter and a sleep diary. During this week, blood pressure is monitored for one 24 hour period. Patients return to the centre for download of

actigraphy data and randomisation. They are asked by a Clinical Research Assistant (CRA) to complete the following questionnaires: ISI, ESS, PSQI and SF-12.

Randomisation

Participants are block randomised via a secure electronic website to receive either AutoCPAP with or without SensAwake.

- SensAwake 'off' arm: SensAwake will be turned off.
- SensAwake 'on' arm: SensAwake will be turned on, and the SensAwake pressure will be set to 4cmH_2O. If the patient is not comfortable with this pressure it can be increased to a maximum of 6 cmH_2O.

The allocation list was generated by a statistician independent from the study investigators.

Treatment

Participants receive training in use of the AutoCPAP device as per usual care. Usual care is standardized across the participating centres. Participants receive in-home therapy for four weeks. During the last week of arm one, blood pressure is monitored over one 24 hour period, whereas the actimeter is worn during the 4 weeks of each treatment arm.

Crossover

Participants return to the centre for the crossover study visit. Full AutoCPAP data (recorded by the device) and actigraphy data are downloaded. They again complete the following questionnaires: ISI, ESS, PSQI and SF-12, and are issued with a new sleep diary. The patient's AutoCPAP device is switched over to the opposite treatment arm by the study coordinator (who is not blinded). Participants receive at-home therapy for a further four weeks. During the last week of arm two, blood pressure is monitored over one 24 hour period.

End of study

Participants attend the study centre where full AutoCPAP data (entire folder on the device 's USB) and actigraphy data are downloaded; they hand in their sleep diaries and again complete the ISI, ESS, PSQI and SF-12 questionnaires. If patients prefer the AutoCPAP with SensAwake, they will be able to continue to use this feature after the conclusion of the study. Participants may obtain a summary of trial results after these have been submitted for publication.

Withdrawal and stopping criteria

Patients have the right to withdraw from the study at any time. In addition, the investigators may withdraw a patient at any time for the following reasons: protocol violation, serious illness or adverse event.

Data management

Sample size

The sample size has been based upon an assumption of a WASO of 58 ± 32 minutes,[33] taking a difference in the mean between the two groups of 15 minutes or more to be clinically significant. An independent statistician estimated a required minimum sample size of 40 (20 in each group) for 80% power. In a cross-over study it is advised to over-recruit to allow for dropouts, so the minimum sample size was set at 48 (24 per group) to allow for 20% drop out, with 12 patients included by each of the four university hospital study centres (Grenoble, Angers, and two Paris hospitals: Bichat and Lariboisière, Assistance Publique Hopitaux de Paris).

Statistical analysis

ITT analysis

All consenting and enrolled patients will be included in the intention to treat analysis. Withdrawal and non-adherence to treatment are outcome measures and so data on any withdrawn or non-adherent patients will be included.

A complete description of the study population will be presented. Continuous variables will be expressed as median and IQR, categorical variables as frequencies and percentages. See Table 1 for all outcome measures by study visit or period.

Each four week treatment arm includes a first week "washout" period, where data will not be analysed.

Table 1. Outcome measurements at study visits

Variable	Measurement	Measurement points*
Primary endpoint		
Objective sleep quality • Wake after sleep onset (WASO)	Actigraphy**	Days 1-7 (Baseline) (Downloaded at V1) During week 4 of each treatment arm. (D 29-35 and D36-63; downloaded at V2 and V3 respectively)
Secondary endpoints		
Objective sleep quality • Total sleep time • Sleep onset latency • Sleep efficiency	Actigraphy**	Days 1-7 (Baseline) (Downloaded at V1) During week 4 of each treatment arm. (D29-35 and D36-63; downloaded at V2 and V3 respectively)
Treatment compliance	CPAP (data recorded by AutoCPAP)downloads	Weeks 2 – 4 of each treatment arm. (D15-35 and D28-35; downloaded at V2 and V3 respectively)
Subjective sleep quality, functioning and quality of life: • Sleep quality • Insomnia severity • Daytime sleepiness • Quality of life	Self-reporting questionnaires : PSQI, ISI, ESS, SF-12	Baseline (V1) on D7 Crossover visit (V2) on D35 End of study (V3) on D63
24-hour blood pressure	24 hour ambulatory	24h during Days 1-7 (Baseline)

	blood pressure monitor	24h during week 4 of Treatment arm 1 (between D29 and D35) 24h during week 4 Treatment arm 2 (between D56 and D63)

