STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

A NOVEL TREATMENT OF COMORBID INSOMNIA AND SLEEP APNEA IN OLDER VETERANS

IIR 12-353

1I01HX001070-01A1

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Research Design and Methods

Both OSA and insomnia increase in prevalence with age, and these conditions commonly coexist in older Veterans. Treatment guidelines for insomnia recommend CBT-I as first-line therapy, but most insomnia behavioral treatment trials (including our own ongoing work) have excluded individuals with clear evidence of moderate-severe OSA. PAP is the standard for treatment of OSA, but adherence with PAP is problematic and best practice to improve PAP adherence when patients have coexisting insomnia is unknown. Given the high prevalence and serious consequences of these disorders, it is clear that research is needed to identify best practices for the management of coexisting OSA and comorbid insomnia in older adults.

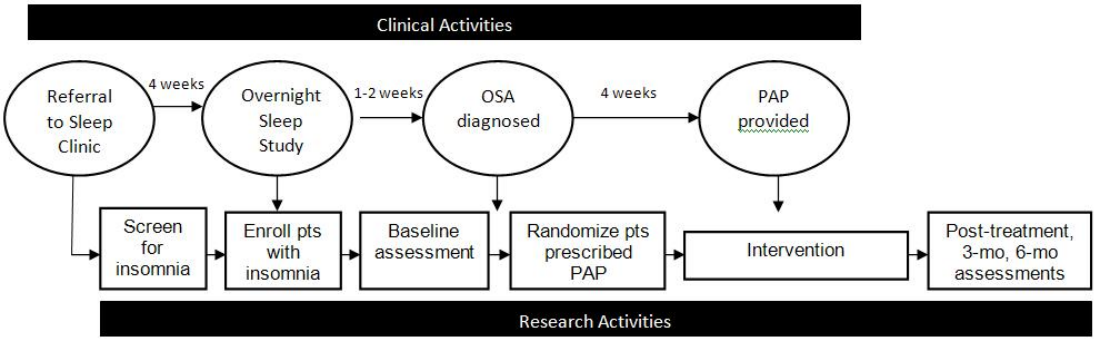
Basic study design

This 3.5 year project will be a randomized controlled trial testing a combined, integrated behavioral approach to management in older Veterans (aged ≥ 50 years) who are diagnosed with OSA, are prescribed PAP therapy, and also meet diagnostic criteria for insomnia. This novel intervention will combine essential elements of a CBT-I intervention (for insomnia) plus a behavioral intervention to improve PAP adherence. The combined, integrated intervention will be provided using allied health personnel compared to an active control condition (consisting of a general sleep and PAP education program) among older Veterans (N=120 total participants, 60 per group). Structured outcome assessments will be collected at baseline, post-treatment (i.e., after completion of the intervention or control condition), and at 3- and 6-months follow-up. A brief telephone interview will be conducted at 12-month follow-up. Outcomes assessed will include subjective (i.e., questionnaire, sleep diaries) and objective (i.e., wrist actigraphy) measures of sleep, objective measures of PAP adherence (downloaded from PAP equipment), mood and other measures of health-related quality of life. Data will also be collected at post-treatment, and at 3- and 6-months follow-up to assess beliefs and attitudes about sleep and OSA. Adherence with key aspects of the intervention will be collected in intervention participants during the treatment phase, and intervention participants will be invited to participate in focus groups after completing their 6-month follow-up to identify factors that act as facilitators or barriers to participation and adherence with the intervention.

Setting

The study will take place in VA GLAHS at the Sepulveda and West Los Angeles campuses, which are located 15 miles apart in the Los Angeles area, and serve a diverse population of Veterans. In fiscal year 2011 (FY11), the West Los Angeles VA campus served 53,913 unique Veterans, and the Sepulveda VA campus served 25,535 Veterans. There were 2,792 unique patients seen in the VA GLAHS sleep clinics at Sepulveda and West Los Angeles in FY11, at least 52% were aged 50 years or older, and the majority (over 80%) were referred for evaluation of OSA. There were 1852 sleep studies performed in FY11, and 1037 new PAP machines were issued during that time period. Based on the literature and our preliminary studies, we estimate that at least 50% of Veterans diagnosed with OSA and prescribed PAP will also meet diagnostic criteria for insomnia. Based on this data, we conservatively estimate that at least 22 Veterans per month will be eligible for the study (i.e., [1037 PAP machines prescribed/12 months] x [.52 aged ≥ 60 years] x [.50 meeting diagnostic criteria for insomnia] = 22.5). Based on consent rates in our prior VA studies enrolling older Veterans for interventional sleep research (e.g., VA HSRD IIR-04-321-3) we expect a 50% consent rate among eligible Veterans, which would provide 10 enrolled Veterans per month, with 50% (5 per month) proceeding to randomization.

Figure 1: Study design



Study Population

- Recruitment and consent

We will use a two-step process to recruit participants for this study. In the first step of recruitment, we will screen for insomnia among Veterans aged 50 years and older who are referred to the VA GLAHS sleep clinics to rule out OSA (based on the reason for referral to the sleep clinic indicated on the electronic consultation form). At our institution, the majority of individuals referred to sleep clinics are referred for possible OSA, and most referred patients receive an ambulatory (i.e., in-home portable) sleep study (rather than a study in the sleep laboratory) to test for OSA. However, we will enroll participants regardless of the location (in-home or in-laboratory) of their OSA testing. Currently, there is a 3-4 week wait for an ambulatory sleep study; the wait for an in-laboratory study is > 4 weeks. We will mail a letter to these Veterans when their referral to sleep clinic is received to briefly introduce the research, and to offer them a mechanism to "opt-out" of further contact by our research team, using a methodology previously approved by our institutional review board. For patients who do not opt out within 7 days of receiving the letter, our staff will contact them by telephone (or in-person if preferred by the Veteran) to complete a brief screening measure for insomnia. The insomnia screener is a brief questionnaire that summarizes key diagnostic criteria for insomnia according to ICSD2[Error! Bookmark not defined.] (see Appendix 1), which we developed, tested and currently use in our ongoing study of CBT-I to treat insomnia in older outpatient Veterans (VA HSRD IIR 08-296, PI Alessi). Veterans who meet diagnostic criteria for insomnia will be invited to participate in the study and an in-person visit will be scheduled to explain study procedures, obtain written informed consent, and begin assessment procedures. After consent, the Veteran will be sent home with a wrist actigraph to wear for 7 days and nights as an objective measure of sleep/wake patterns. Additional baseline data (e.g., demographic information, subjective measures of sleep, assessment of depressive symptoms, medical comorbidity, health-related quality of life) will be collected using structured, validated questionnaires (see below). In addition, one blood sample will be collected. All research data will be collected by trained research staff. All study visits will be performed in dedicated office space, separate from the sleep clinics. Separate research staff will perform assessment versus intervention activities, in order to maintain blinding of both clinic staff and research assessment staff.

In the second step of recruitment, consented Veterans who have completed baseline testing, are diagnosed with OSA (based on sleep clinic physicians interpretation of sleep study results) and are prescribed PAP therapy (by sleep clinic clinicians) will be reminded of study procedures, and invited to participate in the randomized controlled trial. Inclusion criteria will include: 1) age $\geq$ 50 years, 2) meeting ICSD2 diagnostic criteria for insomnia, and 3) diagnosis of OSA with an AHI $\geq$ 15 and prescription of PAP therapy. Exclusion criteria for randomization will include the following: 1) refusal to schedule an appointment to begin PAP therapy, 2) a Mini-mental State Examination (MMSE) score < 24 (used to screen for significant cognitive impairment), and 3) a history of mania (which is a contraindication for the sleep restriction component of CBT-I), major psychopathology (e.g., psychosis) or a psychiatric hospitalization within the prior two years.

