Study Title: CPAP Treatment with SensAwake™ in Post-Traumatic-Stress-Disorder

NCT Number: NCT02549508

Document Date: 06 June 2014

HUMAN RESEARCH PROTOCOL APPLICATION

SUBJECT: IRB REVIEW AND APPROVAL

1. Follow this template and instructions to prepare your protocol. The contents of a protocol should include all the sections in the template. Sections in **bold letters** are to be retained and completed in the final protocol. Any BLUE text must be deleted before submission. Answer NA to any section or subsection that is not applicable.

2. Please use a consistent font, 12 pt, left justified, single spaced.

For assistance, POC: Department of Research Programs, WRNMMC 301-295-8239

WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC)
BETHESDA, MD

1. GENERAL INFORMATION

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1.6 Medical / Research Monitor
NA

1.7 Study Team Responsibilities

Responsibilities	Principal Investigator	Associate Investigator	Collaborator
▪ Study design and general coordination of research	X	X	X
▪ Provide access to subjects	X		
▪ Recruit eligible subjects	X	X	
▪ Screen eligible subjects	X	X	
▪ Obtain informed consent/parental permission/child's assent	X	X	
▪ Conduct research procedures involving direct interaction with subjects	X	X	
▪ Clinical laboratory tests or support	NA	NA	NA
▪ Research laboratory assays, tests, or support	NA	NA	NA
▪ Pharmacy support (i.e. storage, inventory, and dispensing of all investigational drugs used in the research)	NA	NA	NA
▪ Data entry		X	
▪ Data analysis	X	X	
▪ Storing/sharing research data	X	X	
▪ Storing research protocol documents (including consent/information sheets)	X	X	
▪ Storing/sharing specimens for current research	NA	NA	NA
▪ Storing/sharing specimens for future research	NA	NA	NA
▪ Reporting to appropriate IRB(s), institutional officials, and /or sponsor - unanticipated problems involving risks to subjects or others, adverse events, and serious or continuing non-compliance	X	X	
▪ Establishing procedures to ensure subject privacy and confidentiality of research data (DoD 6025.18R; 45 CFR 160 and 164).	X	X	X
▪ Continuing Review by the IRB	X	X	
▪ Post-approval monitoring of the conduct of the research	X	X	X
▪ Data monitoring plan – coordination and communication	X	X	X
▪ Clearance of research-related publications or presentations	X	X	X

2. ABSTRACT

2.1 Purpose
The overall purpose of this research is to examine the application of AutoCPAP with and without SensAwake in subjects with Post-Traumatic Stress Disorder (PTSD), and evaluate whether patients achieve better sleep quality and compliance with SensAwake, compared to the same treatment without SensAwake.

2.2 Research Design
Prospective, randomized, cross-over study.

2.3 Methodology /Technical Approach
All patients diagnosed with OSA and PTSD, and a prescription for Auto CPAP therapy will be approached to take part in the study.

3. OBJECTIVES AND SPECIFIC AIMS

Objective: To compare the effect of AutoCPAP with SensAwake pressure relief to AutoCPAP without SensAwake pressure relief on the comfort and compliance of CPAP therapy in patients with OSA and PTSD.

Hypothesis: AutoCPAP with SensAwake will improve patient comfort and compliance in the PTSD and OSA patients who are naïve to CPAP therapy.

Primary Outcomes:

- Adherence with treatment per night averaged over total time period measured via internal software on the device and reported on using InfoSmart™ software.
- CPAP Acceptance (number of drop outs) – collected for the first treatment arm only.

Secondary Outcomes:

- Subjective sleep quality (Epworth Sleepiness Scale [ESS], Insomnia Severity Index [ISI], sleep diary)
- Subjective treatment efficacy (Patient Global Impression of Change [PGI])
- OSA impact of daily life (Fatigue Severity Scale [FSS], Short Functional Outcomes of Sleep Questionnaire [FOSQ-10])
- Advanced CPAP data: all information collected by the ICON+ CPAP device will be downloaded and collected for the purpose of analysis.
- Complaints during follow up calls and four week visit.
- Objective sleep quality (ActiSleep device – TST (total sleep time), WASO (wake after sleep onset), Sleep efficiency (SE)).

