STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

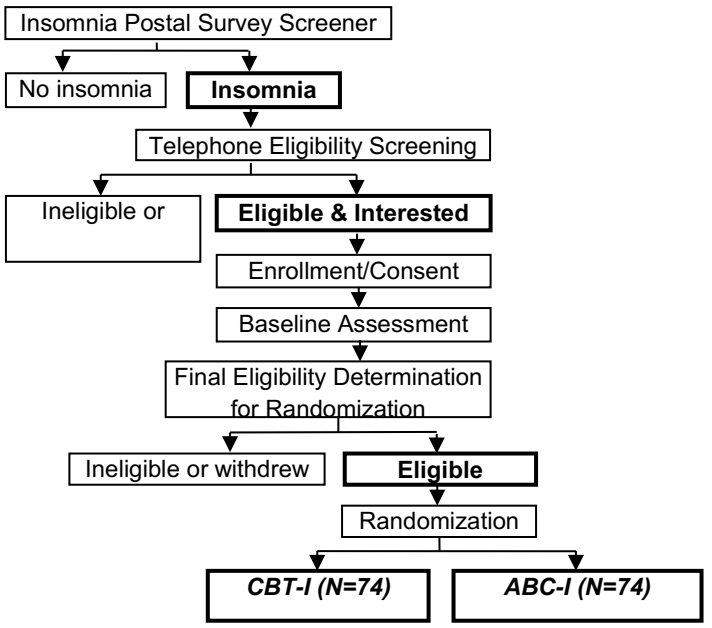
A PATIENT-FOCUSED APPROACH TO INSOMNIA TREATMENT FOR WOMEN VETERANS

3. RESEARCH DESIGN AND METHODS

3.1. Basic Study Design

The proposed study is a 4-year randomized trial to test the effectiveness of a novel treatment program for insomnia among women Veterans receiving outpatient care. The basic design is shown in **Figure 7**. As in our prior work, we will identify potential participants using a postal screening survey, including questions targeting ICSD diagnostic criteria for insomnia.[46] This survey will be sent to women who have received outpatient care (at least one visit) at the VA Greater Los Angeles Healthcare System (VAGLAHS) within the prior six months and live within a 50 mile radius of the Sepulveda Ambulatory Care Center (SACC) where the study will be conducted. Those who return the survey indicating symptoms of insomnia will be contacted by telephone to clarify study eligibility and to invite them for in-person screening/enrollment and baseline assessments. We anticipate enrolling a total of 400 women to achieve the proposed sample of 148 randomized participants (74 to receive ABC-I, and 74 to receive CBT-I). Participants will complete a comprehensive sleep, mental health and physical health assessment at baseline (pre-treatment), immediately after the intervention ends (post-treatment), and 3 months after the end of the intervention (3-month follow-up). The primary outcomes will focus on differences in treatment adherence and attrition. We will also compare the effectiveness of the two interventions in terms of improving self-reported sleep quality and insomnia symptoms, plus objectively monitored sleep/wake patterns (wrist actigraphy) measured at post-treatment and at the 3 month follow-up using a non-inferiority design. Data will be analyzed both for treatment completers and for all randomized participants in an intention to treat analysis. Based on our recent work in this area, we expect to be able to enroll and randomize 148 women Veterans into the study within the proposed time frame. The planned research has been informed by our recently-completed HSR&D funded pilot study,[46] and our ongoing HSR&D funded intervention trail of CBT-I with older Veterans (PI: Alessi).

Figure 7: Study design



3.2. Setting

The proposed study will be carried out within the VAGLAHS where over 7,000 women Veterans receive care each year. All in-person study assessments and treatment sessions will be completed at the SACC or West Los Angeles (WLA) campuses within the VAGLAHS. Unattended overnight sleep recordings (sleep apnea testing and wrist actigraphy) will take place in the participant's home with equipment provided to the participant during their visit to the campus where they will complete the other study assessments.

3.3. Study participants

3.3a. Recruitment: To randomize a total of 148 women Veterans into this trial, we will complete a three-step screening process. Inclusion/exclusion criteria at each step are described in detail below and are specifically aligned with the inclusion/exclusion criteria used to assess the appropriateness of patients for CBT-I.[34] The first step will involve identification of women with insomnia symptoms using a postal screening survey. The second step will involve a brief telephone screening for basic eligibility criteria and interest in participation. The third and final step will take place after written informed consent is obtained and baseline assessments are complete. We chose this 3-step methodology for identification of potential participants because we have found it is an efficient way to identify participants for intervention studies and it will generate a more representative sample than would be obtained by, for example, screening Veterans within medical clinics. We have experience using this approach in a recent randomized trial with older Veterans, and we have based the number of participants expected at each phase of the screening process on this recently-completed study carried out at our facility and on our pilot work with women Veterans. Our general approach was to limit research-related exclusionary criteria to enhance generalizability; thus we will only exclude women with insomnia who would not be appropriate for CBT-I provided in the manner it is being disseminated by VHA, or in

the event they have significant barriers to participation that would also represent barriers to clinical care for insomnia (e.g., active psychosis). For example, women who have conditions likely to impact sleep on an acute basis (e.g., recent surgery) will not be enrolled until their conditions stabilizes. We will not formally exclude them from participation.

3.3b. Insomnia postal survey screener (step 1): Using the survey developed in our pilot study, we will screen women Veterans for symptoms of insomnia. The survey will include items addressing the diagnostic criteria for insomnia and will be used to identify women who meet these basic criteria as potential participants in the trial.[46] The postal survey will be mailed with a brief letter and study information brochure describing the project as research. Women Veterans will be invited to return the survey in a postage paid return envelope. The survey will include an "opt out" box that Veterans may check if they do not wish to be contacted by telephone. They will also be provided with space to list a telephone number and "best time to call" if they wish.

Veterans who do not return the survey within two weeks from the date of the first mailing will receive a second survey with a slightly different letter and information brochure. Veterans who do not return the second survey and who do not return an "opt out" card within approximately 4 weeks after the second mailing, will be contacted by telephone by a research assistant and invited to complete the survey over the telephone. We will follow the same procedures for contacting Veterans as were approved for our project #0006. We will leave up to 4 telephone messages over a 4 week period. Veterans who do not return our call within those parameters will be considered as "not interested" in participating.

In total, we plan to send this brief screening survey to approximately 20,000 women Veterans over the first three years of the study. We will obtain a dataset of names and addresses of all women Veterans who have received care at the VAGLAHS within the last 6 months from VA Health Eligibility Center (HEC) three times during the study period.

Table 3: Estimates for Screening, Enrollment, & Randomization

	Projected N
Postal surveys to be mailed	20,000
Recruitment flyers and letters sent to additional women Veterans	200
Subjects enrolled into study	400
Subjects randomized	148

We will obtain the first mailing list in year 1 of the study. We will then select the subset of women who live within 50 miles of the SACC site where the in-person visits will take place. The list will be put into random order and the survey will be sent to the first 1,700 women on the randomly-ordered list. This will be considered the recruitment sample for year 1. In year 2, we will obtain a revised mailing list, and again select the subset of women who live within 50 miles of the site. We will exclude women who received the postal survey in the first mailing leaving approximately 3,300 remaining individuals. We will put this list into random order and again send the survey to the first 1,700 women on the list. This process will be repeated a third time in year 3 so that each year we will have up-to-date addresses for the women in our recruitment sample. In our pilot work we found that women Veterans with a visit in the prior 6 months were more likely to receive (i.e., surveys were not returned without forwarding addresses) and return a completed survey than women with a visit 6-24 months before the mailing list was generated.

In year 3, the inclusion criteria will be broadened to include Veterans who received care from any VA healthcare facility and who live within 100 miles from SACC.

Additional recruitment strategies: We will also place study flyers/posters in the waiting areas and assessment rooms at West Los Angeles and Sepulveda Ambulatory Care Centers. Specifically, flyers/posters will be placed in the Women's Health clinics, Sleep Medicine clinics, and Primary Care clinics. The flyer/poster will include the study's telephone number.

We will also recruit women Veterans who have a referral to the Insomnia Treatment Program within the Sleep Disorders Clinic at SACC. Due to limited provider availability in the clinics, wait time for an initial appointment is typically 6-12 months. Since study activities only last for approximately 3 months, we anticipate that all of the study activities could be completed before these subjects are seen in the insomnia clinic. Enrollment in the study will not delay the clinical care these women Veterans receive. These potential subjects will be identified using the VISTA clinic appointment menu. Contact information for women Veterans with a referral to the Insomnia Treatment Program will be recorded and a recruitment letter and flyer will be mailed to them. The letter will inform the Veteran that she will be contacted by telephone by a member of the research team within 10 days, unless she returns an "opt-out" postcard enclosed with the recruitment letter.

