CMCVAMC Specific Protocol Summary
Content Requirements for IRB Committee Review

CMCVAMC IRB
Corporal Michael Crescenz VA Medical Center Institutional Review Board

A. **Protocol Title**

1. **Full Protocol Title: The Efficacy of CBT-I in Alcoholics & Its Effects on Remission & Relapse**

2. **Date of Protocol Summary and Version #: Date August 21, 2018 Version #8.**

B. **Principal Investigator's Full Name and Degree: Subhajit Chakravorty, MD**

Approved by CMCVAMC IRB 2
8/22/2018

C. **Co-Investigator's Full Name and Degree**: **N/A**

D. **Financial Sponsor** (Provide the name of the agency, organization, company or person providing funds for the research study.) **VA CSR & D**

E. **Grant** (Provide the name of individual who holds the grant and the grant number, if applicable.) **Subhajit Chakravorty, MD; 1 IK2CX000855-01A2**

F. **Protocol Number** (Provide the financial sponsor's protocol number, if applicable.) **N/A**

G. **Institution(s) responsible for the project:**

1. For single-site studies - CMCVAMC is the only institution involved. Yes ☒ No ☐
2. For multi-center studies.
   - 2.1. CMCVAMC is the Coordinating Center in which the PI is the lead investigator. Yes ☐ No ☐ N/A ☒
   - 2.2. Provide the name of the Coordinating Center. Yes ☐ No ☐ N/A ☒
   - 2.3. List the name of the other sites involved. **N/A**
   - 2.4. Provide the FWA numbers for each of the other sites involved. **N/A**

H. **Background and Significance:**

Alcohol dependence (alcoholism) and insomnia in Veterans occur at rates that are 2-7 times higher than that of the general population. Further, there is evidence that insomnia is a significant risk factor for relapse in abstinent alcoholics. Given these findings, it is surprising that very little research has been conducted to determine whether: the insomnia that occurs with military experiences and/or withdrawal abates with time; the incidence or severity of insomnia is associated with the clinical course of alcoholism; targeted treatment for insomnia during withdrawal is effective; and positive treatment response for insomnia is associated with duration of remission and/or risk for relapse during abstinence. From the few studies that exist, the following tentative claims can be made: 1) alcoholism severity is associated with insomnia severity[1,2]; 2) insomnia is a risk factor for relapse[3-5]; 3) short-term treatment of insomnia during first year of recovery improves sleep continuity via reduction in both time to fall asleep and time awake during the night. While the results from these studies are promising, most investigations were conducted in small samples (all but two studies had final samples of < 20 subjects)[6,7] and were populated by patients with poorly-defined alcohol and insomnia phenotypes (e.g., family history, age of onset, duration of illness, illness severity, type and subtype of insomnia [e.g., psychophysiologic insomnia, idiopathic insomnia, paradoxical insomnia and/or initial, middle, late, or mixed insomnia]). Further, most of the studies did not have follow-ups that evaluated the durability of the insomnia treatment[8-10] and how this was related to occurrence of relapse or other alcohol-related measures (e.g., alcohol craving, number of drinks per day, the occurrence of binge drinking, etc.). In order to address some of these limitations, we propose to conduct a study of standard Cognitive Behavioral Therapy for Insomnia (CBT-I) in 60 alcohol-dependent Veterans during the first year of their recovery. CBT-I was selected as the treatment modality for several reasons. First, CBT-I produces treatment outcomes that are as large, or larger than pharmacotherapy in patients with Primary Insomnia[11,12], and there is a growing body of evidence suggesting that it is as effective in Secondary Insomnia[13-15]. Second, unlike pharmacotherapy, CBT-I

exhibits durable results following treatment discontinuation[16,17] and less likely to interact with medications being used for replacement therapy or management of comorbid illness. Third, there are three small-scale studies with CBT-I showing that the regimen is applicable in the context of alcoholism (i.e., subjects comply with/ benefit from the treatment)[8,9,18].

Chronic insomnia has been associated with high-frequency EEG activity (β and γ, 16-50 Hz), a measure of cortical arousal. In addition, there is a diminished δ and increased high-frequency NREM EEG power among patients with insomnia, as well as an association between high-frequency EEG activity and subjective sleep complaints. High-frequency EEG enhances sensory and information processing, which may contribute to the subjective-objective discrepancy that often characterizes insomnia. Evidence is mixed regarding insomnia-control differences in high-frequency EEG activity during wakefulness. However, high-frequency waking EEG activity significantly correlates with high-frequency EEG activity during NREM and with self-reported hyperarousal symptoms. These findings support the hypothesis that high-frequency EEG power in insomnia is a marker of CNS hyperarousal. On a preliminary basis, we will investigate the role of CBT-I treatment in decreasing the cortical arousal in these patients.

Purpose of the Project:

Insomnia is classified as both a primary disorder and a symptom of other disorders in DSM IV. In the DSM V insomnia will be classified as a primary disorder (i.e., as "Insomnia Disorder") when it occurs in isolation and as a co-morbid disorder when it occurs as a consequence of another medical and psychiatric illnesses. There are three major implications of this paradigmatic shift. First, as a disorder (vs. a symptom secondary to a primary illness), it can no longer be assumed that the "cause" of the insomnia is the primary disorder and that treatment for the primary disorder will result in a resolution of the insomnia. Second, as a co-morbid disorder, insomnia can be conceptualized as co-occurring condition that may interact with other disorders and thus result in greater illness severity in one or both conditions. Third, as a co-morbid disorder, insomnia occurring with other disease states may complicate the treatment of the co-occurring condition (i.e., result in reduced treatment efficacy), and/or the occurring condition will complicate the treatment of the insomnia.

These implications are directly applicable to the insomnia that occurs in association with alcoholism and give rise to the following questions. First, is there evidence that insomnia is a risk factor for the first episode of alcoholism (suggesting that insomnia occurs before and not as a result of the alcoholism). Second, data show that alcoholism severity is greater in patients with insomnia as compared to patients without insomnia and (conversely) that insomnia severity is greater in patients with alcoholism as compared to patients without alcoholism (suggesting that the two disease states interact as independent disorders to reciprocally confer greater morbidity). Third, there is evidence that insomnia complicates the treatment of alcoholism and/or that chronic alcoholism is associated with perpetuation of insomnia (suggesting targeted treatment for both disorders is required when they occur co-morbidly).

Given the newness of the paradigmatic shift, it comes as no surprise that none of the above questions have been addressed in a manner that allows for definitive answers. What is known is that insomnia is highly prevalent in patients with alcoholism, and there are preliminary data to suggest that 1) insomnia is a risk factor for recurrence of alcoholism; 2) alcoholism severity is greater in patients with insomnia as compared to patients without insomnia; and 3) targeted treatment for insomnia in the context of alcoholism diminishes insomnia severity.

Showing that CBT-I is an effective method for managing insomnia in the context of alcoholism will provide clinicians with an additional treatment option for the millions that suffer from insomnia comorbid with alcoholism. Demonstrating that the clinical course of patients with alcoholism is significantly improved by targeted treatment for insomnia will allow for a new and better standard of care and will open a new research window into "how and why" sleep disturbance interacts with the predisposition for, and severity of, alcoholism.