- Randomization

Participants will be randomized to the intervention or control group using a randomized block design based on results from the OSA testing, to increase the likelihood of comparable severity of OSA in both groups. Specifically, individuals will be categorized based on AHI < 30 or AHI $\geq$ 30. Consented participants will be randomized as a block within each category (similar to block randomization techniques we have used in prior research). Available randomization software (e.g., Random Allocation Software, Paradigm) which allows for block randomized sequences for parallel group randomized trials will be used to assign participants to the intervention or control group, using random allocation concealment. Participants and research staff (except intervention staff) will be blinded to group assignment, and additional techniques (e.g., follow-up assessment in some consented, non-randomized participants) will be used to prevent unmasking. It may be difficult to keep assessment research staff blinded to group assignment if participants inadvertently describe their assignment, but all assessment staff will also be blinded to study research questions.

Dependent and Independent Variables (Measurement Techniques)

A summary of all measurement techniques is shown in Table 1.

Baseline Assessment

Consenting participants will receive a baseline assessment. Data will be collected at two separate visits over a seven day period. At the first visit, research staff will obtain informed consent, complete the first part of the baseline assessment, and provide the Veteran with a wrist actigraph device. Using a process similar to that in our ongoing VA HSRD-funded CBT-I trial, the participant will return after one week with the actigraph

and research staff will complete the second part of baseline assessment. Veterans will receive $25 for completing the baseline assessment.

Independent assessment research staff not involved in the intervention will perform baseline, post-treatment, and 3- and 6-month follow-up assessments. All research staff will undergo two weeks of structured training, including review of human subjects protection issues, basic interviewing techniques, cultural sensitivity training, and in-depth instruction on data collection instruments and equipment. Procedure manuals have been written for all instruments and equipment. Senior research staff will observe data collection at least quarterly, and inter-rater reliability will be assessed initially and re-assessed annually, and if new research staff are hired. These procedures have resulted in consistent, reliable data collection in our prior work and we have experience with all measures listed.

Data collection methods and instruments were chosen that are appropriate for use in older people. Specific instruments were chosen based on primary and secondary outcomes of interest, key covariates needed for analyses, efforts to minimize participant burden, our prior experience with these measures and published recommendations for standard assessment in sleep research.[1] For ethical reasons, the participant's primary provider will be notified (with the participant's consent) if our assessments identify any serious, unrecognized sleep disorder, or other severe condition (e.g., severe pain, severe depression). Our research team will also follow our established protocol when there is evidence of any serious, life-threatening situation (e.g., suicidality) identified during interactions with participants (see Human Subjects section).

Medical Chart Review (Data Collected by Research Staff)

- Structured clinical review of comorbidity, illness severity, and medications

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[2] will be used to assess baseline illness severity and comorbidity. We will use data from the medical record to complete the CIRS-G scale. The CIRS-G manual has specific criteria for scoring illness severity. We have extensive prior experience in use of the CIRS-G in a variety of research settings. We will use CIRS-G total score as an independent variable of baseline comordibity in data analyses.

Medications received during each data collection period will be identified from the electronic medical record and a structured medication interview. Medications will be coded by class using a coding system we developed in prior work. We will focus on sedating medications that may affect sleep. With a methodology we used in prior research,[3] sedating medication use will be summarized categorically (i.e., was a certain class of sedating medication received, and at what time); then daily dose(s) will be converted to total daily equivalences by class according to standardized criteria. Because of the intention to treat analysis, major outcomes will be compared between the intervention and control groups regardless of medication status. However, the medication variables (e.g., total daily equivalence of sedating medication at each time point) may be explored as potential covariates in outcome analyses, and use/nonuse of sedating medications may be considered in subgroup comparisons (e.g., subgroup analysis in only participants who did or did not receive sleeping pills).

Questionnaires (Data Collected from Participants)

- Descriptive information will be collected in all participants, including age, gender, ethnicity, **marital status,** and other demographic characteristics.
- Cognitive status

The Mini-Mental State Examination (MMSE) will be used to screen consented individuals for inclusion and to measure baseline cognitive status.[4] This scale assesses orientation, registration, attention/calculation, recall, language and construction, and has standard instructions. MMSE scores range from 0 to 30, where higher scores indicate better mental status. A score below 24 is consistent with dementia or delirium. MMSE total score will be used in determining study eligibility (i.e., MMSE score < 24 is an exclusion criteria) and as an independent variable of cognitive status in analyses.

The Hopkins Verbal Learning Test – Revised (HVLT-R)[5] will be used to estimate verbal learning and immediate and delayed memory functioning, as both sleep and PAP adherence likely impact memory functioning. The HVLT-R consists of a Word List, containing 12 words from three taxonomic categories, which is read aloud to the participant at the rate of approximately one word every two seconds. The Immediate Recall test includes three learning trials. Delayed Recall is assessed following a delay after completion of the Immediate Recall test. Immediately after administration of the Delayed Recall trial, a forced-choice Recognition test is administered. The Recognition test includes the 12 target words, plus 12 distractors (six semantically-related and six semantically-unrelated words). The HVLT-R has been validated in healthy and pathological aging samples.

The Digit Symbol Substitution[6] will be used to estimate processing speed and attention, as both sleep and PAP adherence likely impact these cognitive functions. This task consists of nine digit-symbol pairs (e.g. 1/-,2/⊥ ... 7/Λ,8/X,9/=) followed by a list of digits. Under each digit the subject is instructed to write down the corresponding symbol as fast as possible. The number of correct symbols written within the allowed time (e.g. 90) is the outcome measure.

The Trails A and B[7] tests will be used to estimate processing speed, attention, and executive functioning. Trails A will be used to assess processing speed, while Trails B will be used to assess attention and task switching (executive functions). Trails A requires individuals to connect circles containing numbers in sequential order. Trails B requires individuals to connect circles containing numbers and letters in alternating sequential and alphabetic order. The outcome measures are the time to complete the tasks.

The Forward and Backward Digit Span[8] tests will be used to estimate immediate memory and working memory. The Forward Digit Span tasks requires immediate recall of number presented aurally. The Backwards Digit Span requires mental manipulation and rearrangement of numbers presented aurally. The outcome measures are the total number of correct sequences recalled.

The Letter-Number Sequencing[8] test is another measure of working memory. This task requires mental manipulation and serial rearrangement of numbers and letters presented aurally. The outcome measure will be the total number of correct sequences recalled.

The Control Oral Word Association (COWA)[9] will be used to assess phonemic fluency, which is considered an executive function. Participants will be read a letter (“F”, “A”, and “S”) and asked to generate as many non-proper nouns beginning with that letter as possible within sixty seconds. The outcome measure is the total number of correct words produced for each letter.