For all questionnaires and sleep diary please see appendix A

4. BACKGROUND AND SIGNIFICANCE

4.1 Literature Review.

Obstructive Sleep Apnea (OSA) is a common sleep breathing disorder affecting around 2-4% 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 with therapy has been sub-optimal.[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 on one night 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.[8,12,15-21]

Conceptually, 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™ is a unique pressure relief technology developed by Fisher & Paykel Healthcare which detects irregularity in the flow signal indicative of the transition from sleep to wake. When the transition from sleep to wake is detected the device promptly reduces the pressure to help facilitate a return to sleep.

OSA has been shown to be more common in the PTSD population, with prevalence estimates ranging from 11.9 to 90%.[22-27] Patients with PTSD have been shown to have reduced CPAP adherence compared to controls (2.5±1.8 versus 4.2±2.1 hours per night, averaged over all nights in the study period)[28] and a suggested higher wake after sleep onset (WASO) than normal controls.[29] Therefore, it is hypothesized that SensAwake will be of even greater benefit to OSA patients with PTSD due to the pressure relief provided during wakefulness.

The purpose of this study is to compare adherence and sleep quality outcomes in patients with OSA and PTSD, treated by CPAP with and without SensAwake technology.

4.2 Preliminary Data and/or Findings.
There is no known data for the use of SensAwake in the PTSD/OSA population.

SensAwake has been shown to be able to accurately detect the transition from sleep to wake[30] CPAP/AUTOCPAP 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/AUTOCPAP without SensAwake[31,32] and patients have judged it to be more comfortable and preferred to CPAP without SensAwake.[33]

4.3 Scientific Justification.
As SensAwake provides pressure relief during awake periods, it conceptually would improve comfort with therapy in the general population. More particularly, patients with

high wake after sleep onset (WASO), such as those with PTSD, stand to benefit more from the comfort provided by SensAwake, easing their return to sleep.

4.4 Human Subjects Justification.
The purpose of this study is to evaluate the comfort and compliance of CPAP therapy in patients with OSA and PTSD, therefore the inclusion of human subjects is required to accomplish study goals. Inclusion in the study is not likely to subject any further medical risk to the patient than which they would be subjected to under normal treatment.

5. PLAN

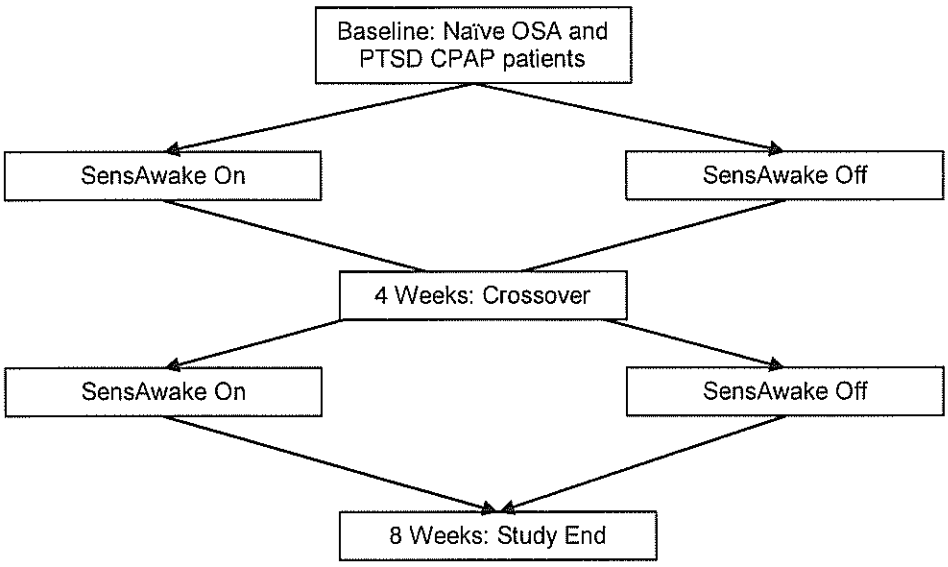
5.1 Study Design

This a prospective, randomized, cross-over trial of 50 patients who will have polysomnography, and a diagnosis of OSA, with a prescription for AutoCPAP, and PTSD as part of normal clinical practice. The anticipated total study duration (for patient recruitment and collection of data is 1 year from the start-date (after the protocol approval letter received). The number of visits for each patient will be 3 visits, although patients may receive further follow-up visits is required as part of normal clinical practice.