I. **Describe the Research Questions or Hypotheses**

Specific Aim 1 (Primary Aim): Determine the efficacy of standard 8-week CBT-I intervention in recovering alcohol dependent subjects. Hypothesis 1: Alcohol dependent participants who receive CBT-I, compared to the QDT, will exhibit greater improvement on the ISI and more durable treatment gains on follow-up at 3 and 6 months. Secondary analyses will assess for group differences in sleep continuity (e.g., average SL, WASO, and TST) over all time points and will evaluate these parameters relative to the meta-analytic norms.

Specific Aim 2: Investigate whether the alcohol dependent Veterans treated with CBT-I have reduced recidivism compared to those in the QDT control condition. Hypothesis 2: Alcohol dependent participants who receive CBT-I, compared to QDT, will exhibit a significantly higher percentage of days abstinent. Secondary analyses will assess for group differences on other alcoholism-related outcomes (e.g., craving, drinks per drinking day, and proportion of heavy drinking days).

Specific Aim 3: Evaluate if subjects treated with CBT-I have a greater improvement in daytime functioning as compared to subjects in the QDT. Hypothesis 3: Alcohol-dependent participants treated with CBT-I will exhibit greater improvement in subjective daily functioning (health-related quality of life [primary end point]), as well as anxiety and depressive symptoms [secondary end points]).

Exploratory Aim(s): Assess the potential relevance of genetic and neurobiologic factors as predictors of illness severity and treatment outcome. Specifically, family history of alcoholism and actigraphic data will be acquired during the course of the proposed project and evaluated for their relevance as correlates of clinical course.

J. **Primary Outcome Variable(s):**

a) The primary sleep outcome measure for the study is the insomnia severity (as assessed with the Insomnia Severity Index scale (ISI) [19,20];
b) The primary alcohol outcome measure is percentage days abstinent (as assessed using the Timeline Follow Back measure (TLFB)[21-26].

K. **Secondary Outcome Variable(s):**

a) The secondary sleep outcome measures are the traditional five sleep continuity values that are obtained from the daily sleep diaries (averaged as weekly values for sleep latency [SL], number of awakenings [NWAK], wake after sleep onset [WASO], total sleep time [TST] and SE%); other outcome measures will include Pittsburgh Sleep Quality Index (PSQI), Composite Scale of Morningness (CSM), Knowledge Assessment Questionnaire (KAQ), the Treatment Evaluation Questionnaire (TEQ), and pre- and post-treatment evaluation questionnaire, Columbia-Suicide Severity Rating Scale Baseline version (CSSR-B) & Columbia-Suicide Severity Rating Scale Follow-up Screener (CSSR-S-FS), and the Epworth Sleepiness Scale (ESS). In a subset of subjects the polysomnographic sleep variables (sleep onset latency, sleep efficiency, wake after sleep onset time) will also be evaluated.
b) The secondary alcohol measures are alcohol craving (assessed with Penn Alcohol Craving Scale, PACS)[27-30], number of drinks per drinking day, and percent of heavy drinking days (assessed with the TLFB)[22-26], Short Index of Problems (SIP).
c) The outcome measures for health and mood are the Short Form-12 item scale (SF-12)[31], the Patient Health Questionnaire 9-item scale (PHQ9)[32,33], the Generalized Anxiety Disorders 7-item scale (GAD7)[34,35], the Beck Depression Inventory-II scale (BDI-II)[36,37] and the State-Trait Anxiety Inventory (STAI)[38], Columbia Suicide Severity Rating Scale (C-SSRS-B), and the Barratt's Impulsivity Scale (BIS), Interpersonal Support Evaluation List (ISEL), and Addictions Severity Index (ASI), Columbia-Suicide Severity Rating Scale Baseline version (CSSR-B) & Columbia-Suicide Severity Rating Scale Follow-up Screener (CSSR-S-FS).
d) Family History of Alcohol Dependence will be assessed using the Semi Structured Assessment of the Genetics of Alcoholism (SSAGA) – Family History Assessment Module (FHAM)[39,40].
e) Other drug use will be assessed using the SCID-I module for abuse and dependence on other drugs[41] as well as with a Urine Drug Screen (UDS). See Figure 1 and Table 1 for details.

L. **Study Design and Methods:**

1. Is this a clinical trial? ☐YES ☒NO

1.1. If yes, what type? Check all that apply. N/A

☐ **Phase I** ☐ **Phase II** ☐ **Phase III** ☐ **Phase IV**

1.2. If yes, this study must be registered on Clinicaltrials.gov.

2. **Design**

2.1. What research methods will be used in the project? Check all that apply.

☒ Surveys/Questionnaires	☒ Interviews	☒ Audio Taping
☒ Behavioral Observations	☒ Chart Reviews	☐ Video Taping
☐ Focus Groups	☒ Randomization	☐ Double-Blind
☒ Control Group	☐ Placebo	☐ Withhold/Delay Treatment
☒ Specimen Collection	☐ Deception	☒ Telephone Survey
☐ Other (Describe)		

Eight Session CBT-I: General Protocol. Cognitive Behavioral therapy is conducted in 8 sessions during which subjects meet individually with the study clinician. Session 1 serves as an orientation. No active treatment is delivered at this time. Sessions 2 & 3 are used to deliver the three main components of the intervention which are Sleep Restriction (SRT) [42,43], Stimulus Control [44-46], and Sleep Hygiene [47-49]. All but two of the remaining sessions are dedicated to the titration of total sleep time and to ensuring patient adherence. One session (session 5) entails the delivery of a specific form of cognitive therapy. The cognitive element targeted in this session is modeled on Barlow's approach to the cognitive restructuring of catastrophic thinking as it occurs in insomnia with panic disorder. This approach was adapted to address the catastrophic thinking as it occurs in insomnia in relation to the consequences of poor sleep. The final session (session 8) is used to engage in a relapse-prevention didactic, i.e., to review first, how insomnia becomes chronic and second, the strategies that are likely to abort an extended episode of insomnia. The specific details for each of the above interventions (e.g., titration rules, stimulus control rules, etc.) and itineraries for each of the individual sessions are detailed in the Penn treatment manual (published by Springer in 2005 [hardback] and re-printed in 2008 [paperback])[50].

Quasi-Desensitization Placebo Therapy (QDT). This form of placebo therapy has been commonly used in prior studies investigating behavioral interventions for insomnia[9,13,51,52]. The therapist presents the QDT as a means to eliminate "conditioned arousal," occurring after nocturnal arousal using 8 sessions on a weekly basis. The therapist initially helps the subject to develop a chronological 12-item hierarchy of commonly practiced activities on awakening at night, like opening eyes and clock watching. As a next step, the subject develops 6 imaginal scenes of himself/herself engaged in neutral activities like reading a newspaper. The therapist then helps the subject pair the neutral scenes with the items from the 12-item hierarchy, which is then practiced by the subject ≥ 2 hours before bedtime.