Table 1: Study Variables and Their Measurement

Independent variables	Hypothesis	Measurement Instrument	Data*
Demographics		Questionnaire	I
Health status measures:			
▪ Illness severity/comorbidity		Comorbidity Index	I
▪ Use of medications		Medication review	MR, I
▪ Cognitive status		Mini-Mental State Examination (MMSE) Hopkins Verbal Learning Test – Revised (HVLT-R) Digit Symbol Substitution Trails A and B Forward and Backward Digit Span Letter-Number Sequencing Control Oral Word Association (COWA)	I I I I I I I I
▪ PTSD		Primary Care PTSD Screen	I
▪ Pain		Geriatric Pain Measure (GPM) pain intensity subscale	I
Dependent variables: Outcomes			
Intervention process measures:			
▪ Beliefs and attitudes about sleep ▪ Beliefs and attitudes about OSA and PAP	4 4	Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) scale Self-efficacy, Knowledge and Decisional Balance Index subscales	I I
Subjective sleep measures			
▪ Self-rated sleep quality ▪ Severity of insomnia symptoms ▪ Daytime sleepiness	1, 3 1, 3	Pittsburgh Sleep Quality Index (PSQI) Insomnia Severity Index (ISI) Epworth Sleepiness Scale (ESS)	I I I
▪ Sleep onset latency, wake after sleep onset		Sleep diary	SR, I
Objective sleep measures:			
▪ Total sleep time, nighttime & daytime sleep percent	1, 3	Wrist actigraphy	M
Quality of life measures:			
▪ Health-related quality of life	2, 3	MOS 12-item Short-form Health Survey (SF-12v2); EuroQol-5D	I
▪ Depressive symptoms	2, 3	Patient Health Questionnaire Depression module (PHQ-9)	I
▪ Anxiety		Patient Health Questionnaire Generalized Anxiety module	I
PAP adherence			
▪ Hours of PAP use per night	1, 3	PAP memory card or modem download	M

*Data source: I=interview, MR=medical records, M=monitoring, SR=self report

- Comorbidity Index[10]: The Comorbidity Index is a validated, self-report measure of physical and mental comorbidity. This 36-item self-report questionnaire has a 30-item physical component and a 6-item mental component and was developed for a population of Veterans. Comorbidity index score and individual comorbid conditions will be used as independent variables.
- Post-traumatic stress disorder

The Primary Care PTSD Screen (PC-PTSD) [11] will be used to estimate the presence or absence of PTSD, since this disorder may impact both sleep and PAP adherence.**Error! Bookmark not defined.** This is a 4-item scale, where endorsement of 3 of the 4 yes/no items suggests PTSD. The scale has a sensitivity of .78, and specificity of .87 compared to clinical diagnosis of PTSD in Veterans. The PC-PTSD will be used as an independent variable of PTSD status (i.e., presence/absence of PTSD and/or number of PTSD symptoms endorsed, 0-4).

- Subjective assessment of pain

The pain intensity subscale (7 items) of the Geriatric Pain Measure (GPM)[12] will be used to assess pain, since pain may affect sleep outcomes. The GPM is a 24-item multidimensional pain measure (with 5 subscales) for use in older adults. The pain intensity subscale will be used to minimize participant burden. Total score on the GPM subscale will be used as a covariate in analyses of sleep and quality of life outcomes.

- Subjective sleep quality

We will measure self-reported sleep quality using the Pittsburgh Sleep Quality Index (PSQI),[13] the Insomnia Severity Index (ISI),[14] the Epworth Sleepiness Scale (ESS)[15] and a sleep diary; all of which have specifically been identified as recommended/essential measures of sleep and insomnia symptoms for standard assessment in sleep research.[1]

PSQI: This is an 18-item questionnaire that assesses sleep quality and disturbances over the last month. The PSQI is a widely used scale that measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

ISI: This is a 7-item scale of self-reported severity of insomnia symptoms, satisfaction with sleep, daytime functioning, impairment and concern caused by the sleep problem.

ESS: This is an 8-item questionnaire that assesses daytime sleepiness. The ESS measures the chances that an individual would doze off or fall asleep under 8 different circumstances (e.g., reading, watching television, sitting quietly). Total PSQI, ISI, and ESS scores will be used at baseline and at each follow-up assessment as dependent subjective measures of sleep.

Sleep diary: Participants will complete a 7-day sleep diary at baseline and follow-up assessments (timed to occur at the same time as wrist actigraphy), which will be used to calculate self-reported sleep onset latency (SOL, time to fall asleep) and wake after sleep onset (WASO, the time spent awake from sleep onset to final awakening) as dependent subjective measures of sleep (see Appendix 2).

- Health-related quality of life

The Medical Outcomes Study 12-item Short-form Health Survey v2 (SF-12v2)[16] will be used as a measure of health-related quality of life. The SF-12v2 Health Survey is a 12-item version of the prior SF-36 (therefore with less participant burden) with evidence for improved format and precision. The SF-12v2 can be scored as a global scale, in 8 domains (physical functioning, physical, bodily pain, general health, vitality, social functioning, emotional and mental health) or as two summary scores (Physical Component and Mental Component Summary Scores). Most population-based descriptive studies of sleep and quality of life have used the longer 36-item version, and very few trials of behavioral interventions for insomnia have included quality of life as an outcome measure at all; these factors make the choice among these scales difficult. In addition, the recently published recommendations for standard research assessment in insomnia trials described above specifically mention the SF-36 as a recommended/essential measure of health-related quality of life.[1] However, after careful consideration of the balance in participant burden and precision, and our own experience with the SF-12v2 in our current work, we have chosen this scale for the current study. We will use the global score, and the Physical Component Summary score and Mental Component Summary score at baseline and follow-up assessments as dependent measures of health-related quality of life.

The EuroQol-5D (EQ-5D)[17] will be used as another measure of health-related quality of life. This 5-item questionnaire was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D included 5 dimensions: mobility, self-care, usul activies, pain/discomfort and anxiety/depression. Total EQ-5D score at baseline and follow-up assessments will be used as a dependent measure of health-related quality of life.

The Patient Health Questionnaire-9 (PHQ-9)[18] will be used to measure depression as another component of health-related quality of life. The PHQ-9 is the depression module of the Patient Health Questionnaire (a self-administered diagnostic instrument for common mental disorders). The 9 items consist of the diagnostic criteria used by the DSM-IV for depressive disorders. The PHQ-9 also measures depression severity. Total PHQ-9 score at baseline and follow-up assessments will be used as dependent measures of depression.

The 7-item Generalized Anxiety Scale (GAD-7) will be used to measure anxiety, which has been demonstrated as an important quality of life outcome in sleep research[19] and may impact PAP adherence. The GAD-7 is a component of the Primary Care Evaluation of Mental Disorders (PRIME-MD) suite of evaluation tools. It was initially developed for evaluation of generalized anxiety disorder, and has also proved useful in screening for other DSM-IV Axis I anxiety disorders. The GAD-7 is a 7-item scale (scores range from 0 to 27), with a cut off score of ≥10 yielding both sensitivity and specificity above .80 for GAD. The GAD-7 score at baseline and follow-up assessments will be explored as a dependent measure of anxiety, but we have not included anxiety as a primary outcome measure in sample size calculations and data analysis (see below).

Caregiving questions (21 items). To explore how caregiving impacts an individual's sleep and quality of life, we will include questions from the National Alliance for Caregiving. Questions pertain to the type and amount of caregiving provided.

- Intervention process measures

The Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) scale, brief version[20] will be used to measure participants' sleep-related cognitions. The DBAS-16 uses a Likert-type scale, and was developed from the original 30-item DBAS. Total DBAS-16 scores at baseline and at follow-up assessments will be compared between groups to measure effects of the intervention on participants' beliefs and attitudes about sleep as a measure of the process of the intervention.