If we find that the address or telephone number listed in the HEC database, or provided by the Veteran on the postal survey, are not valid, we will access the Veteran's CPRS electronic medical record to look for updated contact information. If we are unable to find a working telephone number for those Veterans who

return a postal survey, we will mail the Veteran a recruitment letter and flyer (see attached Recruitment letter for postal survey respondents).

Veterans who cannot be reached by telephone, but who provide an email address on the postal survey, will be sent an email message describing the study with an invitation to contact the research office (see attached Email Recruitment Message).

Table 3 shows estimates for the number of women Veterans who will receive recruitment materials, the number who will be enrolled, and the number randomized.

3.3c. Telephone eligibility screening (step 2): As surveys are returned, women will be contacted by telephone as quickly as possible (within 2 weeks). The study will be explained, verbal consent for screening will be obtained (following procedures previously approved by our IRB) and additional eligibility criteria will be assessed with a screening questionnaire. The screener will include items to assess whether they have experienced a major health event (e.g., surgery) within the past month (in which case they will be re-contacted 3 months later), whether they have stable housing and access to transportation to the medical center, and whether their current health status would prevent them from participating. We will also ask whether they are participating in a drug or alcohol treatment program, and as is standard for CBT-I, individuals with less than 90 days sobriety will be re-contacted 3 months later. Study inclusion criteria will include:

- Female Veteran
- Community-dwelling
- Age ≥ 18 years
- Received care from a VA healthcare facility
- Responses to postal survey indicate symptoms of insomnia
- Did not check “opt-out” box for further contact on postal survey
- Live within 100 mile radius of Sepulveda VA Ambulatory Care Center

Exclusion criteria for enrollment (based on response to telephone screening questions)

- not a female Veteran
- unstable housing (since we may not be able to retrieve costly and difficult to replace monitoring equipment)
- do not have access to transportation to the medical center
- current pregnancy
- significant health or emotional problems, or use of drugs or alcohol

We will offer to re-contact women who have had a recent health event or who plan to relocate and offer them an opportunity to participate in the future. All other interested women will be considered eligible for participation. We will make attempts to accommodate women who wish to participate in the study outside of work hours by offering evening appointments to those who are not able to come in for multiple appointments during the work day.

The same process as described above will be followed for women who contact the study in response to the flyer, the recruitment letter, or who do not opt out of telephone contact by the study. For ~~this~~ these groups of interested women, the postal survey questions will be asked before the screening questionnaire to ensure that the Veteran meets diagnostic criteria for insomnia.

3.3d. Enrollment and Informed consent: Written informed consent will be obtained at the first in-person contact, prior to the collection of research data. At the time of the first in-person interview, research staff will explain the study in detail and answer all questions. Capacity to give informed consent will be evaluated with a brief questionnaire (previously approved by our IRB) that asks the Veteran to recount major procedures and risks of the study. Veterans who are unable to provide informed consent will be excluded; proxy consent will not be pursued. Based on our pilot work, we conservatively anticipate that 11% of women who agree to an appointment initially will cancel the appointment or will refuse consent after learning more about the study. We expect to have an adequate number of available, eligible participants to enroll up to 400 women over the proposed study time period. To randomize a total of 148 individuals, we anticipate needing to enroll a total of 296 women; therefore, we will have a sufficiently large pool of potential subjects to account for any under-estimation of the randomization rate.

We will encourage adequate minority participation by training staff to be culturally sensitive in all interactions, and we will prospectively monitor race/ethnicity of enrolled participants to compare with race/ethnicity data within the overall survey sample so any problems with minority enrollment can be identified

and addressed quickly. In our pilot work, we successfully enrolled a large proportion (56%) of racial/ethnic minority participants using these methods and procedures.

3.4. Procedures

Figure 7 (above) outlines study procedures**.** Once enrolled, participants will complete a baseline assessment lasting 9 days (see **Table 5**, below), and final eligibility determination will be made after the baseline assessment is complete. Women Veterans who meet all study criteria and agree to continue participation will be randomized to receive either the ABC-I program or a similarly-structured CBT-I program. Throughout treatment, adherence will be monitored, and after treatment, selected baseline measures will be repeated to measure the immediate effects of the treatments on sleep. Participants will be re-assessed 3 months later to assess maintenance of gains.

All data will be collected by trained research personnel, using participant interview, medical record review, and participant monitoring. Research staff will undergo structured training, including review of human subjects protection issues, emergency procedures, basic interviewing techniques, cultural sensitivity training, and in-depth instruction on data collection instruments and equipment. We have developed procedure manuals for all instruments and equipment to be used in this study. Adequate inter-rater reliability will be established prior to beginning the study and will be repeated on an annual basis. These procedures have resulted in consistent, reliable data collection in our prior work. The methods and instruments we have selected were chosen to minimize participant burden while maximizing reliability and validity. Assessment staff will be blinded to the intervention group to which the participant is assigned and to the study hypotheses. This blinding and separation of intervention and assessment staff will also facilitate completion of the post-treatment and follow-up assessments by participants who drop-out of the treatment. To offset expenses associated with travel and/or childcare during assessment visits, we will offer a monetary incentive for each assessment visit. Incentives will not be offered for treatment sessions as that would not be consistent with usual care.

Table 5: Screening, enrollment and baseline data collection process

	Day 1 Visit 1	Night 1	Day 2 Visit 2	Nights 2-8							Day 9 Visit 3
Informed consent; demographics	X										
WatchPAT overnight sleep apnea monitoring*	X	X	X								
Questionnaire assessments: Part 1	X										
Questionnaire assessments: Part 2			X								
Wrist actigraphy* and sleep diary			X	X	X	X	X	X	X	X	X
Questionnaire assessments: Part 3											X

*Equipment worn at participant's home

3.4a. Baseline assessment: Once enrolled, participants will complete a 9-day pre-treatment baseline assessment consisting of 3 visits to the SACC or WLA sites where questionnaire assessments will be completed in private offices used for research purposes by study assessment staff (see **Table 7**). At the first visit, participants will complete the informed consent process, will be administered Part 1 of the questionnaires, and will be provided with the WatchPAT recording device for overnight monitoring of sleep apnea. The participant will watch an instructional video on use of the WatchPAT, and application of the equipment will be demonstrated. They will be given a toll-free number to call if difficulties arise with the WatchPAT equipment overnight.

On Day 2, the participant will return for Visit 2. She will return the WatchPAT device, and complete Part 2 of the questionnaire assessments. She will also be provided with a wrist actigraph to wear at home for 1 week, and a sleep dairy to complete each day while wearing the actigraph. At the conclusion of the 1-week actigraphy recording, the participant will return to the facility for Visit 3. She will then complete Part 3 of the questionnaire assessments (described below). Based on our experience, Part 1 of the questionnaire battery will take approximately 30 hour to complete, Part 2 (including the SCID and CAPS) will take approximately 90 minutes to complete, and Part 3 will take 30 minutes to complete. Participants who complete the baseline assessments will be compensated a total of $125 for their travel and time ($75 for questionnaires, $25 for 1 week home actigraphy; $25 for WatchPAT home sleep apnea testing).

3.4b. Final eligibility determination prior to randomization: The final eligibility determination will take place after informed consent is obtained and the baseline assessment is complete. This determination will be made during a weekly meeting of the investigators. At a minimum, the meeting will include one psychologist specializing in Behavioral Sleep Medicine (Dr. Martin), and one Board Certified Sleep Medicine physician (Dr.

Alessi or Dr. Fung). The member of the study team who completed the baseline assessments with the participant will also be in attendance. During this "pre-randomization review" meeting, the final set of exclusionary criteria will be reviewed by the investigators. The final set of exclusion criteria will include:

- significant untreated sleep disordered breathing (AHI > 30) from WatchPat or moderate untreated sleep disordered breathing (AHI between 15 and 30) with daytime sleepiness (ESS > 9)
- restless legs syndrome that accounts for the sleep disturbances reported
- circadian rhythm sleep disorder that accounts for the sleep disturbances reported
- active substance users or in recovery with less than 90 days of sobriety
- unstable medical or psychiatric disorders (which is a contraindication for behavioral treatment of insomnia)
- remission of insomnia

Participants with treated sleep disorders will not be excluded as long as their report and medical records indicate they are adherent to treatment.

Based on our pilot study, we anticipate excluding 35% of participants due to untreated sleep disorders. We expect a small number of women (1%) will experience remission of insomnia during the time period between postal survey screening and randomization. Individuals who no longer meet the diagnostic criteria for insomnia at the baseline assessment will be excluded. A review of the patient's medical record and SCID will be completed as well to evaluate whether the individual has unstable medical or psychiatric conditions (e.g., ongoing chemotherapy, untreated schizophrenia) that would make it difficult to maintain the participant's engagement in the study. We anticipate excluding approximately 12% of individuals who complete baseline for these reasons. These individuals would also not be appropriate for CBT-I under usual care conditions.