* all ±2 days; **gold standard for objective sleep quality in the home; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; ESS: Epworth Sleepiness Scale; SF-12: Short Form 12 Health Survey ; D: day(s) since inclusion; V: study visit

Repeated measures ANOVA will be used to assess differences between the two treatments for actigraphy measures (WASO, Total Sleep Time TST, Sleep Onset Latency SOL, Sleep Efficiency SE), treatment compliance, subjective questionnaire results (ISI, ESS, PSQI, and SF-12) and 24-hr blood pressure measurements (minima, maxima, mean values of the systolic, diastolic and mean arterial pressures and dipping profile). The analysis will include time and treatment as within subject factors and treatment sequence as a between subjects factor. The interaction between treatment and treatment sequence will be tested to ensure there are no carry-over effects influencing the comparison of the treatments. The missing values will be replaced by the median of each group.

Statistical data analysis will be performed using IBM SPSS Statistics version 22 and tested with a significance level of 0.05, by an independent statistician

Ethics

This study is conducted in accordance with the Declaration of Helsinki (last amended 2013), and the recommendations for Good Clinical Practice (GCP-ICHE6). The study was approved by the French regional ethics committee (CPP Sud Est V, IRB N° 6705) on 9 December 2015. All patients are required to give written informed consent before inclusion in the study.

Sponsor

The study sponsor is Fisher and Paykel Healthcare Ltd (Auckland New Zealand). Some responsibilities, such as study monitoring and vigilance are delegated to the "Direction de la Recherche Clinique" (Clinical Research Administration) at Grenoble Alps University Hospital, France. The study sponsor was involved in the study design, but plays no part in data collection, management, analysis and interpretation or writing the article. They agreed to submitting the protocol for publication.

Coordinating centre

The principal investigator is Pr. Jean-Louis Pépin and the study is coordinated by the Grenoble-Alps University Hospital centre.

Insurance

Fisher & Paykel Healthcare Ltd holds insurance through Chubb Insurance, New Zealand Limited.

Confidentiality

In accordance with the existing legislation (French Code of Public Health), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to experimental, research and people who participate, in particular with regard to their identity and the results obtained. These people, along with the investigators themselves are subject to professional secrecy.

During the biomedical research or after its termination, the collected data on persons who participate will be made anonymous before being communicated to the sponsor by the investigators (or any other specialized person). In no case will the names or addresses of the persons concerned appear.

Protocol amendments

To date there are no amendments to the protocol (CIA-151 version D, 09 Feb 2016) that was approved by the ethics committee and the French regulatory authorities.

Publication policy

All publications and presentations relating to the study will be authorised by the principal investigator. The first publication of the trial results will include the PI and the lead investigators at each of the study sites as named authors. Data from the trial can be accessed by research members at the coordinating site only.

Timelines

The trial started in June 2016; patient inclusions will end in June 2017 with expected publication of primary outcome results in 2018.

DISCUSSION

Both insomnia and obstructive sleep apnoea are frequent chronic diseases with numerous co-morbidities and high health resource related costs. A high degree of heterogeneity exists within obstructive sleep apnoea patients regarding clinical presentation, risk factors and consequences.[34] Interventional studies need to be conducted in specific subgroups of patients to progressively delineate personalized medicine for sleep apnoea.

Comorbid insomnia is often undiagnosed, undertreated, or untreated in OSA patients. Pharmacotherapy of insomnia is not recommended as a long-term treatment,[35] but insomnia can reduce tolerance and adherence of patients to CPAP therapy., The addition of

SensAwake to AutoCPAP therapy may improve the comfort of AutoCPAP therapy, and therefore may increase sleep duration, improve a patient's adherence to CPAP therapy and improve quality of life. A strength of our study is to combine objective assessments of sleep indices and patient-centred outcomes. As the addition of insomnia to OSA increases the prevalence of hypertension,[36] the valuation of blood pressure by means of 24h ambulatory BP monitoring adds another strength to the study. We will also investigate whether conjointly improving sleep apnea and sleep duration/quality will allow a better control of nocturnal blood pressure.