We will use the Self-efficacy (5-item), Knowledge (12-item) and Decisional Balance Index (5-item) subscales from the 54-item scale of behavioral determinants of PAP adherence.[21] These subscales provide Likert-type (for the Self-efficacy and Decisional Balance Index subscales) or yes/no (for the Knowledge subscale) response options. In prior work, the full scale (measured at 1-week after start of PAP therapy) predicted PAP adherence, and the DBI individually accounted for 17% of the variance in PAP adherence in adjusted analyses. The Self-efficacy, Knowledge and Decisional Balance Index subscale scores will be compared between groups to measure effects of the intervention on participants' beliefs and attitudes about OSA ad PAP.

- Blood sample

One blood sample (8mL) will be drawn by a study phlebotomist at one of 4 possible locations (CRC at West Los Angeles, Building 200 or Building 25 at Sepulveda, or if requested, at a subjects' home. Blood samples will be processed and stored in the CRC or in a laboratory at Sepulveda (Building 7/C10) until transported to the UCLA Cousins Center for Psychoneuroimmunology for analysis. The blood samples will be assayed for proinflammatory cytokines and corresponding acute-phase proteins (i.e., CRP, TNFα, IL-6, IL-8, and IL-10), which are markers of immune system activity.

Sleep Assessment Monitoring (Data Obtained through Monitoring of Participants)

- Objective sleep quality monitoring

Wrist actigraphy will be used as an outcome measure of the effects of the intervention on sleep. Participants will wear an actigraph on the dominant wrist (unless that arm is paralyzed) for 7 consecutive days and nights at baseline, post-treatment, and at 3-month and 6-month follow-up assessments. The actigraph is a small watch-sized device useful in longitudinal, naturalistic (i.e., not in a sleep laboratory) assessment of sleep-wake patterns. The device contains subminiature solid state accelerometers and, in general, wrist activity below an established threshold is interpreted as sleep; high wrist activity is interpreted as wakefulness. Commercially available software uses validated algorithms that take into account wrist movement immediately before and after an epoch of interest in determining the likelihood of sleep versus wakefulness during that epoch. Wrist actigraphy has been validated as a measure of sleep versus wakefulness in older people.[22] Previously reported agreement between wrist actigraphy and EEG scoring of sleep variables (e.g., total sleep time) in young and older people is 89-95%.

Wrist actigraphy has also been used to estimate circadian rhythms of activity; however the most appropriate analytic techniques to summarize these data and clinical significance of these variables are not clear, so we have not included these circadian variables as main outcomes in the current proposal. We will use analytic software to perform least-squares analyses to fit 24-hour cosine curves to actigraphy data, to

determine the mesor (mean value of the fitted curve), amplitude (height of the curve at its peak) and circadian quotient (amplitude/mesor, where a higher quotient suggests a "better" rhythm).

Careful visual review of raw actigraphy data will be performed to eliminate technical (device failure) and situational (e.g., device removed) artifact, prior to scoring variables with validated software. We will analyze actigraphy data defining "night" and "day" based on participant self-report of their bedtimes and rising times in their sleep diary. The following dependent variables (averaged over 7 days) will be used in analyses as measures of sleep-wake: 1) total sleep, 2) nighttime sleep efficiency (mean total sleep time divided by total valid recording time), 3) daytime percent sleep (total sleep time divided by total daytime recording time), and 4) mean awakening length at night (mean duration of nighttime wake episodes).

- PAP adherence. In addition,
- PAP equipment will be provided by the VA GLAHS Sleep clinics to all intervention and control participants per usual care established clinical protocols. The VA GLAHS Sleep clinics nearly exclusively use Respironics™ devices (Respironics, Inc., Murrysville, PA). The PAP devices are routinely dispensed with heated humidification to minimize upper airway dryness, which may affect adherence. The same clinical staff (i.e., sleep technicians) will provide PAP equipment and usual setup instructions for both intervention and control participants; these clinical staff will be blinded to group assignment. All PAP devices have an internal secure device (SD) memory card that stores PAP usage data and a modem that transmits daily usage to a web-based application (EncoreAnywhere) maintained on a secure server by Philips Respironics, Inc. The data on the server are linked only to the serial number of the PAP modem and do not include any personal identifiers. Authorized research staff will retrieve data from the server using an assigned password. Philips Respironics, Inc. will have no access to the key that links PAP modem serial number to subject identification code or name. For participants who are unable to use the modem because they live outside the modem serve area, research staff will download the SD card (easily performed with an inexpensive reader device) at the time of the follow-up assessments. Data will be obtained after the first week of PAP therapy, at the post-treatment assessment, and at 3- ~~and~~ 6- and 12-months follow-up. Our primary dependent measure of PAP adherence will be the percentage of nights that the PAP equipment was used for $\geq$ 4 hours per night. In addition, we will define “adequate” PAP adherence as PAP usage of $\geq$ 4 hours per night for 70% of days, and we will also record the mean hours of PAP use per night.[23] PAP machines have the capability to sense when the mask is on the patient’s face, so we will be able to assess the hours per night of use at the effective PAP pressure (i.e., mask on at an effective pressure) . Adherence data is automatically stored continuously in PAP equipment, and available by day. We plan to summarize data over the prior 7 days (at all data collection time-points) and/or the prior 30 days where appropriate (i.e., at 3-, 6-, and 12-months follow-up).

Treatment groups

Participants will be randomized to one of two groups: 1) intervention group, who will receive an integrated, manual-based individual CBT-I plus PAP adherence behavioral self-management program, or 2) control group, who will receive an attention control condition (general sleep and OSA education). All participants will be prescribed PAP therapy (through the sleep clinic), and will receive their PAP device through the sleep clinic, as described above. The intervention and control conditions will be provided by research allied health personnel (i.e., not psychologists). The active intervention was designed to have a high enough intensity/potency for efficacy, while avoiding as much as possible the risks of excessive participant burden and excessive costs of implementation into routine care if successful. In addition, the intervention is structured and manual-based (i.e., using a concise intervention manual) in order to be highly translatable to routine care. The intervention and control programs will begin after baseline assessment and randomization, and the intervention or control conditions will begin approximately 2 weeks prior to initiation of PAP therapy. If there is a delay in receipt of PAP equipment, participants will receive a weekly phone call from intervention/control staff to monitor progress and provide reinforcement (of information learned in sessions 1 and 2 in the intervention group, and to encourage continued participation in the control group). If the PAP equipment is received prior to completion of sessions 1 and 2, the intervention/control condition will progress as scheduled below over a 6 week period.

Intervention condition

The intervention provides an integrated behavioral approach to OSA and insomnia, which combines a CBT-I treatment for insomnia with an OSA and PAP self-management program. The aspects of each intervention are integrated seamlessly into one intervention program, provided in individual (i.e., one-to-one) sessions with master’s level allied health personnel (e.g., health educator) (see Appendix 3 for example of session material). The first two sessions will be timed to occur prior to the patient receiving their PAP equipment; sessions 3 – 5 will occur after the participant receives their PAP device, with session 3 timed to

occur approximately one week after receipt of PAP (i.e., during or immediately after the first week of PAP therapy). The intervention is provided in 5 sessions over 6 weeks, to allow for one week (week 5) for the participant to become accustomed to independent self-management of their sleep problems, prior to the final session (week 6). The intervention staff will have weekly supervision with a study psychologist by telephone, where intervention cases currently in progress are reviewed briefly to monitor participant progress (similar to a method used in our ongoing CBT-I trial). Integrity of the intervention will be addressed carefully throughout the study, including formal training of the intervention staff initially with ongoing review and oversight throughout the study and periodic audio-recording of intervention sessions for review by a study psychologist (Dr. Martin). In addition, intervention staff will record specific intervention recommendations made to participants and participant adherence with these recommendations (similar to work in our ongoing trial of CBT-I), to help document the process of the intervention.