We will not exclude individuals who have a psychiatric or medical condition that is stable. For example, we will not exclude individuals with chronic pain, PTSD or depression. We will only exclude these individuals if, for example, their psychiatric medications are being adjusted due to insufficient treatment response. We also will not exclude individuals using medications for sleep. We will track hypnotic medication use throughout the study to evaluate whether the intervention has an impact on sleep medication use, but will not exclude individuals using stable doses of sleep aids or other psychoactive medications.

Table 6 shows the projected number of individuals who are expected to be excluded for the reasons listed above, and the number expected to discontinue participation prior to randomization (5%). We have accounted for this in the derivation of our sample as well. We anticipate that a total of 198 women will be deemed appropriate and will agree to randomization. The required sample size of 148 women is therefore feasible given the projections described here.

Table 6: Estimates of eligibility determination prior to randomization

	Projected N(%)
Number (%) consented and enrolled	**400**
Excluded: untreated sleep disorders	140 (35%)
Excluded insomnia remission	4 (1%)
Excluded: unstable/severe medical or psychiatric condition discovered during assessment	48 (12%)
Number (% of consented) eligible for randomization	**208 (52%)**
Withdraw after baseline, prior to randomization	10 (5%)
Number who agree to be randomized	198 (95%)
Number (%) randomized	**148 (75%)**

3.4c. Randomization: Individuals who complete the study baseline assessment and meet all inclusion/ exclusion criteria will be randomly assigned to one of the two intervention groups: ABC-I (n=74), or CBT-I (n=74). Dr. Martin will make all final determinations regarding eligibility for randomization with input from the study physicians. Both interventions are described in detail below. Randomization procedures will follow the CONSORT criteria for randomized trials.[47] Stratified randomization will be used to help insure that ABC-I and CBT-I groups are balanced in baseline severity of sleep problems. Strata will be based on hours of sleep reported on the screening postal survey (>6 hours vs. ≤6 hours). The number of subjects in each stratum is not expected to be equal, but within each stratum, half will be assigned to each group (ABC-I and CBT-I). This will help to insure balance in baseline severity across the two treatment groups.

Dr. Mitchell (statistician) will generate the stratified randomization sequence. A set of envelopes containing the group assignment will be generated and the data manager (Ms. Jouldjian) will store the randomization envelopes in a secure file drawer that only she and Dr. Martin can access. Once eligibility is determined, Ms. Jouldjian will open the next envelope in sequence within the appropriate stratum.

3.4d. Intervention: Both interventions will involve 5 weekly sessions with a trained interventionist. The ABC-I and CBT-I are described and compared in detail below (refer to **Table 10**). The intervention period is expected to last approximately 5 weeks. Intervention activities will take place in designated, private research offices. All treatment sessions will be audio recorded and reviewed by Dr. Martin to ensure the integrity of the intervention and avoid cross-contamination of the non-overlapping portions of the programs. Interventionists will also maintain a session-by-session check list of information covered and recommendations made. "Progress notes" will be maintained by the interventionist and reviewed during weekly supervision meetings with Dr. Martin.

Since treatment participation is one of the main study outcomes, we will standardize our efforts to complete treatment across the ABC-I and CBT-I groups. Participants will receive a reminder telephone call the day before each of their intervention sessions. If a participant cancels an intervention session, efforts will be made to reschedule. If the participant does not attend the session without advance notice (i.e., “no shows”), we will make up to three attempts to reach the participant by telephone. We will then send a letter to the participant indicating they can call the interventionist to reschedule and continue treatment if they wish. This is the process followed in our ongoing clinical insomnia program and is consistent with current practices. The number of attempts and ultimate outcome will be tracked by the interventionists as well.

3.4e. Post-treatment assessment: The post-treatment follow-up assessment will be conducted over an 8-day period and will be similar in structure to the baseline assessment. Post-treatment assessments will be scheduled by the assessment staff members to occur 1-2 weeks after the scheduled completion of the intervention, and we will make efforts to encourage participants to complete the assessments even if they elect not to complete the intervention program (e.g., gather information by phone, offer evening appointments). The Veteran will then complete selected measures from the Part 1 and Part 2 assessment battery with a member of the assessment staff. She will again be provided with a wrist actigraph to wear at home for 1 week, and a sleep dairy to complete each day while wearing the actigraph. At the conclusion of the 1-week actigraphy recording, the participant will return to the facility to complete selected components of the Part 3 assessment packet.

3.4f. Three-month follow-up assessment: Similar to the post-treatment assessments, 3 months after the end of treatment, participants will be contacted by the assessment research assistant and asked to repeat selected measures from the baseline assessment plus additional measures on healthcare utilization and life events. Similar to the post-treatment follow-up, assessments will be completed over an 8 day period including two visits to the study site. At the first visit, selected measures from the Part 1 and Part 2 assessment battery will be completed, the participant will again be provided with a wrist actigraph to wear at home for 1 week while completing a sleep dairy. She will then complete selected components of the Part 3 of the assessment packet at the end of actigraphy monitoring. We selected the 3-month follow-up time frame as it strikes a balance between the desire to evaluate the longer-term effects of the treatment while considering that longer follow-up intervals may decrease our ability to contact participants for re-assessment. Participants who complete the 3-month follow-up assessments will be compensated a total of $75 for their travel and time ($50 for questionnaires and $25 for 1 week home actigraphy).

In the event that we are unable to contact a participant at the time of the post-treatment or 3-month follow-up assessment (e.g., due to a non-working telephone number), we will mail the participant an abbreviated assessment with a postage-paid return envelope. This mail follow-up assessment will include the ISI, PSQI and the SF-12. The only identifier on the mail follow-up assessment will be the study ID.

3.5. Study variables and measurement techniques

A summary of all study measures, measurement techniques and psychometric properties is provided, and key variables to be drawn from each measure are listed in **Table 7** (screening and descriptive assessment measures), **Table 8** (intervention process measures) **and Table 9** (sleep outcome measures). Assessments have been chosen to maximize reliability and validity, allow for inclusion of constructs likely to increase our understanding of treatment process and outcomes among women Veterans, and allow for multi-method assessment of our main outcomes (i.e., self-reported and objectively-measured). Instruments will be scored using published and/or standard scoring procedures. Our research team has experience with all proposed measures and techniques. We have processes in place (e.g., review of questionnaires by data manager within 24 hours and scoring of sleep recording data within one week of collection) to minimize risk of missing data.

3.5a. Screening and descriptive measures

Table 7: Study variables and measurements at each assessment visit		**Visit**		
Variable	**Measurement Instrument**	**Base-line**	**Post-treat.**	**3m. F/U**
Screening and descriptive measures				
Diagnosis of insomnia disorder	Insomnia screening survey (Appendix 1)[40]	X*		
Symptoms of sleep apnea	Berlin Sleep Apnea Scale; STOP questionnaire	X		
Presence/absence/severity of sleep apnea	WatchPAT overnight sleep apnea monitoring	X		
Symptoms of restless legs syndrome	Restless Legs Syndrome (RLS) questionnaire[48]	X		
Circadian rhythm sleep disorders	Morningness Eveningness Questionnaire (MEQ)[49]	X		
Daytime sleepiness	Epworth Sleepiness Scale	X	X	X
Age, sexual orientation, race/ethnicity, marital status, education	Core demographics questionnaire	X		
Living situation, employment status, menopausal status	Expanded demographics questionnaire	X	X	X
Caregiving questions	Behavioral Risk Factor Surveillance Survey	X		
Self-reported comorbidities	Comorbidity Checklist + SWAN comorbidity items	X	X	X
Medications taken	Medical record listing and participant interview	X	X	X
Medical record review (VA outpatient encounters and inpatient days)	Structured medical record review and utilization questionnaire	X	X	X
Pain	Brief Pain Inventory[52]	X	X	X
Nighttime urination	Nighttime urination questions	X	X	X
Psychiatric disorders	Mini-International Neuropsychiatric Interview (M.I.N.I.)	X		
PTSD symptoms & trauma exposure; nightmare frequency/severity	PTSD checklist for DSM-5 (PCL-5) Disturbing Dream/Nightmare Severity Index (DDNSI)	X	X	X
Depressive symptom severity	PHQ-9[58]	X	X	X
Anxiety symptoms	Patient Health Questionnaire - GAD-7[59]	X	X	X

*Administered during step one, postal screening for insomnia symptoms.

Insomnia screening survey: This survey was developed in our pilot work and specifically queries each of the core diagnostic criteria for an insomnia disorder in the International Classification of Sleep Disorders: Second Edition.[46] The general criteria are A) sleep disturbance that B) occurs despite adequate opportunity for sleep, and C) is sufficiently severe to impact daytime functioning. Insomnia lasting less than 3 months is considered "acute" and since our intervention is designed to target individuals with chronic insomnia, we will use a cut-off of three months or longer to identify those with chronic insomnia.