The results of this study will help both OSA and insomnia specialists in their decision as whether to prescribe AutoCPAP with or without Sensawake for CPAP treatment of OSA patients with insomnia. If positive, this study will be a step forward for personalized therapy in the frequent subgroup of OSA plus insomnia. The interest of different combined therapies including AutoCPAP with pressure relief with or without cognitive behaviour therapy for insomnia will be the next question to investigate.

Author contributions

JLP, FG, RV, BO, MPO, VVB and RT designed the study and wrote the study protocol,

AF, JLP wrote the article based on the study protocol

FG, MPO, RV and BO critically revised the manuscript

MB calculated the sample size and wrote the study statistical analysis plan

JLP, FG, MPO, VVB, and RT are currently including patients in the study

All authors approved the submitted manuscript

Acknowledgements

We thank Drs Marie Destors, Pascaline Priou, Wojtek Trzepizur, Helene Benzaquen, and Ruben Wanono for their advice and participation and Marie Peeters for trial management.

Funding

This study is funded by unrestricted grant from Fisher & Paykel Healthcare Limited (Auckland, New Zealand)

Competing interests

RV and BO are employed by Fisher & Paykel Healthcare Limited. None of the other authors have a competing interest to declare.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_13_____
Funding	4	Sources and types of financial, material, and other support	_15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 & 14___
	5b	Name and contact information for the trial sponsor	_12_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__12_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__12_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4_____
	6b	Explanation for choice of comparators	____4_____
Objectives	7	Specific objectives or hypotheses	____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Box 1 p 6_
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5, Adherence is an endpoint__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_8, _Usual care_
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___5_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__6 & 8___and table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____8____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____8__
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8___
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_6,8 9___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_table 1_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_an endpoint__

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____11___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____11___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___no DMC__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____none _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____11_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____12_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___9_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____9 & 13__
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_These are in French_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA __

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Combination of obstructive sleep apnoea and Insomnia treated by Continuous Positive Airway Pressure with the SensAwakeTM pressure relief technology to assist sleep: a randomised cross-over trial protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-015836.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jul-2017
Complete List of Authors:	Pepin, Jean; Hôpital Universitaire de Grenoble, Gagnadoux, Frédéric ; Bretagne Loire University, INSERM URM 1063; Angers University Hospital, Department of Pneumology Foote, Alison; Grenoble Alps University Hospital, Research Department Vicars, Rachel; Fisher & Paykel Healthcare Limited Ogra, Bhavi; Fisher & Paykel Healthcare Limited Viot-Blanc, Véronique; Assistance Publique - Hopitaux de Paris, Sleep Clinic - Lariboisière Hospital Benmerad, Meriem; Univ. Grenoble Alpes, HP2; Inserm, U1042; Grenoble Alps University Hospital, EFCR Laboratory D'Ortho, Marie-Pia; Assistance Publique - Hopitaux de Paris, Department of Physiology and Functional Exploration - Bichat Hospital Tamisier, Renaud; Univ. Grenoble Alpes, HP2; Inserm, U1042; Grenoble Alps University Hospital, EFCR Laboratory
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	SLEEP MEDICINE, Obstructive Sleep Apnoea, Continuous positive airway pressure

Combination of obstructive sleep apnoea and Insomnia treated by Continuous Positive Airway Pressure with the SensAwake™ pressure relief technology to assist sleep: a randomised cross-over trial protocol

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Word Count: Main text 2312 words, plus 1 box and 1 table

Abstract

Introduction: Obstructive Sleep Apnoea (OSA) is a common sleep breathing disorder affecting up to 17% of the middle-aged population. Continuous Positive Airway Pressure (CPAP) is the primary treatment for patients with OSA, but acceptance and adherence to therapy is sub-optimal in specific subgroups particularly those with insomnia or poor sleep quality (40–80% of OSA patients). Pressure intolerance, particularly during periods of wakefulness, inhibiting sleep onset or return to sleep, is one reason for poor CPAP adherence. AutoCPAPs continually monitor airflow changes and only increase the pressure when the upper airway requires it. Reducing the pressure during wakefulness-sleep transition and wakefulness-after-sleep-onset (WASO) may improve therapy comfort and potentially adherence without compromising therapy efficacy. We hypothesise that SensAwake™, a pressure relief function that reduces CPAP pressure on the transition from sleep to wakefulness and on WASO, may improve objective sleep quality.