Table 2: Session schedule for the intervention group

Week	Session	Session length	Content
1	1	60 minutes	CBT-I: Sleep education, stimulus control, regularize sleep schedule PAP: Understanding OSA and PAP therapy
2	2	30-45 minutes	CBT-I: Introduction to sleep restriction PAP: Review of PAP equipment and set-up procedures, chronic disease management skills, communication skills, patient-provider relationship
3	3	30-45 minutes	CBT-I: Sleep restriction PAP: Review prior week PAP adherence and ongoing problem-solving
4	4	30 minutes	CBT-I: Sleep hygiene, adjust sleep restriction PAP: Review prior week PAP adherence and ongoing problem-solving
6	5	30 minutes	CBT-I and PAP: Review, relapse prevention and long-term management strategies

The CBT-I component of the intervention involves a previously tested, manual-based CBT-I program using content developed in our prior work which improved sleep among older Veterans meeting diagnostic criteria for insomnia (see Preliminary Studies). The intervention will involve education and practical training in key aspects of stimulus control (i.e., reducing anxiety about falling asleep), sleep restriction (i.e., an individualized, structured process of reducing time in bed to decrease nighttime wakefulness and consolidate sleep), sleep hygiene (i.e., establishing behavioral routines to promote restorative sleep), and cognitive therapy (i.e., addressing maladaptive and inaccurate perceptions and beliefs about sleep).

The PAP self-management component of the intervention involves a previously tested OSA disease-specific, self-management intervention based on the chronic disease model using the social cognitive theory and transtheoretical models of behavior change (see Preliminary Studies).[Error! Bookmark not defined.,Error! Bookmark not defined.,Error! Bookmark not defined.] This program includes information specific to OSA, in addition to concepts in chronic illness self-management. Issues covered include: understanding OSA symptoms and consequences, problem-solving difficulties with PAP, managing emotional-cognitive symptoms, learning strategies to increase physical activity, improving communication skills with providers, and developing a patient-provider relationship. The participant's PAP use in the prior week will be reviewed, and a major focus of the program will involve troubleshooting commonly occurring problems with PAP, tailored to the participant's ongoing experience with PAP, in addition to understanding how specific aspects of an individual's use of PAP relates to the management of his/her OSA.

Control condition

The control condition will be administered by research staff using a manual-based education program that focuses on general insomnia and OSA education, and is structured based on the control condition from our prior work (IIR 08-295-1, PI: Alessi). In our prior work, the control program was successful in providing an attention control placebo condition which also encouraged ongoing participation in the trial; an important factor in encouraging control participants to complete follow-up assessments.

Table 3: Session schedule for the control condition

Week	Session	Session length	Content
1	1	30 minutes	Introduction; general sleep and OSA education
2	2	30 minutes	Sleep across the lifespan, general health education
3	3	30 minutes	Sleep and health

4	4	30 minutes	Daytime relaxation techniques
6	5	30 minutes	Daytime stress reduction

Post-Treatment and Follow-up Assessments

Post-treatment and follow-up assessments will be performed by research personnel blinded to group assignment. Participants who can no longer travel to VA GLAHS (e.g., moved away, too ill) will be visited at their living location (if < 30 miles away) or interviewed by telephone (if ≥ 30 miles away). Veterans will receive $25 for each assessment for a possible total of $100 (i.e., baseline, post-treatment, 3-month and 6-month).

Table 4: Time Points for Data Collection and Measures Used

	Baseline	Post-tx	3-mo	6-mo	12-mo
Data Collected by Research Staff					
Blood sample: assayed for proinflammatory cytokines and corresponding acute-phase proteins (i.e., CRP, TNFα, IL-6, IL-8, and IL-10)	✓	✓	✓	✓	
Medication review	✓	✓	✓	✓	
Data Collected from Participants					
Demographic data	✓				
Mini-Mental State Examination (MMSE)	✓				
Hopkins Verbal Learning Test – Revised (HVLT-R)	✓	✓	✓	✓	
Digit Symbol Substitution	✓	✓	✓	✓	
Trails A and B	✓	✓	✓	✓	
Forward and Backward Digit Span	✓	✓	✓	✓	
Letter-Number Sequencing	✓	✓	✓	✓	
Control Oral Word Association (COWA)	✓	✓	✓	✓	
Geriatric Pain Measure (GPM) intensity subscale	✓	✓	✓	✓	
Restless Leg Syndrome scale (RLS)	✓				
Pittsburgh Sleep Quality Index (PSQI)	✓	✓	✓	✓	✓
Insomnia Severity Index (ISI)	✓	✓	✓	✓	✓
Epworth Sleepiness Scale (ESS)	✓	✓	✓	✓	✓
Patient Health Quest. depression module (PHQ-9)	✓	✓	✓	✓	
12-item Short-form Health Survey (SF-12v2)	✓	✓	✓	✓	
EuroQol-5D scale (EQ-5D)	✓	✓	✓	✓	
PHQ GAD	✓	✓	✓	✓	
PC-PTSD	✓				
Caregiving questions	✓	✓	✓	✓	
Dysfunctional Beliefs & Attitudes about Sleep (DBAS-16)	✓	✓	✓	✓	
PAP Self-efficacy, Knowledge and Decisional Balance Index subscales	✓	✓	✓	✓	
Data from Participant Monitoring					
Wrist actigraphy	✓	✓	✓	✓	
PAP adherence		✓	✓	✓	✓
Follow-up Data from Participant/ Record Review					
Sleep clinic visits		✓	✓	✓	

Post-treatment assessment: As is traditionally performed in behavioral insomnia interventional studies, "post-treatment" assessments will be repeated soon after completion of the treatment (either intervention or control conditions). Wrist actigraphy will be repeated for 7 days, in addition to the sleep quality (PSQI, ISI, ESS), cognitive functioning tests (HVLT-R, Digit Symbol Substitution, Trails A and B, Forward and Backward Digit Span, Letter-Number Sequencing, COWA), depression (PHQ-9), quality of life (SF-12v2), caregiving questions, process measures (DBAS-16 and Self-efficacy, Knowledge and Decisional Balance Index subscales), and other questionnaires (see Table 4). A blood sample will also be obtained from each participant. In addition, PAP adherence data will be collected as described above.

Three-month follow-up assessment: The main outcome assessment will be performed at three months after baseline assessment, using the same measures included in the post-treatment assessment.

Six-month follow-up assessment: Follow-up assessment will be performed again at 6 months after baseline assessment (to test for maintenance of outcomes), using the same measures included in the post-treatment and 3-month follow-up assessments.

Twelve-month follow-up assessment: Participants will be contacted by telephone after 12-months for a brief interview. Research staff will administer the three sleep questionnaires (ISI, PSQI, and ESS) and PAP adherence data will be collected.