Patients will be randomized into two groups – a SensAwake group and a non-SensAwake group. Randomization will be completed by a randomization table. The non-SensAwake group will receive AutoCPAP therapy as normal with a Fisher & Paykel Healthcare ICON+, with the minimum pressure set to 4cmH2O and the maximum pressure set to 18cmH2O (as is default in the machines), and with SensAwake disabled. The SensAwake group will receive AutoCPAP therapy as normal with a Fisher & Paykel Healthcare ICON+, with the minimum pressure set to 4cmH2O and the maximum pressure set to 18cmH2O (as is default in the machines), and with SensAwake turned on and the SensAwake pressure set at 4cmH2O (default). After 4 weeks (28 ± 3 days), the two arms of the study will crossover. Patients will be blinded into which arm of the study they are in (study devices are the same for each arm of the study).

Patients will undergo in home treatment for 4 weeks (28 ± 3 days) on the first arm of the study, during which time they will complete a daily sleep diary. After the 4 weeks of treatment, they will come in for their cross-over visit. At the cross-over visit, their CPAP efficacy and compliance data will be downloaded from their machine, and they will answer several questionnaires (ESS, ISI, PGI, FSS and FOSQ-10). At the end of the visit, the device settings will be changed to cross them over to the other arm of the study.

Patients will undergo in home treatment for 4 weeks (28 ± 3 days) on the second arm of the study, during which time they will complete a daily sleep diary. After the 4 weeks of treatment, they will come in for their final visit. Their CPAP efficacy and compliance data will be downloaded from their machine, and they will answer (ESS, ISI, PGI, FSS and FOSQ-10).



5.2 Anticipated Requirements

a. WRNMMC pulmonary function and sleep lab.

b. Recruitment for the study is anticipated to take 6 months. Each patient will receive study follow-up for 8 weeks (56 ± 6 days) from their date of enrolment. This will encompass initial and two follow-up visits (crossover visit at 4 weeks (28 ± 3 days), final visit at 8 weeks (56 ± 6 days)). Any additional visits (initiated by the patient) will be recorded in a log.

c. This study is funded by Fisher & Paykel Healthcare. This incorporates:
   1. $5,000 grant
   2. 50 CPAP Devices (Fisher & Paykel Healthcare ICON+, to be kept by the patient at the end of the study)
   3. 16 ActiSleep devices (to be returned to Fisher & Paykel Healthcare at the end of the study)

5.3 Subject Population

a. Male and female military health care beneficiaries age 18 years and older presenting with the diagnosis of obstructive sleep apnea and post-traumatic stress disorder.

b. All patients who have been referred to the Sleep Disorders Clinic, who are diagnosed with OSA and have an existing diagnosis of PTSD will be asked to participate in the study.

5.4 Sample Inclusion and Exclusion Criteria

a. Inclusion Criteria

- Male and female subjects > 18 years

- Diagnosed with OSA by a practicing sleep physician, within the last six months
- Diagnosed with post-traumatic stress disorder as diagnosed by a behavioral health professional, and quantified by McChord PTSD checklist
- All races and ethnicities will be included
- Naïve to CPAP therapy (has not used CPAP within the last 5 years)

b. Exclusion Criteria

- < 18 years of age
- if mental status is questionable, the patient will be excluded at the discretion of the consenting provider
- Unable/unwilling to follow the directions necessary for CPAP use
- Patients contraindicated for CPAP/AutoCPAP, at the discretion of the consenting provider

5.5 Study Methodology/Procedures

5.5.1 Describe when, where and how the study subjects will be identified and recruited.

All patients in the Sleep Disorders Clinic that are diagnosed with OSA after polysomnography, and with an existing diagnosis of PTSD will be invited to participate in the study prior to randomization. Patients will be screened prior to consent for exclusions.

5.5.2 Consent Process

a. The Consent/HIPAA form will be provided to all patients at the Sleep Disorders Clinic, for review prior to their PSG review appointment (in the waiting room). They will be counseled by one of the study investigators that they may participate in the study if they so choose.
b. All patients will be given a written copy of their consent which includes a written explanation of the study.
c. Patients will be consented at the initial visit. They will not need to repeat the consent process at follow-up visits as detailed above.

5.5.3 Compensation for participation

Subjects will not receive compensation for participating in this study. Subjects will be able to keep the study CPAP device if they wish to continue with therapy at the end of the study.

5.5.4 Research Interventions

Baseline (Screening)
Following a standard of care diagnostic PSG as per the site's operating procedures, eligible subjects will be offered participation in the study. Participants will undergo informed consent and screening prior to any investigational procedures taking place.