Methods and analysis: This is a multicentre, randomized double-blind cross-over clinical trial on patients with both OSA and insomnia. Insomnia is defined as Insomnia Severity Index (ISI) > 15 at screening. Baseline data, including actigraphy, are collected for one week before randomisation (1:1) to either conventional AutoCPAP or AutoCPAP with SensAwake for 4 weeks. After an evaluation visit, patients are switched to the other treatment arm for a further 4 weeks. Allowing for 20% dropout, 48 patients are required. If applicable, repeated measures ANOVA will be used to assess differences in WASO measured by actigraphy (primary outcome), other actigraphy measures, AutoCPAP compliance, subjective questionnaire scores Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Short-Form 12 Health Survey) and 24-hr blood pressure (secondary outcomes).

Ethics and Dissemination: The protocol was approved by the regional Ethics Committee (CPP Sud-Est–V, IRB N°6705) on 09/12/2015, is registered on ClincalTrials.gov (NCT02721329) and started in June 2016 with expected publication of primary outcome results in 2018.

Strengths and Limitations of the study

- This multicentre randomised crossover trial could potentially lead to an alternative to conventional AutoCPAP therapy in a well-defined common OSA having a high rate of CPAP non-compliance.
- While the sample size is just sufficient to analyse objective sleep indices (primary outcome) in a crossover design, it is too small to inform on 24 hour blood pressure and patient-centred outcomes (secondary outcomes).
- The wrist actimeter used has not been previously validated for the measurement of wake-after-sleep-onset (WASO) in this specific patient phenotype associating OSA and insomnia.
- Only one night of blood pressure monitoring is done in each arm of the study. Longer ABPM would be desirable, but wearing yet another device may bias the study.
- Despite having several study sites the sample size is rather small, one limitation being the difficulties in recruitment of willing CPAP naïve patients; restricting the relevance of any secondary analyses such as those on blood pressure.

INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a common sleep breathing disorder affecting up to 17% of the middle aged population[1,2]and is characterized by periodic collapse of the upper airway during sleep. Continuous Positive Airway Pressure (CPAP) is the primary treatment for patients with OSA.[3,4] Despite the effectiveness of CPAP in abolishing upper airway obstruction, acceptance of and adherence to therapy is often sub-optimal particularly in specific phenotypes, including the combination of OSA and insomnia[5,6] or insomnia symptoms.[7]

Pressure intolerance is one possible reason for this lack of adherence. Conventional CPAP generally delivers higher pressure than necessary for much of the night as the needed CPAP pressure is selected based either on one night's titration (in a sleep laboratory) or during several nights at home and pressure requirements can vary considerably with sleeping posture, sleep stage and environmental influences such as alcohol and sedative use.[89] AutoCPAPs address this problem by continually monitoring airflow changes and only increasing the pressure when the upper airway requires it. Research suggests that AutoCPAP generally delivers an overall lower mean treatment pressure than conventional CPAP.[10-16] Despite this, there is limited evidence to suggest that AutoCPAP therapy can considerably improve CPAP adherence and acceptance in an unselected population, but this might be different in OSA patients with concurrent insomnia.[10,14 ,17 -23]

Conceptually, a patient's awareness of pressure occurs only during wakefulness. Thus reducing the pressure during wakefulness may improve therapy comfort and potentially adherence without compromising therapy efficacy. SensAwake™ (Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) is a pressure relief technology that accurately detects irregularity in the flow signal indicative of the transition from sleep to wake.[24] When the

transition from sleep to wake is detected, the device promptly reduces the pressure to help facilitate a return to sleep. CPAP/Auto CPAP with SensAwake has been used in the general OSA population and has been shown to provide the same treatment efficacy at a lower overall pressure as CPAP/Auto CPAP without SensAwake[25,26] and patients have judged it to be more comfortable and preferred it to CPAP without SensAwake.[27]