Unblinded qualitative assessment among intervention participants: After completion of the six-month follow-up assessment, intervention participants will be invited to participate in focus groups (up to 6 focus groups, N = up to 40 intervention participants). Focus groups will take place during years 2 and 3 of the study in an ongoing manner as intervention participants complete their 6-month follow-up assessments. The structure and format of the focus groups will mirror techniques used in our prior qualitative research. The 90 minute focus groups will be moderated by Dr. Martin, who has previous training and experience moderating focus groups. Ms. Josephson (project manager) will take notes during the group. We will use a structured discussion guide to explore the key topics of interest, including participants' 1) experiences with the intervention (e.g., What aspects of the program were most helpful? What aspects were least helpful?), 2) attitudes and adherence with the intervention (e.g., What recommendations were the most difficult to follow? What recommendations are you still following? What recommendations are you no longer following?), 3) perceptions of the program (e.g., What do you think about the format used? What do you think about the materials, such as readability, clarity, and graphics? What other information would have been helpful?), 4) barriers to participation (i.e., What makes it difficult to attend this program?), and 5) facilitators to participation (i.e., What would make it easier to attend this program?) The focus groups will be audio-taped and transcribed.

Data Management

At study entry, each participant will be assigned a unique identification number for entry on data collection forms and computerized files. Participant identifying information will be kept separate, stored in a locked cabinet, with access limited to the principal investigator and data manager. Electronic databases will be stored on the VA GLAHS network server and the local HSR&D Center of Excellence server behind the VA firewall. Using project folders that are part of the architecture of the server, the research team will have varying levels of access to the data. Dr. Alessi (PI), Dr. Martin (co-investigator), Ms. Josephson (project manager), Ms. Jouldjian (data manager) and Dr. Mitchell (statistician) will have complete access to all data files. Other members of the research team will only have access to selected de-identified datasets. Original data forms will be archived and stored in locked cabinets. All data will be entered into a database (SPSS for Windows 20.0) using procedures established in prior work. Equipment-derived data (e.g., actigraphy, PAP adherence data) will be downloaded at the end of each monitoring period, and checked to ensure the equipment functioned properly. Down-loaded files will be backed up, cleaned and processed using specialized software to yield data variables. Separate data sets will be created for each major data type (e.g., equipment data, questionnaires, medical record review). Unit of analysis will be the participant, and data sets will contain all baseline and follow-up measures for each variable. Data in each set will be cleaned by screening for out-of-range or outlier values in frequency distributions, and compared against original data forms for accuracy. Double entry procedures will be used on a 20% random sample of cases in each data set, with additional training and review of data if errors are identified. Sleep and related data will be processed immediately following each participant's sleep monitoring session, and data from other instruments and measures will be entered within three days of data collection. Data will be cleaned weekly. Cleaned data will be merged into the main database for statistical analyses.

Sample size estimates

As described above, participants will be enrolled from the sleep clinics at VA GLAHS Sepulveda and West Los Angeles campuses. Based on FY11 data, at least 1037 patients per year will be diagnosed with OSA and prescribed PAP (using PAP equipment provided by VA GLAHS). We expect at least 52% will be aged $\geq$ 50 years, and at least 50% will also meet diagnostic criteria for insomnia. Based on this data, we conservatively estimate that at least 22 Veterans per month will be eligible for the study (i.e., [1037 PAP machines prescribed/12 months] x [.52 aged $\geq$ 60 years] x [.50 meet criteria for insomnia] =22.5). Based on consent rates in our prior VA studies we expect a 50% consent rate among eligible Veterans, which would provide at least 10 enrolled Veterans per month. We estimate that approximately 50% of enrolled participants

will meet all inclusion and exclusion criteria and be randomized, resulting in approximately 5 randomized participants per month, and our total target enrollment will be 120 randomized participants.

We have extensive experience in methods to encourage participant retention. For example, in our ongoing CBT-I trial in older Veterans, one of 122 participants who have reached the 6-month time-point has died, and only an additional 9 participants have been lost to follow-up due to other reasons, resulting in only 8.2% (10/122) loss by 6-months. In the current proposal, we conservatively estimate 15% loss by 6 months, which would result in approximately 102 (51 per group) participants completing the 6-month assessment. However, as in our prior work, we will monitor enrollment and participant loss throughout the study, to allow adjustment of the timeline and/or enrollment and retention procedures if we do not meet targets. As described in the analysis plan below, we will use standard "intention to treat" analysis, and sample size calculations have been made based on this analysis. Sample size calculations for each major outcome measure (described below) suggest that the target sample size will be sufficient to test our major hypotheses. All sample size calculations are based on 80% power and two-tailed P-value < .05.

Analysis Plan and Hypotheses

The analysis plan for each specific hypothesis is listed below. In addition to hypothesis testing to analyze effects of the intervention on sleep, PAP adherence, depressive symptoms and quality of life, we will develop models showing which covariates predict the values of each of the outcome measures. Prior to hypothesis testing, data will be cleaned, possible outliers identified, and data distributions evaluated for assumptions of analysis (e.g. normality, homogeneity of variance). If necessary, normalized rank transformations as described in Bonate[24] will be performed and normalized rank scores will be submitted to analysis.

Hypothesis 1: Compared to control participants, participants randomized to the intervention will have improved nighttime sleep (i.e., higher sleep efficiency, better self-reported sleep) and better PAP adherence (measured objectively) at 3-months follow-up.

This hypothesis tests for differences between the intervention and control groups in our primary outcome measures of nighttime sleep and PAP adherence, between baseline assessment and 3-months follow-up, which is our primary time endpoint. Subjective measures of sleep outcomes will include sleep diary (sleep onset latency, wake after sleep onset [WASO], and sleep efficiency) and sleep quality (PSQI). The objective measure of sleep outcome will be actigraphy (sleep efficiency), and the objective measure of PAP adherence will be downloaded from the PAP smart card (percent of nights with PAP use $\geq$ 4 hours, and mean hours of PAP use per night). All outcomes will be assessed using intention to treat analyses. A 2 X 2 (time X group; where time = baseline or 3-month assessment; and group = intervention or control) analysis of covariance analysis will be used with Bonferroni-corrected post-hoc comparisons to investigate differences between the groups in terms of treatment effects in the sleep variables (where baseline and 3-month follow-up data will be available). For PAP adherence outcomes, there will be no "baseline" data (i.e., PAP adherence data isn't available until the participant starts PAP therapy), so outcomes between groups will be compared with independent samples t-tests and Chi-square test for difference in proportions.

We expect that the group by time analysis of covariance for the sleep variables will show a difference between groups, and post-hoc analyses will show increased nighttime sleep efficiency and improved self-reported sleep (indicated by lower PSQI scores) in the intervention group compared to the control group. Following review of graphical representation of our longitudinal results (on main outcome measures), we will use repeated measures ANCOVA models to test both linear and nonlinear (i.e., quadratic) differential changes over time. Post-hoc tests within each time point (using Tukey type 1 error control) will be conducted. We expect there will be no difference between intervention and control groups at baseline, but differences will be present at follow-up. Other participant characteristics will be considered as possible covariates to reduce bias in our estimate of treatment effects and to increase precision. The major covariates that we expect to consider are age, cognition (estimated by MMSE) and comorbidity (estimated by CIRS-G). Other covariates we will consider include specific diagnoses and medications that may interfere with sleep, and measures of the intervention process (DBAS-16 scores, Self-efficacy, Knowledge and Decisional Balance Index subscales).