2.2. Describe how randomization or other treatment assignment will be made. **Subjects will be block randomized using a computer generated randomizing sequence.** Participants are randomly assigned to the CBT-I group, or the QDT group. The study biostatistician will create randomization sequences by family history of alcoholism (separate sequences) using a pseudo-random number generator with block sizes of 4. Two boxes of sequentially numbered, sealed, opaque envelopes will be prepared using the randomization sequences and labeled "Family History" and "No Family History". At the time of randomization, the first envelope, in sequential order, is pulled from the appropriate box and opened to reveal the group assignment. All the staff conducting assessments will be blinded to the allocation of treatment arm with the exception of Dr.

Findley, the BSM treatment provider, Ms. Barilla the person overseeing treatment allocation, and Dr. Harb, the monitor for BSM treatment for the study.

2.3. For retrospective research studies, provide the "look-back" period. (e.g., December 1, 1999 through December 31, 2008.) **N/A.**

3. **Study Duration**
   3.1. Provide the estimated length of time to enroll all subjects and complete the study. **Five years.**
   3.2. Explain the expected duration of subject participation including any follow-up. **Eight months.**
   3.3. Specify the projected date of completion of the proposed study. **Dec. 2018.**

4. **Drug Information**. Not Applicable.

5. **Investigational Device**. Not Applicable.

M. **Does this project involve international research?** ☐YES ☒NO

N. **Study Procedure.** Please see Table 1 for all the study-related procedures.

The actigraph: A wristband that the patient wears on his/her non-dominant arm continuously over a 1 week period, measures rest/activity as a surrogate marker for sleep and wakefulness). Actiwatch® (Mini Mitter Company) recordings will be obtained to measure duration of nocturnal inactivity as a proxy for sleep duration during simultaneously recorded, time-linked Stardust II® recordings. Estimated sleep time, the primary actigraph outcome measure, will be used to calculate the total sleep time and quality of sleep at home. Actiwatch® is a compact, wrist-worn, battery-operated activity monitor that utilizes a motion sensor known as an "accelerometer" to monitor the occurrence and degree of motion. Actiwatch® is programmed to collect data using the Sleepwatch software application that runs on an IBM-compatible PC. A sleep diary will be filled out by the subject while using the actigraph. The sleep diary is a subjective log maintained by the subject of the times he falls asleep and awakens over the 24-hour period. The sleep diary filled out by the subject (on the days of the actigraph use) will be used to assess and clarify the sleep wake data as measured by the actigraph. The actigraphy will be done at baseline and during the treatment study weeks. Conduct of the actigraphy during the post-treatment follow-up at 3- and 6-month visits will be deemed optional.

Overnight in-laboratory polysomnography (PSG): a registered polysomnographic technologist will perform the overnight polysomnographic sleep studies at the CMCVAMC sleep center. The polysomnograms will include electroencephalography, electromyography, electrooculography, electrocardiogram, pulse oximeter, and plethysmography to monitor for chest muscle activity. Overnight polysomnograms will be performed using standard techniques (12). The following signals will be recorded using a computer data acquisition and analysis system (Mallinckrodt, Pleasanton, CA): electroencephalogram (C3A2 and O2A1), bilateral electrooculograms, chin muscle activity, bilateral anterior tibialis electromyogram, rib cage and abdominal movement, nasal pressure and snoring (Pro-Tech, Woodinville, WA), body position, and heart rate and oxygen saturation by pulse oximetry (Ohmeda, Louisville, CO). The PSG will be conducted in a subset of up to 20 subjects (up to 10 in the CBT-I arm and up to 10 in the QDT arm) in an equitable distribution across both treatment arms and pending availability of funds. Each subject will have complete 2 PSG studies, one at baseline and one at the end of treatment (within weeks 7-8 of the treatment visits).

1.1. Outline all study procedures.

Table 1: A List of Assessments Involved with Participation in this Study

Table 3. Data Collection Table

Scales		Baseline	Treatment-Related Visits W1	W2	W3	W4	W5	W6	W7	W8	Post-Study F/U 1	F/U 2
Sleep	SDS-CL	■										
	Type III Monitor	■										
	ISI	■	■	■	■	■	■	■	■	■	■	■
	ESS	■	■	■	■	■	■	■	■	■	■	■
	Sleep Diary	■	■	■	■	■	■	■	■	■	■	■
	Actigraphy	■				■				■	■	■
	PSQI		■				■			■	■	■
	CSM		■							■	■	■
	KAQ		■							■		
	TEQ		■							■		
	EQ		■							■		
	Therapist Checklist											
	Polysomnogram	■								■		
Alcohol	SCID-I	■										
	SSAGA-FHAM	■										
	CIWA	■										
	UDS	■										
	SIP	■								■		
	TLFB	■	■	■	■	■	■	■	■	■	■	■
	PACS	■	■	■	■	■	■	■	■	■	■	■
	Breathalyzer	■	■	■	■	■	■	■	■	■	■	■
Psychiatr	SCID-I	■										
	BOMC	■										
	C-SSRS-B	■										
	BIS	■										
	PHQ-9	■	■			■				■	■	■
	BDI-II	■	■	■	■	■	■	■	■	■	■	■
	STAI	■	■	■	■	■	■	■	■	■	■	■
	GAD-7	■	■	■	■	■	■	■	■	■	■	■

Acronyms

Type III Monitor = Type III portable sleep monitor
PSG = Polysomnography
PSQI = Pittsburgh Sleep Quality Index,
CSM = Composite Scale of Morningness,
KAQ = Knowledge Assessment Questionnaire,
TEQ= Treatment Experience Questionnaire;
EQ=BSM Expectancy Questionnaire;
ISI = Insomnia Severity Index,
SCID- = Structured Clinical Interview for DSM-IV-TR Axis I Diagnoses,
SSAGA-FHAM = Semi-structured Assessment for the Genetics of Alcoholism,
CIWA = Clinical Institute Withdrawal Assessment for Alcoholism scale;
UDS = Urine Drug Screen,
SIP – Short Index of Problems Scale,
TLFB = Time Line Follow Back,
PACS = Penn Alcohol Craving Scale,
BOMC = Blessed Orientation Memory Concentration test;
C-SSRS-B = Columbia Suicide Severity Rating Scale – Baseline version
PHQ9 = Patient Health Questionnaire 9-items,
BDI = Beck Depression Inventory,
STAI = State Trait Anxiety Inventory,
GAD7 = Generalized Anxiety Disorders-7 Questionnaire,
PCL-S = PTSD Checklist - specific
QOL = Quality of Life,
SF-12 = Health-Related Quality of Life, Short Form 12,
TBI Screener = Traumatic Brain Injury Screener,
ESS = Epworth Sleepiness Scale
ASI = Addictions Severity Index
ISEL = Interpersonal Support Evaluation List
C-SSRS-FS = Columbia Suicide Severity Rating Scale – Follow-up Screener version

W = Week #,
F/U = Follow up visit.