We have preliminary evidence for the validity of this survey with women Veterans. In our pilot study, we invited women with insomnia based on the postal screening survey to complete a comprehensive evaluation of sleep (n=107), on average, 2.3 months after the postal survey screener. Of the women who completed the assessment, 94% had insomnia according to the ISI,[44] 97% had evidence of clinically-significant sleep disruption on the PSQI,[60] and 80% met DSM-IV criteria for insomnia on the Insomnia Symptom Questionnaire (ISQ).[61] In the proposed project, we will use this postal screening survey to identify women Veterans who are potentially appropriate for the intervention trial and we will repeat the items addressing the diagnostic criteria at baseline, post-treatment and 3-month follow up. Key variable: Presence/absence of an insomnia disorder.

Berlin Sleep Apnea Questionnaire: This 13-item validated scale assesses three domains: 1) presence and frequency of snoring, 2) daytime sleepiness/fatigue, and 3) obesity (BMI will be calculated from height and weight) or hypertension. Frequent symptoms in any two of these three domains indicate a high risk for sleep apnea.

STOP Sleep Apnea questionnaire: This 4-item screening questionnaire assesses four domains: 1) snoring, 2) daytime tiredness/sleepiness/fatigue, 3) observed apneas, and 4) presence of hypertension. Frequent symptoms in any two of the four domains indicate high risk for sleep apnea.

Sleep apnea diagnois and treatment questions: We will ask one question about history of sleep apnea diagnosis and one question about previous use of PAP equipment.

WatchPat Sleep Apnea Assessment: We will use an unattended, home sleep monitoring system to screen patients for sleep apnea. Traditionally, sleep apnea is assessed with overnight laboratory polysomnography (PSG); [62] however, this method has several limitations including cost and inconvenience to participants. As an alternative to laboratory PSG, there are commercially-available devices to screen for sleep apnea in the home setting.[63] VA has been an early adopter of these technologies. Such devices do not provide the same level of detail about sleep architecture as PSG; however, they have several advantages. First, our clinical experience

with women Veterans suggests that attended laboratory PSG, which entails being observed by a (usually male) technician during sleep, may be uncomfortable for this population. Second, some may incur increased burden due to additional childcare needs during the night in the sleep laboratory. Third, requiring participants to attempt sleep in the laboratory at specified times (typically 10pm to 5am) may be frustrating for the subgroup participants who sleep at unusual hours, and we might not capture the sleep-related data needed to assess for sleep apnea. Finally, home sleep testing is less expensive and will enable us to study a larger group of women.

We propose to use the WatchPAT home sleep monitoring system (Itamar Medical, Caesarea, Israel), because of its validity, reliability,[64;65] ease of use, comfort, and low cost (<$100/recording). This wrist-mounted system has an embedded actigraph for detecting sleep, finger tip sensors for measuring peripheral arterial tone (PAT) and pulse oximetry, and a reusable snoring/body position sensor that is placed on the neck. The system measures respiratory disturbances based upon changes in PAT (a reflection of autonomic nervous system changes) and pulse oximetry during sleep. Compared with attended laboratory PSG, studies have demonstrated a high correlation for respiratory disturbance index (RDI) and apnea-hypopnea index (AHI) (r=0.85-0.96). WatchPAT AHI and RDI also have high test-retest reliability in home and laboratory settings.[64;65]

Participants will review a brief video provided by the manufacturer describing use of the WatchPAT device during Visit 1. They will be given the opportunity to practice with the WatchPAT sensors, and will be given a step-by-step instruction booklet and a 24-hour toll-free company-supported telephone advice line to call if difficulties arise overnight. We currently use these procedures in a study in older adults. Infrequently, a participant may be unable to use the WatchPAT system independently (e.g., due to limited dexterity). In such instances, a female research staff member will visit the participant in their home to set-up the WatchPAT.

Eligibility Determination: To determine the presence or absence of sleep apnea, we will use the Medicare National Coverage Determinations, which specify an AHI or RDI of ≥15 events per hour for diagnosis of sleep apnea. (http://www4a.cms.gov/transmittals/downloads/R86NCD.pdf). Participants with an AHI > 30 will not be eligible for randomization. Participants with an AHI between 15 and 30 (moderate sleep apnea) and with daytime sleepiness (ESS score > 9) will also not be eligible for randomization. Participants with an AHI between 15 and 30 of >15 will not be and no daytime sleepiness will be eligible for randomization. We will inform a participant with an AHI > 15 that she may have sleep apnea and, with her permission, will share these findings with her primary care provider. Key variables: Apnea-Hypopnea Index (AHI); presence vs. absence of sleep apnea.

Restless Legs Syndrome (RLS) questionnaire:[48] We will use a 4-item scale developed by the Restless Legs Syndrome Workgroup that addresses the diagnostic criteria for RLS. The RLS questionnaire asks participants about the presence and severity of cardinal symptoms of RLS and how frequently these symptoms occur. Comparison of the first three questions (self-reported symptoms) from this scale with a physician diagnosis resulted in 88% sensitivity and 96% specificity.[48] This measure will be used to identify individuals with and without RLS. Key variable: RLS risk score (high vs. low probability of RLS)

Horne-Ostberg Morningness Eveningness Questionnaire (MEQ):[49] The MEQ is a 19-item measure of chronotype and behavioral patterns related to circadian phase preference. Significant differences in the core body temperature peak has been shown between those who score in the "morning type" versus the "evening type" range on this scale. Key variables: MEQ total score, MEQ chronotype (morning, evening, neither)

Epworth Sleepiness Scale (ESS): This is an 8-item questionnaire that provides a measurement of an individual's general level of 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). Key variable: ESS total score > 9 indicates excessive daytime sleepiness.

Demographic information: Demographic data and other descriptive information will be collected from all participants. This information will be used to describe the sample and to gather information on potentially relevant variables for subgroup analyses. Demographics will include age, gender, sexual orientation, race/ethnicity, marital status, living situation, income, education, employment, menopausal status (using questions derived from the SWAN study[66] including date of last menstrual period, regular vs. irregular menstrual cycles, and surgical menopause), and smoking history. Selected variables will be re-assessed at post-treatment and follow-up. Key variables: age, sexual orientation, race/ethnicity, marital status, living location, children and adults living in the home, level of education, employment status, menopausal status, smoking status.

Caregiving questions: 19-items pertaining to caregiving responsibilities have been adapted from the National 2009-2010 Behavioral Risk Factor Surveillance Survey (BRFSS) and included in the baseline assessment, since caregiving has been shown to be a risk factor for insomnia in women.

Comorbidity checklist: The comorbidity checklist is a validated measure from the Australian Longitudinal Study on Women's Health (www.alswh.org.au). It includes 22 health conditions commonly experienced by women. For the current study, we will also incorporate 5 other items from the SWAN survey inquiring about health conditions that are specifically more common among women (e.g., thyroid disease, breast and ovarian cancer). The total score will range from 0-27 with higher scores indicating greater comorbidity. Key variable: Comorbidity checklist score and individual comorbid conditions

Medications: A medication list will be abstracted from the patient's medical record. This list will be used as a "starting point" to develop a list of medications from all sources for the participant to track during the one-week wrist actigraphy recordings. The information from the medical record will be reviewed with participants, and participants will be queried specifically about use of over-the-counter, herbal and outside (non-VA) prescription medications. Medication data will be coded by drug class using a coding system developed in prior work. We will focus specifically on psychotropic medications that may affect sleep (e.g., antipsychotics, benzodiazepine receptor agonists, antidepressants). Psychotropic medication use will be summarized categorically (i.e., was a class of medication used); then daily dose(s) will be converted into total daily equivalences by class according to standardized criteria.[67] We will look specifically at sedating medications taken at bedtime, presumably for sleep, including hypnotics, sedating antidepressants, sedating antipsychotics and antihistamines. This information will be tracked on the daily sleep diary and used to describe patterns of pharmacological sleep aid use. Key variables: Use and dose of sedating medications at night (presumably for sleep), use and dose of other psychotropic medications; total number of medications.

Medical record review: A structured medical record review will be performed at the baseline and 3-month follow-up assessments to obtain information on utilization of VA healthcare services, including number of outpatient visits in the 90 day period prior to study enrollment, and number and length of inpatient stays in the prior year. Problem list diagnoses (with emphasis on ICD-9 codes for sleep and psychiatric disorders), and active prescribed medications will also be abstracted from the medical record using a structured medical record review employed in our prior VA research.