Sample size calculations were performed for each of the main outcome variables using reported effect sizes and/or calculated effect sizes from reported sample means and standard deviations reported in the literature in prior studies of CBT-I for insomnia and behavioral PAP adherence interventions in outpatient adults (see Table 5). Prior literature indicates that CBT-I is an extremely potent intervention for insomnia, and the studies typically have large effect sizes and small samples. Some caution is warranted, however, since efficacy studies usually employ tightly controlled 'ideal' treatment conditions, which also yield larger effect sizes

than effectiveness studies with more 'real world' conditions. Regardless of these issues, even the most conservative estimates of effect size from the literature suggest we will have an adequate sample size to test our sleep outcomes. A recent meta-analysis of trials of PAP adherence interventions published as a Cochrane review was used in estimating sample size for the PAP adherence component of our intervention;[Error! Bookmark not defined.] this analysis suggests we will have an adequate sample size to test our PAP adherence outcomes.

For the proposed study, we calculated sample size based on the outcome at post-treatment, and either the reported effect size (d) or d calculated from the reported means and SDs. The table below lists sample size needs for the entire duration of the study (i.e., 6 months). Based on an expected 15% loss by six months, the 5th column in the table below projects the sample size needed for each of 2 groups at randomization to maintain sufficient sample size at 6 months to test the selected outcomes.

Table 5 lists expected effect size, shown as the variable "d" (difference between intervention and control groups at follow-up divided by standard deviation). For many outcomes, we list several expected effect sizes from the literature; references for these effect sizes are listed in the second column. The effect size estimates take into account expected change in controls over time, since we expect controls will change, but not as much as the intervention group. The sample size needed at randomization to detect effect size d is shown (column 4), followed by the number of enrolled participants needed for the 6-month analyses (column 5), taking into account expected dropout by this time point. Based on these calculations, 120 randomized participants (60 per group) will be adequate for analyses at both 3 and 6 months. In addition to these main analyses, we will perform follow-up subgroup analysis to identify two or three variables which identify participants who have the greatest positive response to the intervention. Testing for subgroups with better or worse response results in such a small sample that overfitting is a potential problem; this risk is discussed below.

For example, in Table 5 the third row (WASO by sleep diary) shows that to have the needed sample size (N=19 per group) completing the study (i.e., with follow-up assessment data) to test for an effect (based on an expected 15% participant loss by 6 months), we need to enroll 22 participants per group (column 5) at baseline to have 19 participants per group remaining at 6 months follow-up. For all variables listed, we expect an adequate sample size to test our hypotheses. For all sample size calculations, the dropouts are assumed not to change on average. All testing assumes a two-sided .05 significance level with 80% power.

Table 5: Sample size calculations

Outcome	Reference	Reported (or calculated) effect size d	Enroll per group for d: post-test	Enroll per group for d at 6 months
WASO				
Sleep diary	Germain[Error! Bookmark not defined.]	.67	19	22
Sleep efficiency				
Sleep diary	Espie[Error! Bookmark not defined.]	.68	13	15
	Germain[Error! Bookmark not defined.]	.64	16	19
Actigraphy	Edinger[Error! Bookmark not defined.]	.60	27	32
Sleep onset latency				
Sleep diary	Espie[Error! Bookmark not defined.]	.58	20	23
	Germain[Error! Bookmark not defined.]	.80	10	12
Sleep quality				
PSQI, similar scales	Edinger[Error! Bookmark not defined.]	.58	20	23
	Germain[Error! Bookmark not defined.]	1.37	10	12
PAP adherence				
	Cochrane Review[Error! Bookmark not defined.]	.59	47	54
	Olsen[Error! Bookmark not	.55	54	62

	defined.			
	Richards[Error! Bookmark not defined.]	1.12	14	16
Depression				
Hamilton Depression Scale	Germain[Error! Bookmark not defined.]	.67	14	16
Quality of life				
SF-36	Buysse[Error! Bookmark not defined.]	.57	50	58

Hypothesis 2: Compared to control participants, participants randomized to the intervention will report fewer depressive symptoms and better health-related quality of life at 3-months follow-up.

This hypothesis tests for differences between the intervention and control groups in depressive symptoms (using the PHQ-9) and health-related quality of life (using the SF-12v2) between baseline assessment and 3-months follow-up. All outcomes will be assessed using intention to treat analyses in an identical manner as described for Hypothesis 2. For sample size calculations, we used data from studies that used the same instrument as planned for the current proposal (if available) or from studies where similar measures were used, if results from the identical measure were not available (see Table 5).

Hypothesis 3: Compared to control participants, participants who receive the intervention will maintain improvements in sleep, PAP adherence, mood and quality of life at 6-months follow-up.

This hypothesis tests for differential change in outcomes between the intervention and control groups from baseline to follow-up assessment at 6 months, to test for maintenance in differences between intervention and control groups in the key sleep, PAP adherence, depressive symptoms and quality of life outcomes at 6 months follow-up. The statistical analyses used will be the same as described for Hypotheses 1 and 2.

Hypothesis 4a: Among intervention participants, improvements in beliefs and attitudes about sleep and OSA will be associated with improved nighttime sleep and better PAP adherence at 3- and 6-months follow-up.

Hypothesis 4b: Intervention participants will identify factors that act as facilitators or barriers to their participation and adherence with the intervention.

We will measure (in both the intervention and control groups) participants' beliefs and attitudes about sleep (using the DBAS-16) and OSA and PAP therapy (using the Self-efficacy, Knowledge and Decisional Balance Index subscales). We will test for differences between groups in these scales between baseline and 3-months follow-up using analysis of covariance (as described above under Hypothesis 1). These scales will also be included as covariates in secondary analyses of main study outcomes to address the effect of "dose" of intervention received on particular participant outcomes (e.g,. nighttime sleep and PAP adherence). Within the intervention group, we will also review specific aspects of the process of the intervention (e.g., sleep diary data on bedtime, rise time, in-bed time and daytime napping) to further clarify whether key aspects of the intervention were implemented by participants.

In addition, qualitative information will be collected from intervention participants during focus groups conducted after completion of the 6-month follow-up assessment to determine participants' experiences and attitudes about the intervention which may act as potential facilitators or barriers to future implementation into clinical practice (from the patient point of view). We will perform three types of analyses of this data. First, during the focus groups, the moderator will assure face validity and accuracy of understanding as the discussion progresses, and will summarize key points and invite further comment and clarification from participants. The second analysis will be completed immediately following the focus group, where the moderator and note taker will debrief each other, using notes and the audio-recording to generate a description of issues and themes that arose in response to each question in the interview guide. This grounded approach integrates data collection and analysis, so the individuals who are most familiar with narrative responses identify core themes (e.g., difficulty with adhering to certain aspects of the intervention) that emerged in discussions. These themes will be incorporated in the coding system for the final level of analysis. The third analysis will be a note-based[25] aggregation of domains and thematic responses across the focus groups. Transcriptions and audio recordings will be used as reference documentation. Themes (e.g., beliefs about

acceptability of treatment) and specific issues (e.g., barriers) will be identified and inform future broad implementation of the intervention.