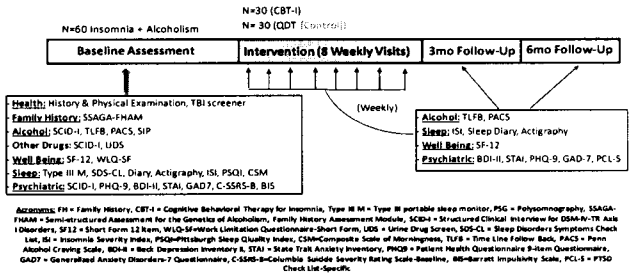
	PCL-S	■								■	■	■
	CSSR-S-FS									■	■	■
	ASI											
	ISEL	■								■	■	■
QOL	SF-12		■							■	■	■
Medical	Charlson's Index	■										
	TBI Screener	■										
Genetic	Blood Sample	■										
H & P	History & Physical Exam	■										

[1] - for research purposes,[2] - for clinical purposes,[3] - routine procedures performed solely for research purposes.
[1]SDS-CL-Sleep Disorders Checklist; [1&2]Type III Portable Sleep Monitor; [1&2] ISI; [1&2] Sleep Diary; [1&2] actigraphy; [3] PSQI; [3] CSM; [3], KAQ [3], TEQ, [3] SCID-I; [1]SSAGA – Semi Structured Assessment for the Genetics of Alcoholism; [1&2] CIWA – Clinical Institute Withdrawal Assessment for Alcohol; [1&2] UDS; [3] SIP; [3]TLFB; [3]PACS; [1&2] Breathalyzer; [1&2]; [1&2] BOMC – Blessed Orientation Memory Concentration test; PHQ-9; [3] C-SSRS-B; [3] BIS; [1&2]BDI-II; [1&2]STAI; [1&2] GAD-7; [1&2] PCL-S; [3] SF-12; [3] Charlson's Index; [1] Blood sample, ESS. ISEL, CSSR-S-FS, & ASI

1.2. **Explain if and how the follow-up of subjects will occur.** The subjects will be initially assessed for eligibility over the baseline assessment period that will last for about a month. This baseline assessment will involve assessments of their alcohol use disorder history, screening for other drug use, assessment for psychiatric disorders, assessment for sleep disorders, and a history and physical examination; see Figure 1 below.

On successful completion of the baseline assessments subjects will be randomized into the treatment arms (CBT-I or QDT). They will be treated for 8-weeks, and will be followed up for 8 sessions. After completion of the active intervention they will be followed up at 3 months and 6 months from the date of the completion of either intervention. All the follow up visits will include assessment of symptoms in the domains of alcohol use, psychiatric symptoms, insomnia and sleep-related symptoms. If a subject decides to end treatment prematurely or is unable to attend any following sessions after completing the first treatment session on Week 1, we will continue to collect follow-up data at the time points of Week 8, and follow-ups at 3-months and 6-months.

Figure 1: Study Overview



1.3. **Describe where, how and who will be conducting study procedures.** a) Screening (in person or over the phone) – will be performed by the study coordinator; b) Assessments – at baseline and for the follow-up visits will be conducted by the study coordinator (in-person, via mailed packet with a self addressed return envelope without date of assessment, or, phone for follow-ups); c) Intervention (CBT-I or QDT) - will be conducted by the behavioral sleep medicine specialist associated with the study (TBA); d) Urine drug screen – will be conducted by the study coordinator or obtained from the

patient's electronic medical record if one was done during the time the patient is undergoing the baseline assessment period; d) Blood sample - will be drawn up and processed by Dr. Chakravorty, or the designated staff member associated with the study, including the study coordinator after IRB approved training and at the CMCVAMC laboratory services as a back-up option; e) Overnight polysomnography will be done at the CMCVAMC sleep center by their credentialed sleep technicians. Dr. Chakravorty will serve as a back-up staff member for any of the study-related procedures.

1.4. **If a survey study, specify the estimated amount of time that subjects will need to complete the questionnaires/tools.** N/A

1.5. **If a blood draw, specify the amount of blood to be drawn in milliliters and in teaspoonful or tablespoonful and specify how often and where the blood will be drawn.** About one tablespoon (~15ml).

2. **Data Collection**

2.1. Provide

2.1.1. **The mode of data collection, e.g. telephone, in-person, questionnaire, interviews.** The initial screening will occur over the phone or in person using the IRB-approved telephone screening questionnaire (see attached telephone screen) similar to the one used in our CBT-I pilot study. Veterans who have positive screen will undergo baseline evaluations to further determine study eligibility. Once eligible they will be randomized into one of the study arms and treated for 8-weeks followed by a post-study follow up visits at 3 months and 6 months. All the assessments (in-person, questionnaires, and interviews) will occur during the baseline phase, treatment phase and post-study follow up phase, and will target evaluation of symptoms pertaining to sleep and insomnia, alcohol consumption (and other drugs if applicable), and psychiatric symptoms; see Table 1 for list of assessments and the time frame for their use, as well as Figure 1 for the study design. If the subject is unable to make it to the CMCVAMC during the week 8 time point or for the 3-month or 6-month follow-up, then the research team will complete the questionnaires with the subject over the phone or have the subject complete them at home via mailed questionnaire packet with telephone follow-up when necessary.

2.1.2. **The precise plan for how data is to be collected or acquired.** Most of the assessment measures will involve interviews (e.g. for the SCID form, or for the initial CBT-I session). During the treatment or follow-up phase, if the subject is unable to meet the research team at the CMCVAMC to complete the study questionnaires and interviews in-person, then the research team will complete the interviews and questionnaires by phone with the subject or have the subject complete the questionnaires via mailed packet and follow-up by telephone if any interviews are needed. The only exceptions to this rule are for the actigraphs and the portable sleep monitors. Actigraphs will be worn on the wrist for a few days at a stretch and the Veteran will be maintaining a sleep diary for the sleep-wake schedule. The monitor has sensors attached to the body recording oxygen saturation, airflow (nasal pressure), thoracic movements, snoring, body position and the heart rate. The apparatus measures nasal pressure, which is an accepted surrogate marker of air flow (instead of using oro-nasal thermistors, used in the earlier portable monitors); see Table 1 for details on the assessment measures and the time frames of assessments. All the staff conducting assessments will be blinded to the allocation of treatment arm with the exception of Dr. Findley, the BSM treatment provider, Ms. Barilla the person overseeing treatment allocation, and Dr. Harb, the monitor for BSM treatment for the study. Overnight polysomnography data, will be obtained by the sleep technologist

at the CMCVAMC sleep center. The data will be captured electronically and will be analyzed by the physicians at the CMCVAMC VISN 4 Sleep Center sleep center as well as the research team.

Exact location where data will be collected. The initial screening will be conducted over the telephone or in person, either within the MIRECC office space of Room # 228 or in any available locked office space in the ARU/MHC on the 7th floor or 2nd floor of the main building. If the subject is unable to travel to the CMCVAMC for the week 8 or follow-up assessments, then the research team will complete them with the subject by phone or have the subject complete them via mailed packet with telephone follow-up if necessary. The source documents will be stored in the locked desk drawer of the study coordinator (in room # 228). All the rest of the source documents will be stored in the above-mentioned locked desk drawers of the study coordinator (in room # 228). Data from REDCap will be stored on VA servers located within a VA data center inside the VA firewall which afforded the same network protections as all VA sensitive clinical data. The electronic data, including any data pulled from REDCap see below for details Data from the actigraph will be stored locally on the desktop and backed up on compact disks and stored in the locked office drawer of the research assistant in the MIRECC office space with restricted access. Data from the polysomnographic sleep studies will be captured at the CMCVAMC Sleep Center. The data from the scored polysomnographic studies will be transferred via compact discs to the MIRECC VISN-4 secure databases.