Consenting subjects will then be block randomized to either ICON Auto CPAP with or without SensAwake. To obtain adequate blinding, the devices will be set to 'Simple Mode', so that the participants cannot see the pressure settings;

- SensAwake 'off' arm: SensAwake will be turned 'off' in the clinician menu.
- SensAwake 'on' arm: SensAwake will be turned 'on' in the clinician menu, and the SensAwake/minimum pressure will be set to 4 cmH2O, if the patient is not comfortable with this pressure it can be increased to a maximum of 6 cmH2O. In the event a patient is not comfortable on 6 cmH2O and a higher pressure is required this must be approved by the trial sponsor.

All participants will complete baseline questionnaires (ESS, II, PGI, FSS, FOSQ-10). Participants will also be issued and trained on the use of the sleep diary (sleep diary will consist of four weeks data, a new diary will be issued when crossover occurs) and ActiSleep device (if applicable). There will be 16 ActiSleep devices available for the trial, participants will be set-up on a device if available. When a participant with the ActiSleep watch completes the study it can be cleaned and re-used on the next participant recruited in the trial.

Week Four (Crossover)
Participants will return to the facility for a daytime appointment. At the conclusion of the treatment arm full CPAP data (entire FPHCARE folder on InfoUSB of device) data will be downloaded from each participants CPAP, and actigraphy data will be downloaded from the ActiSleep device (if applicable). All participants will complete the following questionnaires - ESS, ISI, PGI, FSS, FOSQ-10, at this time-point, and will be issued with a new sleep diary. The participants device will be swapped over to the opposite treatment arm by the study coordinator (who is not blinded).

Eight weeks (study end)
All participants will attend a daytime appointment at the site. At the conclusion of the study full CPAP data (entire FPHCARE folder on InfoUSB of device) will be downloaded from each participant's CPAP, and actigraphy data will be downloaded from the ActiSleep device (if applicable). All participants will complete all questionnaires (ESS, ISI, PGI, PGI-T, FSS, FOSQ-10) at the end of the study. Participants will return their sleep diary and ActiSleep device (if applicable), accessories and packaging to the investigators. Participants will be unblinded, and will get to choose which arm they would like to return to standard care on. Participants will be able to keep the trial CPAP if they wish to, or they may return to another prescribed CPAP device..

5.5.5 Data Collection

Demographic variables:

- Age
- Gender
- Race (self-identified)
- Rank (active duty)
- Branch of service

Clinical variables:

- Height

- Weight
- Body mass index
- Self-reported Pregnancy status
- History of asthma, COPD, restrictive lung disease, vocal cord dysfunction, pulmonary embolism, congestive heart failure, atrial fibrillation, ischemic heart disease, non-specific lung disease, non-specific heart disease, history of obstructive sleep apnea, central sleep apnea, obesity hypoventilation syndrome, insomnia, non-specified sleep disorder,
- History of CPAP use
- History of post-traumatic sleep disorder

5.5.6 Collection of Human Biological Specimens

N/A

5.5.7 Banking of Human Biological Specimens

N/A

5.5.8 Study Time Line

Patients will be evaluated at their initial visit and follow-up visits.

Each patient will have a unique numeric identifier. For example, "0009." 0009-1 is the initial visit, and 0009-2 is a follow-up, 0009-3 is a second follow-up, and so on.

EVENTS	Before baseline	Baseline	4 wks	8 wks
Screening	X			
Informed Consent		X		
Demographics		X		
Questionnaires: ESS, ISI, PGI, FSS, FOSQ-10		X		
Issue sleep diary		X		
Issue actigraphy device (if applicable)		X		
Commence in-home trial on investigational device		X		
CPAP and actigraphy data downloaded (if applicable for actigraphy)			X	
Return sleep diary, issued new sleep diary			X	
Questionnaires: ESS, ISI, PGI, FSS, FOSQ-10			X	

Crossover treatment arm			X	
CPAP and actigraphy data downloaded (if applicable for actigraphy)				X
Questionnaires: ESS, ISI, PGI, PGI-T, FSS, FOSQ-10				X
Return sleep diary and actigraphy device				X
Switched to preferred treatment method				X

5.6 Investigational Drugs/ Investigational Devices

5.6.1 Approval Status of Study Drugs

N/A

5.6.2 Approval Status of Study Devices

The study device is FDA-approved device (510(k) number K094040. The product codes for the study device are listed below:

ICON+ AUTO	ICONAAN, ICONAAN-HT, ICONAAJ

5.7 Statistical Considerations

5.7.1 Data Analysis Table

The primary and secondary outcomes measured are tabulated below, each measured at baseline and at 4 weeks after the first phase of the study and at 8 weeks after the second phase.