The prevalence of insomnia symptoms in OSA patients is estimated to be 40 – 80%,[7,28-32] and existence of insomnia has been shown to negatively affect CPAP compliance in some studies.[33,34] It is proposed that insomnia patients are preoccupied with external factors that may be perceived as a threat to sleep, which results in a higher wake-after-sleep-onset (WASO), the amount of time a person spends awake from when they first fall asleep to when they do not attempt to go back to sleep. Besides wakening it takes account of difficulty in getting back to sleep, that may be further exacerbated by the presence of CPAP.[33] It is therefore hypothesized that the pressure relief that SensAwake provides during wakefulness may be of a greater benefit to patients with OSA and insomnia if it can facilitate the return to sleep. There is no known published data on the use of SensAwake in the OSA/Insomnia population.

Primary research objective

The primary objective is to compare the at-home objective sleep quality (WASO) when using AutoCPAP with SensAwake versus AutoCPAP without SensAwake in patients with a diagnosis of OSA and insomnia.

Secondary Research Objectives

The secondary objectives are to compare AutoCPAP compliance, other measures of objective sleep quality (total sleep time (TST), sleep onset latency (SOL) and sleep efficiency

(SE)), daytime sleepiness, subjective sleep quality, insomnia, quality of life, and 24h blood-pressure.

METHODS AND ANALYSIS

Study Design

This is multicentre prospective 1:1 randomised, double-blind, crossover trial.

Patient entry and screening for insomnia

Out-patients diagnosed with OSA by Polysomnography (PSG) at one of the participating tertiary hospital sleep centres (Grenoble, Angers, and Bichat and Lariboisière hospitals in Paris, France) between November 2016 and October 2017, eligible for CPAP treatment under local requirements (Apnoea Hypoxia Index (AHI) >30 with no more than 20% central respiratory events) are asked to answer an Insomnia Severity Index (ISI) questionnaire[35] to screen for insomnia. If they meet the study inclusion/non-inclusion criteria (Box 1) they are asked by the sleep physician for their written informed consent (available as a supplementary file) and are enrolled into the study.

Box 1

Inclusion criteria

- Age > 18 years.
- Diagnosed with OSA and eligible for CPAP treatment under local requirements (AHI>30 with no more than 20% of central respiratory events).
- Naïve to CPAP therapy, i.e. have not been prescribed, or used CPAP in the last 5 years.
- Insomnia Severity Index (ISI) score > 15
- Fluent in spoken and written French

Non-inclusion criteria

- Significant uncontrolled cardiac disease, and/or Left Ventricular Ejection Fraction (LVEF) < 45%, and/or severe lung disease
- Co-existing sleep disorder, such as predominant central sleep apnoea
- Previous or current diagnosis of sleep phase delay
- Pregnancy
- Patient receiving cognitive behavioural therapy or other intervention to treat insomnia. Subjects may be using hypnotics, but there shall be no change in hypnotic use during the protocol or during the 4 weeks preceding enrolment into the study.
- Diagnosed with clinical depression and/or Hospital Anxiety and Depression (HAD) score > 11 and/or currently using anti-depressants and/or anxiolytics within the last 6 months.
- Participating in another clinical trial for the duration of participation in this study.
- Patient protected by the Law, under guardianship or curatorship,
- Patient not covered by a health insurance
- Patient unable or unwilling to give informed consent

Materials

Nighttime actigraphy, the gold standard for measuring objective sleep quality in the home, is recorded using a wGT3X-BT wrist monitor from ActiGraph, (Pensacola, FL 32502 USA). This is a standard actigraphy device that uses an adapted version of the Cole-Kripke Algorithm.[36,37]

The AutoCPAP device is the ICON^{TM}+Auto from Fisher & Paykel Healthcare Ltd (Auckland, New Zealand)). This has an integrated heated humidification system and is intended for use on adult patients for the treatment of OSA at home or in a sleep laboratory. The ICON+ treats OSA by delivering a continuous flow of air at a pressure prescribed by the physician to maintain the airway open. In AutoCPAP mode, the device auto-adjusts the therapeutic pressure between a set minimum and maximum in response to respiratory events (apnoea, hypopnoea and flow limitation). SensAwake responsive pressure relief technology is a comfort feature that is available in the ICON+ Auto device. It functions by detecting wakefulness using the flow signal and promptly reduces the pressure to a more comfortable level to allow the patient to return to sleep. The ICON+ records and reports industry standard metrics such as adherence, leaks, and treatment efficacy data.