Women in our pilot study typically received all non-emergency care at VA facilities. We will, however, inquire about non-VA utilization, including outpatient visits in the 90 days prior to the assessment, and inpatient hospitalizations in the prior year at non-VA facilities. While there are some limitations to reliance on self-report utilization data, obtaining HIPPA authorization to obtain non-VA hospital or medical records is beyond the scope of the current project and may be viewed as intrusive by some participants. We will repeat the medical record review after the 3-month follow-up to obtain utilization data during the study period. Key variables: medical record diagnoses, number of VA and non-VA outpatient visits in past 90 days; number and length of VA and non-VA inpatient hospitalizations in prior year; number of medications prescribed

Brief Pain Inventory-Short Form:[52] The 9-item version of the Brief Pain Inventory is a self-administered questionnaire that measures pain severity, pain treatments used, and daily interference of pain over the prior week. The BPI has been shown to be a valid measure of pain in patients with arthritis and low back pain and is sensitive to changes in either condition. The BPI has also been shown to have high construct validity and is well-correlated with more generic pain measures such as the SF-36 Bodily Pain subscale (r=0.61-0.74). Key variables: Pain severity score, Pain interference score

Nighttime urinary symptoms: Since nighttime urination is a common cause of nighttime awakening, we will ask two questions that inquire about the frequency and impact of nighttime urination. Key variables: Frequency of nighttime urination, bothersome rating.

Mini-International Neuropsychiatric Interview (M.I.N.I.) The M.I.N.I is a standardized structured interview for diagnosing DSM-IV-TR2 lifetime and current Axis I mental disorders. The M.I.N.I. will be administered by trained clinicians (Dr. Martin, Dr. Culver) who have completed a structured training program and have established test-retest and inter-rater reliabilities >0.90. The M.I.N.I. has been validated against the SCID and is recommended by the National Institute of Mental Health as a time-efficient alternative to the SCID. Individuals will not be excluded due to the presence of an Axis I disorder; however, this will be considered an important descriptive variable and will be used for conducting sub-group analyses of patients with specific comorbidities. Key variables: Presence vs. absence of DSM-IV Axis I disorders.

PTSD checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. Prior to administering the PCL-5, the interviewer will ask the participant 5 questions to assess whether she meets DSM-5 criterion A (witnessed or experienced a life-threatening event). Only participants who meet criterion A will be administered the PCL-5. Possible scores range from 0 – 80, with higher scores indicating greater post-traumatic stress. Key variables: Total PCL-5 score.

Disturbing Dream and Nightmare Severity Index (DDNSI):[57] The 5-item DDNSI is an expanded version of the Nightmare Frequency Questionnaire[68] that captures the frequency and severity of nightmares over the prior week, month or year, including the frequency, impact on sleep, nightmare intensity, and level of distress caused by the nightmares. The total score ranges from 0 to 37, and a score ≥10 predicts clinically significant nightmare complaints. Based on our pilot data, 72% of women who reported bad dreams in the past month had experienced bad dreams more than once per week. We will therefore administer the one week version of the measure. Although we will not directly assess nightmares in the treatment, recent work with Veterans suggests treatment of insomnia can reduce nightmare frequency.[12;69] We will gather these data in the proposed trial as a result of these recent findings. Key variable: DDSNI total score for the past week

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 is a 9-item depression module in the Patient Health Questionnaire (a self-administered diagnostic instrument for common mental disorders) which is part of the Primary Care Evaluation of Mental Disorders (PRIME-MD) suite of evaluation tools.[59] The PHQ-9 will be used to measure depressive symptom severity. The items align to the DSM-IV diagnostic criteria for depressive disorders. The PSQ-9 is widely used to screen for depression within VA. Key variable: PHQ-9 total score

Generalized Anxiety Disorder-7 (GAD-7): The GAD-7 scale is a component of the PRIME-MD suite of evaluation tools.[59] The GAD-7 was initially developed for evaluation of Generalized Anxiety Disorder (GAD), 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, and specificity above .80 for Panic, Social Anxiety and PTSD. The GAD-7 is less sensitive in screening for panic (.74), social anxiety (.72) and PTSD (.66). A more robust measure of PTSD will be used in the current study as described above PCL-5 and M.I.N.I.). Key Variable: GAD-7 total score.

3.5b. Attrition and Adherence Monitoring Measures (Aim 1)

Table 8: Study variables and measurements gathered during the intervention		**Session**				
Variable	**Measurement Instrument**	**1**	**2**	**3**	**4**	**5**
Adherence Monitoring Measures (Aim 1)						
Treatment attendance	Attendance log	X	X	X	X	X
Adherence to bedtime and rise time and other recommendations	Daily sleep dairies with electronic date/time stamp	X	X	X	X	X
Intervention Process measures						
Components of psychological flexibility	Acceptance and Action Questionnaire-II (AAQ-II)[70]	X				X
Treatment Outcome Expectations	Credibility/Expectancy Questionnaire (CEQ)[71]	X				X
Beliefs and attitudes about sleep	DBAS-10[72]	X				X
Sleep hygiene habits	Sleep Hygiene Index[73]	X				X

Treatment attendance: One of the main study outcomes will be rates of treatment completion versus dropout. To measure this construct, we will track attendance at each session, and will consider an individual to have "completed" treatment if they attend 5 60-minute sessions with the interventionist. A dichotomous variable will be computed to indicate whether the treatment program was completed or not. While not one of the main study outcomes, we will also monitor rates of cancellations/rescheduled appointments. As described above, the process for maintaining participants in treatment will be standardized across the two intervention programs. Key variable: treatment completion versus dropout.

Daily sleep diaries with electronic date/time stamp: Participants will complete an expanded version of the baseline sleep diary during the intervention portion of the study. The diary will be completed each morning, and an electronic date/time stamp will be used to document the time at which the diary was completed. This will increase the likelihood that the participant will complete the diary daily rather than completing it on the day of the intervention session. The diaries will be reviewed in detail each week by the interventionist and recommendations will be based on the sleep diary. In addition, this will be used as a measure of treatment adherence to the behavioral recommendations using the process developed by Matthews et al.[18] Each week the interventionist will make recommendations for behavior changes, and we will use the sleep diary to calculate the mean number of minutes the participant goes to bed in advance of their scheduled bedtime and the mean number of minutes they get up later than their scheduled rise time (note that going to bed later than the assigned time or getting up earlier than the assigned time is consistent with the recommendations and is not considered non-adherence). We will then compute the mean minutes of deviation for each participant. We will also compare rates of adherence to other between-session activities, and a percent of days the activity was conducted will be computed for each participant (note that for some participants, recommendations may not be made in some weeks).Key process variables: Minutes of deviation from assigned bedtime and rise times; Days per week participant adhered (within 15 minutes) to assigned bedtime, rise time and time in bed.

3.5c. Intervention Process Measures

Intervention process measures will be completed by randomized participants at the end of the first treatment and final (fifth) treatment sessions. We have selected this approach since some measures cannot be completed until the individual has a basic understanding of the treatment program she will receive.

Acceptance and Action Questionnaire-II (AAQ-II):[70] The AAQ-II is a 7-item questionnaire to assess experiential avoidance as conceptualized in ACT (higher scores suggest more avoidance). The AAQ-II has acceptable psychometric properties. In a recent study of 376 adults with depression or anxiety symptoms, using a unidimensional item response theory (IRT) model, the AAQ-II was found to be a unidimensional measure of experiential avoidance with satisfactory reliability. Key variable: AAQ-II total score

Dysfunctional Beliefs and Attitudes about Sleep – 10 item (DBAS-10):[72] The DBAS-10 is an abbreviated version of the original 28-item DBAS examining beliefs about the immediate and long-term negative consequences of insomnia as well as beliefs about the need for control over insomnia. This 10-item version has been shown to be well correlated (r=0.83) with the full scale and sensitive to cognitive changes resulting from cognitive-behavioral therapy for insomnia. Key variables: DBAS total score

Sleep Hygiene Index (SHI):[73] The 13-item sleep hygiene index is based on diagnostic criteria for inadequate sleep hygiene, and has superior reliability compared to other (typically longer) sleep hygiene questionnaires (Chronbach's α=0.66). This measure will be used to identify sleep hygiene related behaviors, including the use of alcohol, caffeine and tobacco within 4 hours of bedtime. Key variable: SHI total score

Credibility/expectancy questionnaire (CEQ):[71] The CEQ is a 6-item questionnaire used both at the beginning and end of treatment. *This questionnaire will be administered at the end of the first treatment session and again at the end of the final treatment session in both the ABC-I and CBT-I groups.* Since this measure cannot be used until the individual understands the type of treatment she will receive, it will not be assessed until after session 1 when information about the treatment is avaiallbe. The post-treatment items will be administered at the end of the final treatment session as well (session 5). Differences in scores between the ABC-I and CBT-I groups will be explored. Key variable: CEQ total scores at the beginning and end of treatment

3.5d. Sleep Outcome Measures (Aims 2 & 3)

Wrist actigraphy: Participants will wear an actigraph (Actiwatch Spectrum, Minimitter/Respironics, Bend, OR) on the non-dominant wrist for 7 consecutive days and nights. The actigraph is a small watch-sized device useful in longitudinal, naturalistic (i.e., not in an overnight sleep laboratory) assessment of sleep-wake patterns, such as in this proposal. Actigraphs are commercially-available devices which 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. We have experience with over 1,000 recordings with the device we propose to use, and have experienced less than 1% data loss due to human or device error.