2.1.3. Data management will occur through the VA REDCap (Research Electronic Data Capture), a secure web application and back-end database model, developed at Vanderbilt University with collaboration from a consortium of institutional partners. Approved study staff will enter data directly into REDCap, which obviates the need for transferring written data into electronic form; this significantly improves the quality of data. The VA has licensed its own version of REDCap housed on VA servers located within a VA data center inside the VA firewall and therefore afforded the same network protections as all VA sensitive clinical data. REDCap was developed specifically around HIPAA Security guidelines and is recommended to Penn Medicine researchers by our Office of Human Research. Relevant HIPAA-compliant features include password-protected access to the system, restriction of access to specific clinical trial data to designated users, audit trails of access and data updates, and built-in de-identification functions that can be used when exporting data for analysis. REDCap has been disseminated for use locally at other institutions and currently supports 170 academic/non-profit consortium partners on six continents and 13,000 research end-users (www.project-redcap.org). Approved study staff can access REDCap through a web-based interface and securely input data from any location at the time of data collection minimizing the need for travelling with either electronic or paper versions of sensitive information.

VA REDCap database administrators will have control over electronic access rights to REDCap databases. Only VA IRB approved individuals will be granted access to this database. This database keeps time-stamped information on people accessing, inputting, and altering data in the database.

2.1.4. **Exact location where data entry will take place.** Data entry will primarily take place in the locked office space of the MIRECC (room # 228B) which

has a restricted access to authorized staff only. Data entry may occur secondarily in the Dr. Chakravorty's locked office space (Room # 218, Bldg. 3), and in the available locked private office space of the ARU or the MHC on the seventh floor of the CMCVAMC main building. The PSG data will be acquired and evaluated at the CMCVAMC similar to other studies done in the past.

2.1.5. **The "title" of individual(s) collecting the data and analyzing the data, e.g. principal investigator, research coordinator.** Principal investigator (Dr. Chakravorty), study coordinator, the behavioral sleep medicine provider, phlebotomy staff at the CMCVAMC laboratory services, and any other staff designated by Dr. Chakravorty after approval of the CMCVAMC -IRB.

2.2. **Provide a time line for each aspect of the study.** See Table 2 for details related to the proposed activities associated with the study.

Table 2. Gantt Chart of Proposed Activities Related to the Project

	Year 1				Year 2	Year 3	Year 4	Year 5			
	Q1	Q2	Q3	Q4				Q1	Q2	Q3	Q4
Set-up											
Enrollment											
Closeout of Study											
Education											
Data Analysis											
Dissemination											
Merit Review Application											

Q1 = 1st Quarter, Q2 = 2nd Quarter, Q3 = 3rd Quarter, Q4 = 4th Quarter

2.3. Chart/Records/Data Review (retrospective and/or prospective)

2.3.1. Provide the planned or approximate number of charts/records/data to be accessed

2.3.1.1. CMCVAMC **All subjects**

2.3.1.2. Other site. N/A.

2.3.2. **Does this protocol employ an Honest Broker?** ☐YES ☒NO

2.3.2.1. If yes, provide name of individual. N/A

2.3.2.2. **If no, explain who will access the charts/records.** Study-related staff; they will currently include Dr. Chakravorty, the study coordinator, and the behavioral sleep medicine specialist.

2.3.2.3. **Describe from what database charts/records/data will be accessed.** Initial prescreening may be conducted by evaluating the CPRS (the electronic clinical charts of the patients) in order to alert their providers about the Veteran's option of participating in this study. After obtaining informed consent for the Veteran after he has signed the HIPAA form, we will access his clinical chart to evaluate for past and current clinical assessments and treatments as part of his/her baseline assessments.

3. **Future Use of Data and Re-Contact**, if applicable.

3.1. **If any of the participant's data are going to be retained after the study for future research, the following information must be provided to the participant:** The blood sample for the genetic analyses. This explained in the informed consent form and the HIPAA form.

3.2. **Where will the data be stored?** The blood samples for the genetic analyses will be stored at a freezer space within the CMCVAMC (Research Building, 4th floor, freezer room), as designated by the CMCVAMC R & D staff. When all the samples have been collected and samples are ready for analyses we will transfer the samples with the coded identifier (and without any of the 17 HIPAA identifiers) from the CMCVAMC to the designated laboratory at the University of Pennsylvania after obtaining the required CMCVAMC -IRB authorization. The samples will be destroyed at the University of Pennsylvania after the genetic tests have been conducted.

3.2.1. **Who will have access to the data?** The Principal Investigator and the study coordinator and the regulatory agencies (CMCVAMC -IRB, and designated VA CS R & D staff). The staff associated with the genetic analyses laboratory and the statistician, both within the University of Pennsylvania will have access to the coded data (without the 17 HIPAA identifiers).

3.3. **If the subject is going to be re-contacted in the future about participating in future research, this must be specified. Describe the circumstances under which the participant would be re-contacted whether within the VA or outside the VA.** N/A

3.3.1. **If subjects will receive aggregate study results at the end of the study, the informed consent document must contain this information.** N/A

4. **Specimen Collection**

4.1. **Give the source of all specimens and whether they were collected for research, treatment or diagnosis.** Blood samples will be collected for genetic analyses related to research.

4.2. **State where specimens will be stored, secured and when discarded.** The blood samples for the genetic analyses will be stored at a freezer space within the CMCVAMC (Research Building, 4th floor, freezer room), as designated by the CMCVAMC R & D staff. When all the samples have been collected and samples are ready for analyses we will transfer the samples with the coded identifier (and without any of the 17 HIPAA identifiers) from the CMCVAMC to the designated laboratory at the University of Pennsylvania after obtaining the required CMCVAMC -IRB authorization. The samples will be destroyed at the University of Pennsylvania after the genetic tests have been conducted.

4.3. **Explain how destruction of samples will be substantiated.** The samples will be destroyed at the laboratory within the University of Pennsylvania using their standard protocols for destruction. A form certifying the destruction of the samples will be issued by the staff from the laboratory at the University of Pennsylvania.

O. **Genetic Testing, if applicable**

1. **Explain if the study is looking for an association between a genetic marker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value.** The future study will explore for an association between single nucleotide polymorphisms (SNPs) of candidate genes and their relation with subjective and objective insomnia variables in the recovering alcoholic subjects. At this point it is not clear if the genetic marker has a predictive value.

1.1. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve participant counseling.

1.2. Describe if the study is based on the premise that a link between a genetic marker and a specific disease or condition is such that the marker is clinically useful in predicting the development of that specific disease or condition. **N/A.**

1.3. Will the subject be notified of the results and the provision for genetic counseling?
☐ Yes ☒ No ☐ N/A

1.3.1. If yes, explain further.

1.4. If biological specimens are used in this protocol, please respond to the following questions by checking the appropriate box:

	YES	NO	N/A
a. Does the project involve genetic testing?	☒	☐	☐
b. Will specimens be kept for future, unspecified use?	☒	☐	☐
c. Will samples be made anonymous to maintain confidentiality?	☐	☒	☐
d. Will specimens be destroyed after the project-specific use is completed?	☒	☐	☐
e. Will specimens be sold in the future?	☐	☒	☐
f. Will subjects be paid for their specimens now or in the future?	☐	☒	☐
g. Will subjects be informed of the results of the specimen testing?	☐	☒	☐
h. Are there any implications for family members based on specimen testing results? (If yes, they may be participants.)	☐	☒	☐
i. Will subjects be informed of results obtained from their DNA?	☐	☒	☐

1.5. **Will specimens be de-identified**? ☐YES ☒NO ☐ N/A

1.5.1. **If yes, please describe the procedures to be used.** The specimens will be coded using study specific identification number.