The choice of CPAP mask is left to the patient, physician and/or home care provider and is the same as for usual care with CPAP.

24 hour ambulatory blood pressure monitors are those normally used by the centres and are fitted and data collected by qualified clinical research assistants (CRA) blinded to the study arms during weeks 1, 5 and 9 of the study.

Answers to the validated French versions of the self-reported questionnaires: ISI, Epworth Sleepiness Scale (ESS)[38], Pittsburgh Sleep Quality Index (PSQI)[39] and Short-Form 12 Health Survey (SF-12)[40] will be analysed as recommended by the authors of the questionnaires.

Baseline data collection

All patients wear a wrist actimeter for 1 week to record baseline sleep data. Participants are issued with and trained in the use of the actimeter and a sleep diary. The diary (from Fisher & Paykel Healthcare Ltd) requires participants to record each morning what time they went to bed, what time they went to sleep, what time they woke up, and what time they got up. During this week, blood pressure is monitored for one 24 hour period. Patients return to the centre for download of actigraphy data and randomisation. They complete the following questionnaires: ISI, ESS, PSQI and SF-12 supervised by a CRA.

Randomisation

Participants are block randomised via a secure electronic website to receive AutoCPAP either with or without SensAwake.

- SensAwake 'off' arm: SensAwake function off. OR
- SensAwake 'on' arm: SensAwake function on. When wakefulness is detected, SensAwake will automatically drop the pressure to the set SensAwake pressure. In the ICON+ Auto Device, the minimum pressure, is also the SensAwake pressure. The SensAwake pressure is the pressure that the device will drop to during wakefulness. So if the patient is experiencing a pressure of 12cm H20, and their SensAwake pressure is 4cm H20, then it will drop from 12cm H20 to 4cm H20. The default SensAwake pressure is set to 4cm H20, however, for patients with higher therapeutic pressures, 4cm may be too low and result in discomfort. Therefore, the SensAwake pressure can be increased to 6cm H20 to account for this.

The allocation list was computer generated by a statistician independent from the study investigators.

Treatment

Participants receive training in use of the AutoCPAP device as per usual care. Usual care is standardized across the participating centres. Participants receive in-home therapy for four weeks. During the last week of arm one, blood pressure is monitored over one 24 hour period, whereas the actimeter is worn during the 4 weeks of each treatment arm.

Crossover

Participants return to the centre for the crossover visit. Full AutoCPAP data (recorded by the device) and actigraphy data are downloaded. They again complete the questionnaires: ISI, ESS, PSQI and SF-12, and are issued with a new sleep diary. The patient's AutoCPAP device settings are switched over to the opposite treatment arm by the site coordinator without showing them to or discussing them with the patient or disclosing the settings to the physician. Participants receive at-home therapy for a further four weeks. During the last week of arm two, blood pressure is monitored over one 24 hour period.

End of study

Participants attend the study centre where full AutoCPAP data (entire folder on the device's USB) and actigraphy data are downloaded; they hand in their sleep diaries and again complete the ISI, ESS, PSQI and SF-12 questionnaires. If patients prefer the AutoCPAP with SensAwake, they will be able to continue to use this feature after the conclusion of the study. Participants may obtain a summary of trial results after these have been submitted for publication.

Withdrawal and stopping criteria

Patients have the right to withdraw from the study at any time. In addition, the investigators may withdraw a patient at any time for the following reasons: protocol violation, serious illness or adverse event. In the event of a serious adverse event unblinding may be done through the site coordinator.

Statistics

Sample size

The sample size was calculated based upon an assumption of a WASO of 58 minutes ± SD[41] and allowing for the crossover nature of the study. It assumes that the standard deviation of the difference between the two treatments is approximated by the standard deviation derived from WASO single time assessments. The largest estimate of the WASO between individual SD was used: 46 minutes in Natale et al.[41] On this basis a sample size of 40 completers of both treatments is required (2 sequence groups of 20/group each) to detect a difference of 15 minutes or more as statistically significant (two-tailed alpha=0.05) with 80% power. In a cross-over study it is advised to over-recruit to allow for dropouts, so the minimum sample size was set at 48 (24 per group) to allow for 20% drop out, with 12 patients per centre.