Variable	**Measured as**
CPAP compliance	Hours used
Treatment Efficacy	Apnea-Hypopnea Index
Patient QOL	ESS, ISI, FSS, FOSQ-10 Questionnaires
Patient Comfort	PGI Questionnaire
Subjective sleep quality	Subject sleep diary
Objective sleep quality	ActiSleep device – TST, WASO, SE (if applicable)

The outcome measures will be compared between the two treatments using a repeated measures ANOVA. The sequence of treatments will be entered as a fixed between-subject

factor and treatment (SensAwake on or off) as a within subject factor.
Baseline demographic and clinical data will be summarised for the entire cohort suing standard descriptive statistics including means, medians standard deviations, ranges and frequencies and percentages.
Additional analyses will explore the effects of baseline measures on CPAP compliance for both treatments.

5.7.2 Sample Size Estimation

Existing data suggests that CPAP adherence without SensAwake is likely to average 2-3 hours over the 4 week period, for this patient population[28]. For SensAwake to provide a clinically significant improvement in adherence this would need to improve by at least 0.5 hours. For this crossover design if 50 participants are randomized and complete both phases of the study the study will have sufficient power to show a difference of 0.5 hours or more as statistically significant (2-tailed α=0.05) with 80% power. This calculation assumes a within-subject standard deviation of 0.9 hours.

6. HUMAN SUBJECT CONSIDERATIONS

6.1 Anticipated Benefits

Direct benefit: Participants may benefit from participation by improved comfort and compliance with their CPAP therapy. Participants will be able to choose either treatment mode at the end of the study.

6.2 Risks and Discomforts

Physical:

- More likely risks are dryness/nasal congestion, and general discomfort with CPAP therapy. This can often be attenuated with heated humidification of the CPAP air, which will be available to all subjects in this study. These risks are no greater in this study than with standard practice treatment.
- Less likely risks include These risks are no greater in this study than with standard practice treatment.
- Rare but serious risks include vessel/lung injuries due to the pressurized air, but patients susceptible to these risks are contraindicated for CPAP therapy and excluded from the study. These risks are no greater in this study than with standard practice treatment.
- No chemicals or medications are administered with the CPAP device.

6.3 Actions to Minimize Risks

a. **Safety Monitoring Plan**
Patients will receive extensive education and training prior to CPAP initiation. This includes instruction on basic sleep hygiene and behaviors along with teaching on OSA and sleep physiology. Patients will also meet for a second

time with a sleep physician prior to initiation with therapy to ensure all questions are answered. They will have contact information for the respiratory therapists who work for the DME vendor and for our clinic. The DME vendor is available by phone or email, 24-7.

There will be a 4 week follow-up (which is part of the protocol) appointment to download adherence and respiratory data from the CPAP machine. This appointment also includes assessment for mask leak, comfort and fit. A second follow-up will occur at 8 weeks at which time a similar assessment will occur.

b. Safety Analysis Plan

Safety analysis will include detailed analysis of adherence and respiratory report that is provided via the CPAP machine. This includes any evidence of breathing abnormalities associated with untreated sleep apnea. Assessment of blood pressure and vital signs will occur at all follow-up visits and patients will have validated questionnaires administered that will allow physicians to objectively determine the quality of their sleep. Breathing abnormalities well be addressed as needed with machine adjustments.

c. Confidentiality Protection

- All hard copy paper documents collected in patient encounters which are tied to the study's data collection will be kept in individual sections of a binder (s), which will be locked in a file cabinet in the Lead Investigator's office.
- Patient specific data will be collected in an Excel spreadsheet and saved the Lead Investigator's and Associate Investigators' H-drives at WRNMMC. These spreadsheets will contain de-identified patient data.
- The master list of patient identifiers will be kept as a hard copy in the Lead Investigator's office, and will be secured as noted above.
- No patient specific data will be stored on the computer or placed in computerized software packages for statistical analysis that contains personal identifiers.
- No patient specific data or statistical analysis information related to the project will be emailed outside of the institution (WRNMMC). Obviously, final, de-identified statistical analysis related to presentation or publication in table or graphical format, which does not contain personal identifiers, will be presented with appropriate institutional publication clearance and approval.

d. Certificate of Confidentiality

N/A

6.4 Reporting Adverse Events and Unanticipated Problems

Expected adverse events which are not serious are reported on the Continuing Review Progress Report (CR). Continuing Review is generally performed on a 12-month cycle, falling on the anniversary month of the protocol's initial approval. More frequent Progress Reports may be required at the discretion of the IRB.