1.5.2. **Include at what point in the process the specimens will be de-identified**. The specimen will receive a coded identification (not associated with any combination of his/her social security number) number at the time of collection and will not have any of the 17 HIPAA identifiers associated with it. Prior to genetic analyses the data will be transferred to the designated laboratory of the University of Pennsylvania with an approval obtained from the CMCVAMC - IRB. On completion of the genetic analyses, the data from the test results will be retained at University of Pennsylvania laboratory database where a fresh code will be issued to identify the genetic results (independent of the code allocated at the CMCVAMC). This recoded data will be pooled with the results of other similar subjects who have had the genetic analyses at the laboratory and the statistical analyses will then be conducted. In summary, the blood sample for genetic analyses will initially be coded at CMCVAMC with a identification code not related to any combination of his social security number. During the genetic analyses procedure at the University of Pennsylvania the sample will be recoded again with a fresh code and the results will be pooled with the results of other subjects on whom the same genetic analyses will be conducted.

1.6. Describe what measures will be taken to minimize the following risks from breaches of confidentiality and privacy resulting from participating in **THIS aspect** of the research project:

1.6.1. **Physical:** The paper pencil data relating to the genetic assessment will be stored in the locked desk drawers in locked offices of MIRECC (Room 228 B), and the PI's locked office space (Room # 218, Bldg. 3). Electronic data relating to genetic assessment will be stored in the password protected online VA servers in the MIRECC (\\vhaphifpcmirecc\Research Studies\Chakravorty). The physical samples will be stored with only the coded unique identification numbers and without any of the 17 HIPAA identifiers.

1.6.2. **Psychological:** Prior to sample collection patient will be notified that the testing is purely to assess for research related purposes, and not for clinical testing of any disorder. Every effort will be made by the study staff to alleviate or minimize emotional discomfort associated with the collection of the blood

sample and explain to the patient that the sample will be stored using only a coded identifier and without any of the 17 HIPAA identifiers.

1.6.3. **Financial:** Patient will be notified that the genetic sample donation will be voluntary in nature.

1.6.4. **Social:** Since the blood sample will be stored only with a coded identifier (without the 17 HIPAA identifiers) and the genetic analyses will be conducted to assess for experimental associations of SNPs with insomnia symptoms, the subject will be explained that the social ramification of the loss of blood sample will be minimal to none.

1.6.5. **Legal harm:** Since the blood sample will be stored only with a coded identifier (without the 17 HIPAA identifiers) and the genetic analyses will be conducted to assess for experimental associations of SNPs with insomnia symptoms, the subject will be explained that the legal ramification of the loss of blood sample will be very minimal to none.

P. **Banking of Collected Specimens**

1. **Will collected specimens be banked?** ☒YES ☐NO ☐N/A

1.1. **If yes, specify the location where specimens will be banked.** Within a designated freezer space within the CMCVAMC (Research Building A218) as recommended by the CMCVAMC -IRB.

1.1.1. If the location is a non-VA site, has the mandatory approval from the Chief Officer of Research and Development (CRADO) been obtained through submission of a tissue banking application (*VA Form 10-0436* - Off-site Application for an Off-site Tissue Banking Waiver)? ☐YES ☒NO ☐N/A

1.1.2. If applicable, attach a copy of the VA Form 10-0436

1.2. **Explain how destruction of banked samples will be substantiated.** After transfer to the designated laboratory at the University of Pennsylvania with CMCVAMC -IRM approval, the samples will be evaluated for the genetic analyses. The samples will be destroyed at the laboratory within the University of Pennsylvania using their standard protocols for destruction. A form certifying the destruction of the samples will be issued by the laboratory staff at the University of Pennsylvania.

Q. **Subject Recruitment** (characteristics of the study population)

1. **Provide the planned or targeted enrollment at**:

1.1. CMCVAMC - **86**

1.2. Other sites - **N/A**

1.3. Not applicable; chart review or use of previously collected data - ☐

2. **Screening and/or Eligibility Requirements**

2.1. Describe:

2.1.1. **Inclusion criteria:** a) Male and female Veterans between the ages of 21 and 70 years; b) DSM IV diagnosis of alcohol dependence over the past year (as determined by the SCID-I[41]); c) Self-reported sleep latency or wake time after sleep onset >30 min on three or more nights per week for ≥1 month and a score of ≥15 on the Insomnia Severity Index (ISI)[20]; d) No current alcohol withdrawal symptoms at baseline: CIWA score < 8 (CIWA[53] is the Clinical Institute Withdrawal Assessment scale for alcohol withdrawal signs and symptoms); e) abstain for ≥ 4 weeks from heavy drinking and < one year of abstinence from alcohol use prior to the baseline study assessments as assessed by subjective report or breathalyzer; f) Ability to speak, understand and print in English, g) Capacity to give written informed consent.

2.1.2. **Exclusion criteria:** a. DSM-IV criteria for dependence on any other substance including benzodiazepines, and excluding nicotine dependence; b.

Positive urine drug screen for opioids, cocaine, or amphetamine. Tetra Hydro Cannabinol (Δ9-tetrahydrocannabinol is one of the main psychoactive ingredients of marijuana) is not considered an exclusion criteria; c. Patient is currently in alcohol withdrawal as assessed by the Clinical Institute Withdrawal Assessment Scale (CIWA) total score ≥ 8 [53]; d. A lifetime DSM-IV diagnosis of Bipolar I or II disorder, Schizophrenia, or other psychotic disorder, as determined on the SCID-I[41], and current (past month) DSM-IV diagnosis of Major Depressive Disorder; e. Presence of unstable medical diagnosis e.g. congestive heart failure, leading to interference with sleep, as reported on history, examination, and/or review of clinical chart during baseline assessments; f. Current use of any medications that may influence the drinking behavior, e.g. naltrexone or acamprosate; g. Evidence of severe cognitive impairment as assessed by the BOMC (Blessed Orientation-Memory-Concentration test weighted score ≥ 16); h. Untreated patients with the diagnosis of moderate-severe obstructive sleep apnea with Total Apnea-Hypopnea Index (AHI-T) of ≥ 15 events/hour of sleep; i. Subject's inability to give informed consent.

2.2. **List all screening and/or eligibility requirements.** A Veteran who is less than or 70 years old, suffers from alcoholism and insomnia, and is currently sober or not indulging in heavy drinking within the last one year, not currently dependent on other drugs (excluding nicotine or marijuana), is medically and psychiatrically stable, and is interested in participating in the research study and eligible for care within the VA healthcare system.