Potential Shortcomings in the Proposed Analysis

There are statistical problems we may encounter in analyses, including the statistical handling of participant dropout, possible differential treatment effects across randomization blocks, and the risk of overfitting the data. To deal with dropouts, we will use standard "intention to treat" analysis. The main independent variable will be whether a participant is in the intervention or control group, rather than whether the participant actually receives the intervention. If the participant rejects the intervention at some point after randomization, but allows us to collect follow-up data, we will use standard “intention to treat” analysis. If the participant stops providing data, we will do analyses using all available data, and then repeat analyses after estimating missing data using an EM (expectation-maximization) algorithm, which is less subject to bias than other methods such as carrying forward the last available value; results from both analyses will be reported. It is important to address dropouts, since those who complete the study may be more compliant or healthier than those who drop out. To understand how “completers” may differ from “dropouts”, we will compare their baseline characteristics. Dropout rates and characteristics of dropouts will also be compared between groups.

To address the risk of a differential effect of the intervention between randomization blocks, we will test for a block by group interaction. If one is present (suggesting the treatment is more or less effective for one stratification group over another), the results cannot be pooled, which impacts statistical power. However, we anticipate overall treatment effect will overshadow any differential effects across stratification blocks.

Finally, there is a risk of overfitting the data when we perform follow-up subgroup analyses to identify characteristics of participants who have the greatest positive response to the intervention. We will address this issue in two ways. First, we will use factor analysis with the full sample to group the independent variables into a small number of factors, then use clinical judgment and the literature to pick one representative variable from each factor. Second, we will use repeated split-sample methods in fitting the data. These methods repeatedly test the fit developed on part of the data on the remaining data. We have extensive experience with these methods to address potential shortcomings in analysis, and additional local expertise and resources are readily available to advise the study team on these issues.

Limitations of the Proposed Research

There are three major limitations to the proposed research that will be addressed here. First, although we will measure the effects of the intervention on attitudes and beliefs about sleep and PAP therapy, we may not be able to determine a causative association between other aspects of the process of the intervention and study outcomes. In addition, our qualitative data collection will focus on the experience of intervention participants, and may not address other issues of future implementation (e.g.., barriers and facilitators at the provider and healthcare facility level). However, we will seek advisement from the local HSR&D Center of Excellence on these other implementation issues and, if the proposal is successful, we plan to pursue additional funding for work aimed at implementation of the intervention into clinical practice. Second, we will not be able to test the role of CBT-I alone or the PAP adherence program alone, as compared to the combined, integrated intervention in determining outcomes. This would require a 4-group study design (i.e., CBT-I alone, PAP adherence program alone, integrated CBT-I plus PAP adherence program [our intervention], control group), which would at least double the necessary sample size. In fact, comparison of active treatment conditions (e.g., CBT-I alone versus integrated CBT-I plus PAP adherence program) would likely require an even higher sample size to achieve adequate power for statistical analyses. Based on our clinical experience, we believe a behavioral approach to managing coexisting OSA and insomnia in older Veterans must address both conditions in an integrated manner, as included in the current proposal. Third, because we have chosen an active control condition (rather than a usual care control condition), we will not be able to test for a difference between our intervention and usual care. However, based on our experience in testing behavioral interventions and current thought on how to best address the “placebo” effect with behavioral interventions, we feel it is essential to provide an active, “social attention” control condition to address a possible placebo effect. In addition, we’ve found that an active control condition keeps participants randomized to the control group engaged in the research, maintains contact with them to a similar degree as the active treatment group, and thereby helps prevent greater dropout among controls.

Dissemination and Implementation Plan

As in our prior work, we will make extensive efforts for broad dissemination of research findings and implementation of the methods tested in this proposal. Research findings will be disseminated at local, regional and national geriatrics/gerontology, health services and sleep meetings and in publications in high impact journals. Findings will also be disseminated via educational venues of the VA GLAHS GRECC, our local VA HSR&D Center of Excellence, and the UCLA/VA Multicampus Program in Geriatric Medicine and Gerontology. The senior researchers involved in this proposal have extensive professional links, both within and outside the VA, nationally and internationally, allowing for extensive dissemination. For example, Dr. Alessi is a Member of the Board of Directors and is currently President of the American Geriatrics Society, Immediate Past Chair of the Health Sciences Section of the Gerontological Society of America, a member of the VA National Geriatrics Task Force, and a prior Chair of the Circadian Rhythms Section of the American Academy of Sleep Medicine. Dr. Martin is a nationally recognized behavioral sleep medicine specialist and is one of 3 national trainers in the ongoing VA Evidence Based Practice roll-out of CBT-I for VA mental health professionals. In addition, our GRECC provides extensive training to staff and trainees at VA GLAHS, and findings from this study will be incorporated into this training, which can be disseminated regionally and nationally. Dr. Zeidler is Associate Director of our Sleep Medicine Fellowship Program here, and will disseminate findings through educational venues in our sleep program. We will also incorporate findings from this study into ongoing quality improvement projects at VA GLAHS.

We also have an extensive implementation plan that focuses on local and national implementation. Locally, if the intervention is successful, these methods will immediately be implemented at VA GLAHS through our local insomnia treatment programs (which Dr. Martin directs) and OSA treatment in our VA GLAHS sleep clinics (staffed by Dr. Zeidler). Both these programs are housed within the VA GLAHS American Academy of Sleep Medicine accredited Sleep Disorders Center (directed by Silverio Santiago, MD, who has provided a letter of support for this proposal). The treatment materials and manuals developed for this intervention will be immediately adopted for use within these clinical programs. This local dissemination will rapidly allow access to this intervention at our medical center, and will provide information as to whether the intervention remains effective when implemented clinically. In an ongoing process, we will track whether clinical outcomes from initial local implementation of this treatment program are comparable to outcomes obtained in the proposed trial. If needed, revisions will be made to the treatment prior to dissemination beyond VA GLAHS. As part of this local implementation, we will solicit feedback from clinicians and trainees who use the intervention program and materials, to modify the intervention materials prior to broader implementation.

We believe that broader implementation outside VA GLAHS will require additional funding. If the intervention is successful, we will propose a 3-step approach for broader implementation. The first step will be to develop a patient screening algorithm that can be used to identify Veterans who are appropriate for the intervention. We believe that development of a structured algorithm must be included with the intervention program materials to help clinicians identify Veterans who are most appropriate for the intervention. This algorithm will be based on screening methods implemented in the current proposal, modified based on findings of the study. Second, using results from the intervention focus groups performed in the current proposal, we will identify patients' perspectives on potential facilitators and barriers to implementation of the intervention. These results will be used to modify the intervention methods prior to broader implementation testing. Finally, using these results and intervention materials from the larger study, we will develop an implementation package for broader implementation, which will provide the actual tools needed to implement this model of care into current clinical practice. Toward that aim, we will develop a multi-component intervention implementation package that will include screening tools, treatment materials, treatment adherence monitoring techniques, key pre- and post-intervention outcome measures, and training materials for providers who implement the intervention. This implementation package will be based on our research findings, input from Veterans who completed the program, and consultation from experts in behavioral treatment of insomnia and in adult education methodologies. We'll test the revised materials in an iterative process, until ready for implementation.

We believe this type of intervention will be most easily implemented in the context of sleep clinics, which house the expertise to oversee the CBT-I and PAP adherence aspects of the intervention. It is possible the intervention can be implemented with oversight at a distance from the site of implementation, which would provider for even broader implementation. Dr. Martin is one of three national trainers for the Evidence-Based Psychotherapy Rollout of CBT-I. In this program to date, over 400 VA mental health providers have completed training in CBT-I; this resource provides a tremendous opportunity for implementation of an intervention combining CBT-I and the behavioral PAP adherence program.

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