For multi-center studies, a summary of adverse events study-wide or the report of the Data Safety Monitoring Board (DSMB) should be included with the CR.

Serious Adverse Events: The PI, within 24 hours, must report all serious adverse events (SAE) occurring in subjects enrolled at WRNMMC IRB. This is accomplished by submitting an adverse event report to the IRB via IRBNet. For protocols involving investigational drugs or devices, the investigator must also report a serious adverse event to the sponsor of the IND or IDE immediately (within 24 hours). Unexpected (but not serious) adverse events occurring in subjects enrolled at WRNMMC which, in the opinion of the PI, are possibly related to participation in the protocol must be reported by the PI within 5 working days to the IRB using the same procedure.

Unanticipated problems involving risks to subjects or others (UPIRTSOs) must be reported to the IRB within 24 hours and a written follow up received within 5 working days.

For all serious and/or unexpected adverse events, the PI must forward a copy of the adverse event report to the Research Monitor for the protocol.

7. HIPAA AUTHORIZATION

i. Are you intending to collect subject's Protected Health Information (PHI) and any of the following 18 personal identifiers?

___ No – HIPAA does not apply – go to question #**iv**
_X__ Yes – please check which ones:

_X_ 1. Names
___ 2. Street address, city, county, 5-digit zip code
___ 3. Months and dates of major life events (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)
___ 4. Telephone numbers
___ 5. Fax numbers
___ 6. E-mail addresses
___ 7. Social security number
_X_ 8. Medical record number
___ 9. Health plan beneficiary number
___ 10. Account number
___ 11. Certificate/license number
___ 12. Vehicle identification number (VIN) and/or license plate number
___ 13. Device identifiers and serial numbers
___ 14. URLs (Uniform Resource Locators)
___ 15. Internet protocol address number
___ 16. Biometric identifiers, such as finger and voice prints
___ 17. Full face photographic images or any comparable images
__X_ 18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just dates, city/state/zip, and/or "other unique identifier" (#18 of the above)?

___ Yes – then your dataset may qualify as a Limited Data Set – please complete a Data Use Agreement and submit with your protocol. Then go to question #**iv**.

_X_ No – Go to question #**iii.**

iii. Is obtaining patient Authorization "impracticable"?
___ Yes – Authorization may qualify to be waived by the IRB. Submit a Request for Waiver of Consent/HIPAA to the IRB.
_X_ No – Research subjects will need to sign a HIPAA Authorization. Complete the HIPAA Authorization template portion of the Consent Template.

iv. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

The Lead Investigator and Associate Investigators will participate in collecting, storing and analyzing data. The consent forms, questionnaires, and any additional paperwork with patient data will be kept as hard copies in respective binders, to be locked in a file cabinet in the Lead Investigator's office. Files that are saved to the computer will be saved to the investigators' H-drives at WRNMMC. These files will be password protected. Patient names will be de-identified and a master list will be kept as a single paper copy by the Lead Investigator. All data files that are used in statistical analysis software will be de-identified. No research files will be emailed outside of the institution (ie. outside of Outlook email at WRNMMC).

v. When will you destroy the research source documents, data file, and the master code?

Within 5 years of completion of publication of any study results, or as dictated by the Department of Clinical Investigations and/or Institutional Review Board.

vi. Will research data including Identifiable Protected Health Information be sent outside of WRNMMC?
___ Yes – Please explain assurances you have received from the outside party that they will appropriately follow confidentiality protections, follow the HIPAA requirements, and abide by the provisions of your Authorization. NOTE: If yes, an impact statement from WRNMMC IT department is required to ensure data transmission meets applicable standards.

_X_ No

8. INVESTIGATOR AGREEMENT

By submitting this protocol and providing an electronic signature in IRBNet, or an ink signature below, I agree to the following statements:

General Assurance: I agree to conduct the study as outlined herein. I certify that all procedures involving human subjects have been described in full.

Starting the Study: I understand that I cannot begin the study until I have received an approval letter documenting approval by the WRNMMC IRB.

Consent: I am responsible for assuring the quality of each subject's consent in accordance with current federal regulations. This includes ensuring that any "designee" that obtains consent on my behalf is completely familiar with the protocol and is qualified to perform this responsibility.