2.3. **Explain any special test or evaluations potential subjects may have to undergo before they are actually determined to be eligible for the study.** Subjects will undergo an extensive baseline evaluation to determine their eligibility and their ability to participate in the study. These tests will include the following: a) *Insomnia Severity Index* (to assess their current insomnia symptoms); b) *Structured Clinical Interview for DSM-IV diagnoses* (SCID, to assess their current psychiatric status); c) *Time Line Follow Back measure* (TLFB, to assess their quantity and frequency of alcohol use, nicotine use, and cannabis use in the last 90 days of drinking within the past year); d) *Type III portable sleep monitor* to screen for moderate – severe obstructive sleep apnea syndrome; e) *History & Physical examination* (to assess for medical stability to participate in the study); f) *Urine Drug Screen* – to screen for the use of other psychoactive drugs.

2.4. Not Applicable; subjects not recruited; chart review. ☐

3. **If applicable, indicate what populations will be targeted for recruitment as participants. Check all that apply.**

Males	☒
Females	☒
Inpatients	☒
Outpatients	☒
VA Employees	☒
Non-English Speaking**	☐
Veteran Family members***	☐
Non-Veterans***	☐
Other (Specify)	☐
Not Applicable, chart review	☐

3.1. **For non-English speaking subjects - If an investigator proposes to use a participant population that does not speak or read English, a copy of the translated document, as well as the English version, needs to be forwarded to the IRB for approval. Translator certification is also required. **N/A**

3.2. ***If non-veterans will be recruited for this study, explain why sufficient veterans are not available to participate in the project [VHA Handbook 1200.5, paragraph 16a]. Veteran's spouses/partners, caregivers, etc. are considered non-veterans for the purposes of this study. **N/A**

3.3. ***Has approval to recruit non-veterans been received from the ACOS/R&D and Medical Center Director?

3.3.1. ☒ Not Applicable

3.3.2. ☐ Pending

4. **Does this project target a specific race or ethnic group as participants?** ☐YES ☒ NO

If yes, check all that apply.

Race	
American Indian or Alaskan Native	☐
Asian	☐
Black or African American	☐
Native Hawaiian or other Pacific Islander	☐
Black, not of Hispanic origin	☐
White, not of Hispanic origin	☐
Other	☐

Ethnicity	
Hispanic or Latino	☐
Not Hispanic or Latino	☐
Other	☐

4.1. Provide justification why this/these group(s) was/were chosen.

5. **What is the age range of participants?** Check all that apply.

Children (Under 18) Requires Waiver from CRADO (VHA Directive 2001-028, Research Involving Children)	☐
Young Adults (18-21)	☒
Adults (22-70)	☒
Seniors (Over 70)	☐
Over 89	☐
Not Applicable, chart review	☐

6. **Are there specific reasons why certain populations (i.e., age, gender or ethnic groups) are excluded as participants?** ☒YES ☐NO ☐N/A

6.1. **If yes, specify reasons.** Alcohol dependent Veterans older than 70 years of age may have a poor health status, more likely to have psychiatric disorders in addition to a higher level of insomnia. Further, they may have difficulty with the demands associated with participation in this study, which includes multiple baseline visits, weekly follow-up visits, the post-intervention follow-up visits, use of the actigraphy and recording daily sleep diaries at home and the use of the portable sleep monitor.

7. **Does the project require enrollment of the following classes of participants?**

	YES	NO
a. Employees	☒	☐
b. Individuals with impaired decision making capability	☐	☒
c. Pregnant women	☐	☒
d. Economically and/or educationally disadvantaged persons	☒	☐

e. Prisoners	☐	☒
f. Illiterate, limited, or no English language proficiency	☐	☒
g. Terminally ill patients	☐	☒

7.1. **If applicable, what is the justification for including any of the above classes of participants in the project?** Only those employees who are Veterans themselves and are eligible for care within the VA systems will be eligible for this study. Many of the Veterans recovering from alcoholism are unemployed and reside in shelters and also suffer from insomnia; they also have limited social supports. Participate in this treatment study will help them to understand their illness, increase contact with health care providers, receive reminders for upcoming appointments with providers within the system when needed as we have done in the past, help them monitor their own symptoms, develop a sense of overall efficacy, decrease their sense of loneliness and isolation, and help them promote behaviors associated with health living.

7.2. **If the project requires enrolling any of the above classes of participants describe any project-specific measures or special considerations, steps, or safeguards to ensure that these individuals are adequately protected.** Only those employees who are Veterans and are eligible for care through the VA system will be eligible for participation in this study. In line with experiences from our current study and our past clinical trial we will use standard procedures to recruit, treat and follow-up Veterans recovering from alcoholism. In addition, our research staff is trained to be sensitive and to be sensitive to the unique needs of Veterans from an economically disadvantaged background.

8. **Describe the exact plan how subjects will be identified and recruited for the study.**

8.1. **Discuss methods, e.g., referrals from physician offices, clinics, programs, or through advertisements and brochures.** The prospective subjective will enter the study from the following mechanisms: 1) referral from providers and case managers; 2) self-referrals in response to advertisements posted within the CMCVAMC, and satellite VA veteran housing support programs (IMPACT, Fresh Start, Snyder House, and Veteran's Multi-Service Center (VMC); 3) self-referrals in response to the advertisement posted in Craigslist.com.

8.2. **If using a clinic, be specific about who will identify the potential subject and how that information will be transmitted to the research staff.** The potential subjects will be identified by the Veterans providers or by the research staff who will then discuss the study with the identified Veteran's provider or case manager. The following clinics and programs will be targeted for recruitment of Veterans: 1) Addiction Recovery Unit (ARU) of the CMCVAMC; 2) Mental Health Clinic (MHC) of the CMCVAMC; 3) Primary Care Clinics (PCC) within the CMCVAMC; 4) Community Based Outpatient Clinics (CBOCs) associated with CMCVAMC; 5) Behavioral Health Laboratory (BHL) of the CMCVAMC; 6) inpatient psychiatry units; 7) CMCVAMC Sleep Center; 8) Veteran housing support programs (IMPACT, Fresh Start, Snyder House, and VMC,).

8.3. **If snowball method will be used, discuss the process and how the first individuals will be recruited.** N/A.

8.4. **Describe how information will be disseminated to subjects, e.g. handouts, brochures, flyers and advertisements.** The following materials will be used to aid

recruitment (after appropriate approval from the CMCVAMC -IRB): recruitment flyer; craigslist advertisement; clinician flyer.

9. **Informed Consent**

9.1. Informed Consent will not be sought. ☐

9.2. Written informed consent from participants (VA Form 10-1086 is attached). ☒

9.3. Written informed consent from participants' legally authorized representative (LAR) as required by VA policy and/or applicable state laws (VA Form 10-1086 is attached). ☐

9.4. Request Waiver of Documentation of Informed Consent ☐

9.5. List the **title** of the key personnel involved in the following activities:

9.5.1. Person Obtaining Consent

9.5.1.1. **Provide the title(s) of individual(s).** Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with this study

9.5.1.2. **Type of training received to perform this process.** All the training on topics required by the Philadelphia Institutional Review Board (IRB) prior to conducting an informed consent session (including the CITI training for good clinical practices).