Wrist actigraphy has been validated as a measure of sleep in numerous studies, and evidence-based guidelines direct use of this technology.[75] Previously reported agreement between wrist actigraphy and polysomnography scoring of sleep variables (e.g., total sleep time) in young and older people is .89-.95.[76] We have developed highly standardized research procedures and protocols for the use and scoring of actigraphy for research application, and we have trained, experienced members of our research team to apply these protocols. In our pilot work, women Veterans tolerated the actigraph devices well, with only 2 out of 107 individuals removing the devices prior to the one week recording period ended (one because of unexpected travel, and the other because of paranoid ideations about the monitoring device). One week of recording is recommended for individuals with weekday-weekend variability as less than one week of actigraphy can miss variation in sleep measures.[75] While there are limitations to the use of wrist actigraphy in patients with PTSD, in part because of more movements occurring during sleep itself,[77] we feel that alternative methods of measurement of sleep in the home sleep environment have significant limitations. For example, many women might not agree to home polysomnography (which typically requires a technician to set up the equipment at the patients' home or at a clinical facility earlier in the day) therefore limiting the generalizability of our study findings by potentially biasing the sample.

As in our prior and ongoing work, we will perform careful visual review of raw actigraphy data to eliminate technical (device failure) and situational (e.g., device removed) artifact, prior to scoring variables with the software that accompanies the device. As is the recommended standard, we will analyze actigraphy data defining "night" and "day" based on participant self-report of their bedtimes and rising times from a brief sleep diary they will maintain while wearing the device. Key variables: Percent and hours of sleep at night, percent and hours of sleep during the day (i.e., napping), time in bed at night, nighttime awakenings

Table 9: Sleep outcome variables and measurements at each assessment visit		**Visit**		
Variable	**Measurement Instrument**	**Base-line**	**Post-treat.**	**3m. F/U**
Sleep Outcome Measures (Aims 2 & 3)				
Objective nighttime % sleep, hours of sleep, nighttime awakenings, daytime sleep	Wrist actigraphy	X	X	X
Insomnia symptom severity	Insomnia Severity Index (ISI)[44]	X	X	X
Subjective Sleep Quality	Pittsburgh Sleep Quality Index (PSQI)[60]	X	X	X
Sleep diary reported sleep efficiency, hours of sleep, nighttime awakenings, daytime sleeping	Daily sleep diaries	X	X	X
Diagnosis of insomnia disorder	Survey of ICSD diagnostic criteria	X	X	X
Sleep effort	Glasgow Sleep Effort Scale[45]	X	X	X
Secondary outcome measures				
Health-related quality of life	MOS, 12-item short-form health survey (SF-12)[74]	X	X	X

Insomnia Severity Index (ISI):[44] The ISI is a 7-item instrument using Likert-type scales that measures perceived severity of insomnia symptoms from 0 (not at all) to 4 (very much). The total score ranges from 0 to 28, with higher scores indicating greater insomnia severity. The ISI correlates well with scores on the PSQI (r=0.67), and with sleep diary measures (r's=0.32-0.91).[44] Key variable: ISI total score

Pittsburgh Sleep Quality Index (PSQI):[60] The PSQI is a widely-used 18-item questionnaire that assesses sleep quality and disturbances over the last month. The PSQI measures sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The PSQI has a sensitivity for distinguishing normal and abnormal sleepers of 89.6%, and a specificity of 86.5% (kappa=0.75, p<.001).[60] The PSQI also has good test-retest reliability over 1 month (r=0.85; p<.001).[60] We will use the 3-factor scoring system, which has been shown to have superior psychometric properties compared to the original 7-factor scoring system.[78] Key variables: PSQI total score and 3 subscale scores

Daily sleep diaries: Participants will complete a sleep diary for one week at baseline, post-treatment assessment and at the three month follow-up assessments. We will use the sleep diary developed in our pilot study, which is based on the American Academy of Sleep Medicine Consensus Sleep Diary[79] and was adapted using a cognitive interviewing process[80] during our pilot project. Key outcome variables: Self-reported sleep efficiency (time asleep out of total time in bed), hours of sleep, time to fall asleep, time awake at night, and number of nighttime awakenings

Glasgow Sleep Effort Scale (GSES):[45] The GSES is a 7-item self-report that measures sleep effort. It uses a 3-point Likert-like scale (0=low effort, 2=high effort) and has been shown to discriminate between insomniacs and good sleepers. The total score will be computed and used as a main measure of sleep effort. Key variable: GSES total score

3.5e. Quality of life Outcome Measure

Medical Outcomes Study, 12-item short-form health survey (SF-12v2): The SF-12v2 is a shorten version of the SF-36v2.[74] The test-retest reliability of the SF-36 generally exceeds 0.80 with the mental and physical summary scores exceeding 0.90.[81] The SF-12v2 consists of two summary scores (Physical Component and Mental Component) from the SF-36v2, each of which has a score range of 0-100. We have previously found that poor sleep at baseline predicts worsening quality of life over a 6-month period among older adults,[82] showing that it is sensitive to the effects of poor sleep quality. *In accordance with the RE-AIM framework,[83] assessment of quality of life is an important aspect of measuring the overall impact of an intervention.* Key variables: SF-12 mental and physical component scores

3.6. Interventions

For both the ABC-I and CBT-I programs, materials are designed and tailored for women Veterans. Examples used will be directly geared toward the target population. In the ABC-I program, issues specific to women's sleep including changes in sleep associated with menopause and the menstrual cycle will be incorporated into the "sleep education" portion of the programs. Interventionists (ABC-I and CBT-I) will be trained to frequently pause to check participant understanding and treatment sessions will be designed to be interactive to facilitate participant engagement. Each session will begin with an outline of what will be discussed and end with a summary of the topics reviewed. At the conclusion of each session, a written outline of what was discussed with the specific, individualized recommendations written down in clear language will be provided to the participant.

3.6a. The ABC of Insomnia (Acceptance and the Behavioral Changes to treat Insomnia - ABC-I): The ABC-I program will involve 5 weekly sessions of 60 minutes each with the study interventionist (see **Table 10)**. Sessions will incorporate the key components of sleep restriction, stimulus control and targeted sleep hygiene

recommendations. In place of specific or traditional cognitive therapy exercises, we will incorporate select exercises and strategies targeting each of the six essential components of Acceptance and Commitment Therapy (ACT). The added exercises and concepts were designed specifically to improve adherence to the behavioral components of insomnia treatment. Each exercise is introduced to preempt expected obstacles to adherence introduced in that session. For example, metaphors are introduced to describe temporary discomfort (e.g., home renovation) alongside introduction of a regular sleep schedule and reduced time in bed. **Appendix 5** shows the patient materials for Session 1 currently used at the UCSD Moores Cancer Center. Throughout treatment, participants will be asked to complete a daily sleep diary. We developed and tested a sleep diary in our HSR&D funded pilot study, and had an excellent rate of completion (105 out of 107 women completed the diary at least 5 out of the 7 nights). At each session, the diary will be reviewed and discussed. It will be used as a tool for refining treatment recommendations and adjusting each week's action plan.

3.6b. Cognitive-Behavioral Therapy for Insomnia (CBT-I) Program: The ABC-I program will be compared to CBT-I, provided in the same format to control for non-specific aspects of the ABC-I program and to evaluate the comparative effectiveness of the two treatments (see **Table 10**). Participants will maintain the same daily sleep diary throughout the treatment. The sleep restriction, stimulus control and sleep hygiene components will be analogous to what is provided within the ABC-I. The CBT-I program will also involve 5 60-minute meetings with the interventionist. In place of mindfulness and ACT-based exercises, cognitive therapy exercises and techniques will be utilized.