Statistical analysis

All consenting and enrolled patients will be included in the intention to treat analysis. Withdrawal and non-adherence to treatment are outcome measures, thus data on any withdrawn or non-adherent patients will be included.

A complete description of the study population will be presented with continuous variables expressed as median and inter-quartile range (IQR), and categorical variables as frequencies and percentages. See Table 1 for all outcome measures by study visit or period.

Each four week treatment arm includes a first week “washout” period, where data will not be analysed.

Table 1. Outcome measurements at study visits

Variable	Measurement	Measurement points*
Primary endpoint		
Objective sleep quality • Wake after sleep onset (WASO)	Actigraphy	Days 1-7 (Baseline) (Downloaded at V1) During week 4 of each treatment arm. (D 29-35 and D56-63; downloaded at V2 and V3 respectively)
Secondary endpoints		
Objective sleep quality • Total sleep time • Sleep onset latency • Sleep efficiency	Actigraphy	Days 1-7 (Baseline) (Downloaded at V1) During week 4 of each treatment arm. (D29-35 and D56-63; downloaded at V2 and V3 respectively)
Treatment compliance	CPAP (data recorded by AutoCPAP)downloads	Weeks 2 – 4 of each treatment arm. (D15-35 and D28-35; downloaded at V2 and V3 respectively)
Subjective sleep quality, insomnia, daytime sleepiness and quality of life: • Sleep quality • Insomnia severity • Daytime sleepiness • Quality of life	Self-reporting questionnaires : PSQI, ISI, ESS, SF-12	Baseline (V1) on D7 Crossover visit (V2) on D35 End of study (V3) on D63
24-hour blood pressure	24 hour ambulatory blood pressure monitor	24h during Days 1-7 (Baseline) 24h during week 4 of Treatment arm 1 (between D29 and D35) 24h during week 4 Treatment arm 2 (between D56 and D63)

* all ±2 days; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; ESS: Epworth Sleepiness Scale; SF-12: Short Form 12 Health Survey ; D: day(s) since inclusion; V: study visit

Repeated measures ANOVA will be used to assess differences between the two treatments for actigraphy measures (WASO, Total Sleep Time (TST), Sleep Onset Latency (SOL), Sleep Efficiency (SE)), treatment compliance, subjective questionnaire results (ISI, ESS, PSQI, and SF-12) and 24-hr blood pressure measurements (minima, maxima, mean values of the

systolic, diastolic and mean arterial pressures and dipping profile). If requirements for parametric repeated measures ANOVA are not met then a non-parametric Wilcoxon signed-rank test will be used. The analysis will include time-related factors (WASO, TST, SOL) and treatment as within subject factors and treatment sequence as a between subjects factor. The interaction between treatment and treatment sequence will be tested to ensure there are no carry-over effects influencing the comparison of the treatments. In the case of missing data for the primary outcome it will be derived from the available WASO data at both post treatment times (V2, V3). For both post treatment times, missing data will be imputed from baseline outcome measures and any post baseline assessments. Statistical data analysis will be performed using IBM SPSS Statistics version 22 and tested with a significance level of 0.05, by an independent statistician.

Ethics

This study is conducted in accordance with the Declaration of Helsinki (last amended 2013), and the recommendations for Good Clinical Practice (GCP-ICHE6). The protocol (F&P CIA-151 version C) was approved by the French regional ethics committee (CPP Sud Est V, IRB N° 6705) on 9 December 2015. The final version (F&P CIA-151 version E/ID-RCB: 2015-A00135-44) including changes requested by the French regulatory authority (ANSM) in February 2016 and amendments post start of patient inclusions aimed at improving enrolment (inclusion period increased, HAD score >11 instead of 8) was approved on 2 May 2017. All patients are required to give written informed consent before inclusion in the study.