Adverse Events: I understand that I must report research related or possibly research related serious adverse events within 24 hours to the IRB. If the IRB has required a research monitor, the research monitor will also review the relatedness and the serios nature of the adverse event. I will report unexpected (but not serious) adverse events that may possibly be related to participation in the protocol within 5 working days to the IRB using the same procedure.

Training: I verify that the personnel performing these procedures described in this protocol are technically competent, have been properly trained, and are appropriately qualified.

Compensation: I am aware that members of the research team are not authorized to accept any form of personal compensation for our efforts in conducting this research.

Modifications: I am aware that all changes to the protocol must be approved by the IRB before implementation. Examples of changes to protocols that require IRB approval include change of on-site PI, addition of personnel on study, increased sample size, addition of other data points, sources of outside funding, and addition of data collection sites.

Deviations to the Protocol: I am aware that any protocol deviations discovered by either the PI or auditing official will be immediately reported to the IRB. All corrective actions will be documented and become a part of the master study file, along with the report.

Duplication of Effort: I have made a reasonable good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

Reports: I agree to provide a Continuing Review Progress Report 30 days prior to the anniversary of the protocol's initial approval or as stipulated by the IRB. I agree to submit a final report within 30 days following closure, completion or termination of the study.

Maintain Study Files: I agree to maintain a Study File that must be kept for three years from the date the study is closed (32 CFR 219.115(b) and that HIPAA authorizations will be retained for 6 years. If IND medication or IDE appliances are used, the file must be kept for 2 years after Food and Drug Administration (FDA) approval and can then be destroyed; or if no application is filed or approved, until 2 years after the study is discontinued and FDA notified (21CFR 312.62(c). I acknowledge that research data is the property of the Command and will not be removed without prior approval. When I am scheduled to PCS or ETS, study records will be given to a new PI or the Department Chief, or turned over to the Department of Research Programs.

This file may be inspected at any time by Department of Research Programs, DoD oversight entities, the FDA, and/or other applicable regulatory agencies responsible for the oversight of research. This file will include:

A. The approved protocol and applicable amendments.
B. The IRB minutes granting approval to initiate the study.
C. IRB approval letter.
D. Each Consent Form/HIPAA Authorization signed by the subject or Legally Authorized Representative (LAR)
E. Continuing Review Progress Reports.
F. Reports of adverse effects.
G. Reports of any significant new findings found during the course of the study.
H. All study documents generated from study date.
I. Publications, abstracts, reprints resulting from study data.
J. All information pertaining to an investigational drug or device.

Publications: I am aware that advertisements, abstracts, presentations or publications resulting from research protocols must have their products cleared by the Public Affairs Office, undergo Operation Security (OPSEC) review, undergo review for release of actionable medical information, and Publication Clearance.

HIPAA Compliance: I will provide each research participant with a copy of their signed and dated HIPAA Authorization and will immediately notify the IRB Privacy Board when a research participant revokes his/her signed Authorization, and I will no longer seek to obtain PHI pertaining to that individual for this research project, or any other purpose absent a separate authorization or appropriate waiver.

Applicable Regulations: I am familiar with applicable regulations governing research, and will adhere to all of the requirements outlined in the DoD Assurance for the WRNMMC.

I understand that if I fail to comply with any of these responsibilities, all projects for which I am an investigator may be suspended.

PRINCIPAL INVESTIGATOR
MAJ(P) Aaron Holley, MC, USA
Director, Sleep Laboratory
Pulmonary and Critical Care Medicine

WRNMMC LEAD INVESTIGATOR
MAJ Jacob Collen, MC, USA
Fellow, Sleep Medicine
Pulmonary and Critical Care Medicine

10. LEADERSHIP ACKNOWLEDGEMENT

I concur with the submission of this proposal to the Department of Research Programs for review and approval.

DEPARTMENT CHIEF
CDR Anthony Nations, MC, USN
Chief, Pulmonary Clinic
Pulmonary and Critical Care Medicine