Table 10: ABC-I and CBT-I treatments: Session-by-session content, activities and homework

	Topics covered	Session activities	Homework
Session 1	**ABC-I: Learning How to Surf: An introduction to the ABC of Insomnia program (sleep education, sleep hygiene and stimulus control + ACT; see Appendix 3)**		
	• Enhance motivation to adhere to behavioral prescriptions (values) • Futility of trying to control sleep • Sleep education: insomnia (3P model), sleep stages and macrostructure among women • Lifestyle habits that enhance or hinder sleep among women • Introduce and explain daily sleep diary	• Insomnia and what is important to you • Metaphors: Chinese finger trap; surfing • Leaves on a stream exercise • Action plan: sleep hygiene changes; stimulus control	• Draw life with and without insomnia • Implement action plan (sleep hygiene practices) • Daily sleep diary
	CBT-I: Getting Started with CBT-I (sleep education, sleep hygiene and stimulus control)		
	• Sleep education: sleep regulation, insomnia (3P model), sleep stages and macrostructure • Introduce stimulus control concepts • Lifestyle habits that enhance or hinder sleep • Introduce and explain daily sleep diary	• Discuss classical conditioning and insomnia • Action plan: sleep hygiene changes; stimulus control	• Implement action plan (sleep hygiene practices) • Detailed daily sleep diary
Session 2	**ABC-I: Renovating your Home (sleep restriction therapy + ACT)**		
	• Learn about the homeostatic and circadian sleep processes (sleep regulation) • The rationale behind sleep restriction • Discussion of short-term discomfort for long-term benefits	• Review/discussion of sleep diary • Introduction of key metaphors: pizza dough, silly putty; piggy bank; hiking; home renovation • Action plan: daily sleep schedule	• Implement action plan (sleep schedule) • Daily Sleep diary
	CBT-I: Scheduling Sleep (sleep restriction therapy)		
	• Learn about the homeostatic and circadian sleep processes • The rationale behind sleep restriction	• Review/discussion of sleep diary • Action plan: daily sleep schedule	• Implement action plan (sleep schedule) • Daily sleep diary
Session 3	**ABC-I: Taking Your Mind for a Walk (ACT exercises)**		
	• Adjust time in bed • Understand the concept of dirty vs. clean discomfort • Experience cognitive diffusion	• Review/discussion of sleep diary • Troubleshooting techniques: physicalizing and visualization • Take your mind for a walk • Two scales metaphor • Action plan: revise sleep schedule	• Implement action plan (sleep schedule) • Use troubleshooting techniques as needed • Daily sleep diary
	CBT-I: Thoughts about Sleep (cognitive therapy)		
	• Adjust time in bed • Discuss validity of sleep-related thoughts • Discuss utility of sleep-related thoughts	• Review/discussion of sleep diary • Develop coping cards • Action plan: revise sleep schedule	• Implement action plan (sleep schedule; coping cards) • Daily sleep diary
Session 4	**ABC-I: Acceptance & Commitment (ACT exercises)**		
	• Adjust time in bed • Review progress and challenges	• Review/discussion of sleep diary • Addressing barriers and obstacles • Action plan: new ways to face obstacles	• Implement action plan (sleep schedule; strategies to address obstacles) • Daily sleep diary
	CBT-I: Progress and Obstacles (cognitive therapy)		
	• Adjust time in bed • Review progress and obstacles • Use cognitive strategies to address barriers to adherence	• Review/discussion of sleep diary • Addressing barriers and obstacles using cognitive-therapy methods • Action plan: identify obstacles and strategies to address them	• Implement action plan (sleep schedule; strategies to address obstacles) • Daily sleep diary
Session 5	**ABC-I: If Not Tonight, Tomorrow Night (relapse prevention + ACT)**		
	• Adjust time in bed • Understand relapse prevention techniques	• Review/discussion of sleep diary • Action plan for relapse prevention	• Use tools/skills for future sleepless nights
	CBT-I: Sleeping Well Over the Long-Term (relapse prevention)		
	• Adjust time in bed • Discuss relapse prevention and coping	• Review/discussion of sleep diary • Action plan for relapse prevention	• Use tools/skills for future sleepless nights

3.7. Data management:

Each participant will be assigned a unique ID which will be entered into computerized files and used on study forms. Only the ID number will be linked to participant data in databases and on paper documents. Using existing protocols, we will secure all paper records and electronic data files in compliance with current VA data security policies. Original study forms will be archived and stored in locked cabinets in approved research areas. All data will be coded by the data manager, then entered into databases using procedures established in prior work to minimize errors. Datasets will be cleaned by screening for out-of-range values, and comparing a random sample of 10% of entered data to original data collection forms. Problems with data entry will be addressed in an ongoing manner. Double entry procedures will be used on a second, 10% random sample of cases in each dataset, with additional training and review of data if errors are identified. Cleaned data will be scored and aggregated, then data will be merged into one main database for statistical analyses.

3.8. Data analysis plan

3.8a. Overview: Below we provide an overview of the study design considerations, and the analysis plan for each aim. We first present the approach for Aim 1, which involves traditional between-groups comparisons. Given the comparative effective approach required by Aims 2 and 3, we discuss these separately, and provide details regarding the structure of hypothesis testing for this method. In particular, we focus on the null hypothesis testing procedure and the determination of the clinically-meaningful effects (i.e., delta or δ) to be considered with respect to non-inferiority.

3.8b. Study Design Considerations: The equivalency of the two treatment groups at baseline is produced by the random assignment to groups. Randomization (combined with the ITT analysis strategy) should produce groups that differ only by chance with respect not only to factors related to study outcomes, and also to the outcomes themselves. Nevertheless, the adequacy of the randomization will be assessed by comparing the groups across outcomes measured at baseline. We will use a stratification based on hours of sleep reported on the postal survey >6 versus ≤6 hours) to assign participants to strata for randomization. We have chosen stratified randomization to further increase the likelihood that the groups will be equivalent at baseline. The inclusion of covariates in such a situation would not be for the purpose of ensuring the comparability of the groups (because that comparability is created via randomization), but covariates may be used to enhance statistical power by reducing error variance.

We anticipate that some participants will not complete the intervention; however, we will continue to collect post-treatment and 3-month follow-up data, regardless of whether they complete the intervention program. Participants will be offered monetary incentives for providing post-treatment and follow-up assessments, regardless of whether they complete the intervention program to which they were assigned. We anticipate this will maximize the completeness of data; however, some data loss is unavoidable. In our recent study of older Veterans, we were able to obtain follow-up data for up to one year in 90% of randomized participants.

To preserve the equivalency formed by randomization of participants to the intervention and control groups, intent-to-treat (ITT) analyses will be used including all randomized participants for hypothesis testing. ITT analysis requires complete data, so missing data will be imputed. If imputation is necessary, we will use multiple imputations. These results will be compared to an "as treated" analysis where only those with complete data will be analyzed, thus no imputations will be required. We will use this approach since the "as treated" has the benefit of not imputing any data, but also has the drawback of not analyzing all participants as randomized and therefore the potential for introducing bias into the results.

3.8c: Data Analysis for Aim 1:

Testing of Hypothesis 1, that participants in the ABC-I program will be less likely to discontinue treatment and will show better adherence to behavioral recommendations than participants in the CBT-I program) will involve a series of statistical comparisons between the ABC-I and CBT-I groups. To test whether the participants in ABC-I are less likely to discontinue treatment, the percentage who dropout in the ABC-I group will be compared to the percentage who dropout in the CBT-I group. This comparison will be made using a two-by-two X^2 test of whether dropping out (1=yes 0=no) is independent of treatment group assignment (1=ABC-I, 2=CBT-I). To compare measures of adherence to behavioral recommendations (based on electronically time-stamped sleep diary data), a two group t-test will be used. The main variables of interest will be the minutes of deviation from the assigned earliest bedtime and latest rise time for each session. We will calculate the mean number of minutes the participant goes to bed in advance of their scheduled bedtime and the mean number of minutes they get up later than their scheduled rise time (note that going to bed later than the assigned time or getting up earlier than the assigned time is consistent with the recommendations and is not considered non-adherence). We will then compute the mean minutes of deviation for each participant. We

will also compare rates of adherence to other between-session activities, and a percent of days the activity was conducted will be computed for each participant.

Sample Size Calculations: To assess the power for Aim 1, we considered preliminary data gathered using the proposed intervention and previously published research. To estimate the power to compare dropout rates for each of the two groups, we used our preliminary data and published studies of ACT-based interventions and CBT-I.[17;18;84-87] Based on those sources, we conservatively anticipate the dropout rate for ABC-I will be 22% compared to 45% for CBT-I. **Table 11** shows the required sample size to detect this difference (n=178) and other potential differences. The rows show dropout rates for ABC-I ranging from 16% to 28%, and the columns show dropout rates for CBT-I, ranging from 39% to 51%. Each cell shows the total N (for the two groups combined). The current study would need 148 subjects (74 per group) to have 80% power to detect a difference in dropout rates as found in the previous research.

Aim 1 also addresses differences between ABC-I and CBT-I in adherence to sleep restriction and stimulus control recommendations. Again, based on previously-published studies[17;18;84-87] and our own preliminary data, we estimate that participants who complete the CBT-I intervention will deviate from their recommended bed time by an average of 29 minutes (SD=36 minutes) per night, while participants in the ABC-I program will deviate from their recommended bed time by an average of 9 minutes (SD=19 minutes). To detect a difference of this size with 80% power, we would require a total of 66 participants (33 per group). Similarly, we anticipate that individuals in the CBT-I group will deviate from their recommended rise time by 36 minutes (SD=40 minutes), while individuals in the ABC-I program will deviate from their recommended rise time by only 6 minutes (SD=14 minutes). To detect a difference of this magnitude with 80% power would require a total of 32 observations (16 per group). Using the proposed sample size required to detect a difference in dropout rates (n=148) we will have ample statistical power to detect differences in adherence.