Sponsor and Coordination

The study sponsor is Fisher and Paykel Healthcare Ltd (15 Maurice Paykel Place, East Tamaki, Auckland, New Zealand) and was involved in study design. The sponsor holds insurance through Chubb Insurance, New Zealand Limited. The Grenoble-Alps University Hospital centre is

coordinating the study and the principal investigator is Pr. Jean-Louis Pépin. Monitoring, vigilance and communication of important protocol modifications are delegated to the "Direction de la Recherche Clinique" (Clinical Research Administration) at Grenoble Alps University Hospital, France.

Confidentiality

In accordance with French legislation people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to experimental, research and people who participate, in particular with regard to their identity and the results obtained.

The collected data will be made anonymous before being communicated to the sponsor (or to any other specified specialist). In no case will the names or addresses of the persons concerned appear. Anonymised data from the trial can be accessed by research members at the coordinating site only.

DISCUSSION

Both insomnia and obstructive sleep apnoea are frequent chronic diseases with numerous co-morbidities and high health resource related costs. A high degree of heterogeneity exists within obstructive sleep apnoea patients regarding clinical presentation, risk factors and consequences.[42] Interventional studies need to be conducted in specific subgroups of patients to progressively delineate personalized medicine for sleep apnoea. Likewise, insomnia has a broad spectrum of causes, among them being CPAP use. This is why we chose to include only CPAP naïve patients; although this may restrict our enrolment rate.

Comorbid insomnia is often undiagnosed, undertreated, or untreated in OSA patients. Pharmacotherapy of insomnia is not recommended as a long-term treatment[43] but insomnia

can reduce tolerance and adherence of patients to CPAP therapy., The addition of SensAwake to AutoCPAP may improve the comfort of AutoCPAP therapy, and therefore may increase sleep quality and duration, improve a patient's adherence to CPAP therapy and improve quality of life. One strength of our study is to combine objective assessments of sleep indices and patient-centred outcomes. As the addition of insomnia to OSA increases the prevalence of hypertension,[44] the valuation of blood pressure by means of 24h ambulatory BP monitoring adds another strength to the study. We will also investigate whether conjointly improving sleep apnoea and sleep duration/quality will allow a better control of nocturnal blood pressure.

The results of this study will help both OSA and insomnia specialists in their decision as whether to prescribe AutoCPAP with or without Sensawake for CPAP treatment of OSA patients with insomnia. If positive, this study will be a step forward for personalized therapy in the frequent subgroup of OSA plus insomnia.

Author contributions

JLP, FG, RV, BO, MPO, VVB and RT designed the study and wrote the study protocol,

AF, JLP wrote the article based on the study protocol

FG, MPO, RV and BO critically revised the manuscript

MB calculated the sample size and wrote the study statistical analysis plan

JLP, FG, MPO, VVB, and RT are currently including patients in the study

All authors approved the submitted manuscript

Acknowledgements

We thank Drs Marie Destors, Pascaline Priou, Wojtek Trzepizur, Helene Benzaquen, and Ruben Wanono for their advice and participation, Marie Peeters for trial management and Rebecca Thomson for help in revising the manuscript.

Funding

This study is funded by unrestricted grant from Fisher & Paykel Healthcare Limited (Auckland, New Zealand)

Competing interests

RV and BO are employed by Fisher & Paykel Healthcare Limited. None of the other authors have a competing interest to declare.

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Supplementary file

- Patient Information and consent form (original versions are in French)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_12_____
Funding	4	Sources and types of financial, material, and other support	_15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 & 14___
	5b	Name and contact information for the trial sponsor	_12_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__12_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__12_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4_____
	6b	Explanation for choice of comparators	____5_____
Objectives	7	Specific objectives or hypotheses	____5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___6 and ClincalTrials.gov (NCT02721329)__ ___
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Box 1 p 6_
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5, Adherence is an endpoint__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_8-9, _Usual care_
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___5_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__6 & 8___and table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___9-10___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____12_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____8____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____8__
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__8___
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_6,8 9___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_table 1_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_an endpoint__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____12-13___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___11-12___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____12____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___no DMC__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____none _____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___13_(as per usual monitoring procedures)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____12_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____13_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____12-13_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____13_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___9_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____9 & 13__
	31b	Authorship eligibility guidelines and any intended use of professional writers	_per ICMJE____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___none as yet_
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Translations from French originals available as supplementary documentation _

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA __

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.