11. REFERENCES

1. Young T et al. The occurance of sleep disordered breathing among middle aged adults. N Engl J Med 1993; 328: 1230-5.
2. Sullivan C et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981; 1: 862-5.
3. Gay P et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 2006; 29: 381-401.
4. Weaver T et al. Night-to-night variability in CPAP use by patients with obstructive sleep apnea. Sleep 1997; 20: 278-83.
5. Kribbs NB et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993; 147(4): 887-95.
6. Berry RB et al. The use of auto-titrating continous positive airway pressure for treatment of adult obstructive sleep apnea. Sleep 2002; 25(2): 148-73.
7. Oskenberg A et al. The sleep supine position has a major effect on optimal nasal continuous positive airway pressure; relationship with rapid eye movement and non-rapid eye movements sleep, body mass index, respiratory disturbance index, and age. Chest 1999; 116: 1000-6.
8. Ayas NT et al. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep 2004; 27(2): 249-53.
9. Behbehani K et al. A sleep laboratory evaluation of an automatic positive airway pressure system for treatment of obstructive sleep apnea. Sleep 1998; 21(5): 485-91.
10. Boudewyns A et al. Two months follow up of auto-CPAP treatment in patients with obstructive sleep apnoea. Thorax 1999; 54(2): 147-9.
11. d'Ortho MP. Auto-titrating continuous positive airway pressure for treating adult patients with sleep apnea syndrome. Curr Opin Pulm Med 2004; 10(6): 495-9.
12. d'Ortho MP et al. Constant vs. automatic continuous positive airway pressure therapy: home evaluation. Chest 2000; 118(4): 1010-7.
13. Randerath WJ et al., editors. Autoadjusting CPAP therapy based on impedance efficacy, compliance and acceptance; 2001.
14. Teschler H et al. Automated continuous positive airway pressure titration for obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996; 154(3 Pt 1): 734-40.
15. Hudgel DW & Fung C. A long-term randomized, cross-over comparison of auto-titrating and standard nasal continuous airway pressure. Sleep 2000; 23(5): 645-8.
16. Hukins C. Comparative study of autotitrating and fixed-pressure CPAP in the home: a randomized, single-blind crossover trial. Sleep 2004; 27(8): 1512-7.
17. Konermann M et al. Use of conventional and self-adjusting nasal continuous positive airway pressure for treatment of severe obstructive sleep apnea syndrome: a comparative study. Chest 1998; 113(3): 714-8.
18. Meurice JC et al. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1996; 153(2): 794-8.

19. Randerath WJ et al. Prospective randomized comparison of impedance-controlled auto-continuous positive airway pressure (APAP(FOT)) with constant CPAP. Sleep Med 2001; 2(2): 115-24.
20. Teschler H et al. Two months auto-adjusting versus conventional nCPAP for obstructive sleep apnoea syndrome. Eur Respir J 2000; 15(6): 990-5.
21. To KW et al. A randomized cross-over study of auto-continuous positive airway pressure versus fixed-continuous positive airway pressure in patients with obstructive sleep apnoea. Respirology 2008; 13(1): 79-86.
22. Krakow B et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. J Nerv Ment Dis 2002; 189:618-22.
23. Krakow B et al. Nightmares, insomnia, and sleep-disordered breathing in fire evacuees seeking treatment for posttraumatic sleep disturbance. J Trauma STress 2004; 17:257-68.
24. Krakow B et al. Complex insomnia: insomnia and sleep disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry 2001;49:948-53.
25. Sharafkhaneh A et al. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep 2005; 28:1405-11.
26. Krakow B et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for comorbid sleep-disordered breathing. J Psychosomatics 1998;39:168-71.
27. Spoormaker VI et al. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev 2008; 12:169-84.
28. Collen JF et al. The impact of posttraumatic stress disorder on CPAP adherence in patients with obstructive sleep apnea. J Clin Sleep Med 2012; 8(6):667-672.
29. Kobayashi I et al. Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. Psychophysiology 2007; 44:660-669.
30. Ayappa I et al. Irregular Respiration as a Marker of Wakefulness During Titration of CPAP.Sleep 2009; 32(01):99-104.
31. Dungan GC et al. A randomized cross-over trial of the effect of a novel method of pressure control (SensAwake) in Automatic Continuous Positive Airway Pressure Therapy to treat sleep-disordered breathing. J Clin Sleep Med 2011; 7(3): 261-7.
32. Cumin D et al. Randomized crossover evaluation of a novel implementation of pressure relief technology – SensAwake and fixed pressure CPAP. World Association of Sleep Medicine Conference 2011; [poster]: T-I-065.
33. Powell ED et al. Long-term patient feedback on a novel automatic ramp feature in fixed pressure CPAP. World Association of Sleep Medicine Conference 2011; [poster]: T-I-054.

12. BUDGET

Will any outside organization provide funding or other resources? Yes (X) No ( )

Further detail of the budget is included in the Clinical Research Agreement with Fisher & Paykel Healthcare.