Table 11: Sample size to detect differential dropout rates between CBT-I and ABC-I. N=148 (74 per group) is adequate to measure the expected difference. Other measureable differences with N=148 are shown in **bold**.

	CBT-I dropout rate						
ABC-I Dropout rate	39%	41%	43%	45%	47%	49%	51%
16%	**134**	**116**	**102**	**90**	**82**	**74**	**66**
18%	162	**138**	**120**	**106**	**94**	**84**	**76**
20%	200	168	**144**	**124**	**108**	**96**	**86**
22%	252	206	174	**148**	**128**	**112**	**98**
24%	326	260	212	178	152	**130**	**114**
26%	436	336	268	218	182	154	**134**
28%	612	448	344	274	224	186	158

3.8d: Data analysis for Aims 2 and 3 (Hypothesis 2: ABC-I and CBT-I will be similarly effective in improving self-reported and objectively measured sleep from baseline to post-treatment; Hypothesis 3: ABC-I and CBT-I will be similarly effective in improving self-reported and objectively measured sleep from baseline to 3-months follow-up).

Two Step Hypothesis Testing of Non-inferiority: Hypotheses 2 and 3 seek to show that ABC-I is not inferior to CBT-I in terms of treatment effects (i.e., changes in sleep quality). Non-inferiority is established by framing the null hypotheses in terms of the difference between the treatment means and comparing this difference to a pre-specified value, delta (δ), which represents the equivalence margin.

Table 12: Hypothesis testing in a non-inferiority study comparing ABC-I to CBT-I.

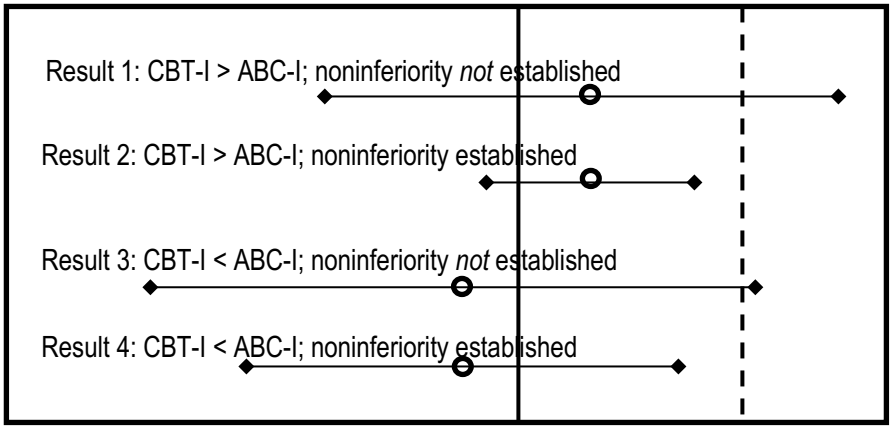
	Hypotheses	
Type of study	**Null hypothesis (H_0)**	**Research Hypothesis (H_1)**
Traditional comparative study	There is no difference between ABC-I and CBT-I	There is a difference between ABC-I and CBT-I
Non-inferiority study	ABC-I is inferior to CBT-I	**ABC-I is not inferior to CBT-I (H2 and H3)**

Determination of delta (δ): We elected to use a value of δ equivalent to an effect size of d=0.40. (i.e., 4/10ths SD). With respect to ISI, this represents a 2 point difference between the treatment effects. For PSQI, this represents a 1.4 point difference, and for actigraphically-estimated sleep percent, a difference of 5%.

Description of analysis: With respect to this study, non-inferiority is established by showing that the efficacy of ABC-I is no more than δ units less than CBT-I (**Table 12**).[88] This is tested by formulating a one sided null hypothesis that the difference between CBT-I and ABC-I is greater than or equal to δ (i.e., H0: $mu_{CBT\text{-}I}$-$mu_{ABC\text{-}I} \geq$ δ) against the alternative hypothesis that the difference is less than δ (i.e., HA: $mu_{CBT\text{-}I}$-$mu_{ABC\text{-}I} <$ δ). If the null

hypothesis is rejected, then the non-inferiority of ABC-I is established. For Aims 2 and 3, this two step process avoids the pitfall of erroneously interpreting a failure to reject the null hypothesis as evidence of no difference between the treatment groups. **Figure 8** illustrates four hypothetical patterns of results with respect to the outcome ISI using δ =2. In Result 1, the mean of CBT-I is greater than ABC-I and the confidence interval of this difference includes δ, and the noninferiority of ABC-I is not established. In Result 2, the mean of CBT-I is greater than ABC-I, however, the confidence interval excludes δ and the noninferiority of ABC-I is established. Result 3 shows that the mean of ABC-I is greater than CBT-I and the confidence interval excludes δ, establishing the non-inferiority of CBT-I. Result 4 shows that the mean of ABC-I is greater than the mean of CBT-I, however, the confidence interval includes δ so the noninferiority of ABC-I is not established.

Figure 8: Depiction of possible results for non-inferiority testing of ABC-I compared to CBT-I. The figure shows mean differences and 95% CI.



Statistical Analysis: To conduct the non-inferiority tests of Hypotheses 2 and 3, we will first use a 2 (group) by 3 (time) mixed model analysis of variance (ANOVA). The ABC-I vs. CBT-I groups will form the 2-level between groups factor, and the 3 time points (baseline, post-treatment, follow-up) will form the within groups factor. The null hypothesis will be that the differences between groups are greater than or equal to delta, as specified above, for ISI (2 points), PSQI (1.8 points) and sleep percent (5%).

Hypothesis 2 will compare the impact of the ABC-I to CBT-I at post-treatment (as compared to baseline) in terms of self-reported (ISI total score and PSQI total score) and objectively-measured (actigraphically-measured nighttime percent sleep) sleep quality variables. For each outcome measure, a 2 (group) by 3 (time) mixed model analysis of variance (ANOVA) will be performed. To directly test the impact of ABC-I vs. CBT-I on the change in outcomes from baseline to post-treatment, a planned interaction comparison will be tested that crosses treatment group (ABC-I vs. CBT-I) with time using a 1-1-0 contrast for the time factor). This interaction comparison will be used to directly test this hypothesis, that the ABC-I group shows greater positive changes (from baseline to post-treatment) on the outcome measures as compared to the CBT-I group.

Hypothesis 3 will explore whether improvements seen at post-treatment are maintained over a 3-month follow-up time period. As with hypothesis 2, for each outcome measure, a 2 (group) by 3 (time) between/within analysis of variance (ANOVA) will be performed, but two interaction contrasts will be examined. The primary contrast of interest will examine impact of ABC-I (compared to CBT-I) on the change from baseline to 3 month follow-up by applying a -1 0 1 contrast to time and interacting that with treatment group. This interaction contrast will assess the impact of the ABC-I (compared to CBT-I) from baseline to the 3 month follow-up, assessing the persistence of the treatment effects. A secondary contrast will examine the change from post-treatment to six month follow-up by applying a 0 -1 1 contrast on time and interacting that with treatment group. This secondary comparison will assess differences in changes from post-treatment to 3 month follow-up for the ABC-I and CBT-I groups. Conceptually, this second contract will test whether there is either continued improvement after post-treatment (i.e., sleep is better at 3 months follow-up compared to post-treatment, or whether there is relapse (i.e., sleep is worse at 3 months follow-up compared to post-treatment).

Sample Size Calculations: For Aims 2 and 3, the required sample size was determined based on the minimum clinically-meaningful difference between the two treatments, rather than on the estimated effect size for an active treatment versus control condition. This non-traditional approach is required for comparative effectiveness designs.[88] To develop estimates of clinically-meaningful differences between treatments, we examined studies of CBT-I in the published literature.[89-91] We then considered clinically meaningful changes in ISI and PSQI scores and in objectively-measured sleep percent. We determined that a difference between the two treatment groups of more than 2 points on the ISI or PSQI, or more than 5% in objectively-measured sleep percent would constitute a clinically-meaningful difference between the treatments. This represents an effect size of approximately d=0.40 (that is, 4/10s of a standard deviation for each outcome measure). The required sample size (with alpha=.05 and.80 power) to detect for an effect size of 0.40 is n=138. We plan to randomize

a total of 148 individuals into the trial, and therefore will have sufficient statistical power for hypothesis testing as proposed. Due to the use of ITT and missing data imputation methods, data for all participants will be analyzed regardless of treatment dropout.

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