9.5.2. **Pre-Recruitment Screening** (the use of medical records and other data bases to determine populations and individuals eligible for the study), Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with this study, after appropriate authorizations. Personnel involved will include the following: Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with the study.

9.5.3. **Recruitment Process** (the process in which individuals are contacted and first introduced to the study and to the possibility of participating as subjects), Veterans will be solicited through referral from treatment providers (ARU, inpatient unit, primary care providers, providers at the CBOCs affiliated with CMCVAMC, case managers at the veteran housing support programs affiliated with the CMCVAMC (IMPACT, Fresh Start, Snyder House, VMC), referrals after initial assessment by the Behavioral Health Laboratory, and self-referrals (in response to IRB-approved advertisements) posted in the medical center and other areas like veteran housing support programs, in the electronic media (Craigslist). Personnel involved will include the following: Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with this study.

"BHL conducts clinical assessments on all patients referred from primary care. At the completion of the clinical assessment, all patients potentially eligible for IRB approved and MIRECC approved research will be informed of these projects and asked if they can be contacted by appropriate study personnel to discuss the particular study in accordance to that protocol's procedures."

9.5.4. **Informed Consent Process** (the process by which recruited subjects are fully informed about participating in the study and then formally give their voluntary consent for participating). Personnel involved will include the following: Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with this study.

9.5.5. **Screening of Recruited Subjects** (those activities in the protocol in which a final determination of eligibility of prospective subjects is made during the

early phases of the study, using laboratory data, inclusion and exclusion criteria, and other person-specific information). Personnel involved will include the following: Principal investigator, study coordinator, behavioral sleep medicine practitioners associated with this study.

9.5.6. Include the breakdown of each individual's responsibilities:

9.5.6.1. **Principal Investigator.** He may fulfill any of the roles required for the study, including, answering questions for prospective participants, informed consent procedure for participation for assessment for study entry, baseline assessments, assessments as part of the study visits, conducting the cognitive behavioral therapy sessions, scheduling the participant sessions, post-study assessments, conducting the urine drug screens, drawing blood and preparing the blood sample for storage in the freezer, coordinating clinical care with other providers.

9.5.6.2. **Co-Principal Investigator,** N/A

9.5.6.3. **Research Coordinator.** S/he will be involved in answering questions for prospective participants, informed consent procedure for participation for assessment for study entry, baseline assessments, assessments as part of the study visits including the urine drug screen test at baseline, drawing blood samples (after completion of the requisite training), scheduling the participant sessions, post-study assessments.

9.5.6.4. **Additional research staff by title.** a. Phlebotomy – either Dr. Chakravorty or a designated staff certified and IRB-approved to draw blood will conduct the blood draws and prepare the samples for the storage in the designated R & D freezer space; b. Certified Behavioral Sleep Medicine Provider: s/he will conduct the CBT-I and the QDT sessions for the participants; the Principal Investigator, Dr. Chakravorty will conduct CBT-I or QDT as a backup provider.

9.6. Will informed consent be obtained from potential subjects prior to determining eligibility?
☒YES ☐NO ☐N/A

9.6.1. If no, provide justification and a HIPAA Waiver of Individual Authorization for Disclosure of Protected Health Information.

9.7. **Define when a subject is enrolled into the study, e.g. after the subject signs the informed consent or after randomized to treatment.** After he is randomized into a treatment arm.

9.8. Describe:

9.8.1. **The process when informed consent will be obtained and protecting patients' privacy.** The principal investigator or the trained research staff will schedule a session with the prospective participant. In this session the prospective participant will be explained about the research study in details along with the associated risks including discomfort with the use of portable sleep monitor or elaborating on his past history of alcohol dependence as well as the benefits from the study as well as the other treatment alternatives available. On comprehending and after been given the chance to ask questions related to the study, the participant will complete the informed consent quiz and then subsequently sign the informed consent document.

The participant will be assigned a 4-digit unique identifying number for this study. This 4-digit identification number will not be related to the last 4 digits of his social security number or a 4 digit number generated by scrambling his social security number. The link between the 4-digit coded identification number and the participant's name and social security number will be stored on paper in a locked cabinet in room # 228 B of in the locked cabinet in Dr. Chakravorty's office in Room # 218, Bldg 3 as well as backed-up electronically in the password protected VA online drives. Data will be recorded after the participant consents to the data collection; data will be collected in a private room in the office space of the MIRECC on the 2nd floor, or the mental health clinic, or the addiction recovery unit, or in the inpatient units of CMCVAMC. The source documents or the case report form will be stored in the locked cabinet in room number 228 B of the MIRECC office space or in the locked cabinet in room (TBA)in CMCVAMC, depending on the available space. All the data will be entered into password protected online servers, using the 4-digit identification number issued to the subject. All the personal identifiers as identified by HIPAA will be removed from the data spreadsheets. The portable sleep study data will be downloaded in the CMCVAMC sleep center or in the MIRECC office spaces and the final data will be downloaded onto a disk and transported physically by the research staff to the MIRECC storage area and uploaded to the online servers. Actigraph data will be downloaded onto the specific software that currently exists on one personal computer in Dr. Chakravorty's office in Room # 218, Bldg 3, and the password protected desktop computer of the principal investigator in the locked room, room # 218 of building 3, a building with restricted entry. In addition, a backup copy of the actigraph data will be maintained on compact disks, as recommended by the manufacturer, in a locked cabinet of the principal investigator's office. All the discs will be stored in the principal investigators locked office in Room # 218 of the research building with restricted access, in a locked cabinet.

9.8.2. **Any waiting period between informing the prospective participant and obtaining consent.** The waiting period will be dictated by the availability of the Veteran and the staff member's availability in going through the informed consent session.

9.8.3. **Steps taken to minimize the possibility of coercion or undue influence.** The subjects will be reminded of the voluntary nature of the study during the initial screening, during the informed consent session, as well as tested in the informed consent quiz.

9.9. Provide the language

9.9.1. Used by those obtaining consent. English

9.9.2 **Understood by the prospective participant or the legally authorized representative.** N/A

9.10. **Provide location where informed consent will be obtained.** The informed consent session will be conducted in any available private office space available on the 7th or 2nd floor (mental health clinic/ARU clinic), MIRECC office spaces (room # 228), the inpatient units on the 7th floor, or in any available office space in the primary care clinics.

10. **Waiver or Alteration of Informed Consent Requirements/Waiver of Requirement to Obtain Documentation of Informed Consent**

10.1. Are you requesting a waiver or alteration of informed consent? *(Check all that apply)*

10.1.1. No ☐

10.1.2. Yes; provide justification. ☐

10.1.3. Yes; for recruitment purposes only. ☒

10.1.3.1. An IRB may approve a consent procedure which **does not include, or which alters,** some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- ☒ 1. The research involves no more than minimal risk to the subjects;
- ☒ 2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- ☒ 3. The research could not practicably be carried out without the waiver or alteration; and
- ☒ 4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation
- ☐ 5. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
  a. Public benefit or service programs;
  b. Procedures for obtaining benefits or services under those programs;
  c. Possible changes in or alternatives to those programs or procedures; or
  d. Possible changes in methods or levels of payment for benefits or services under those programs.

10.2. **Are you requesting a waiver to obtain documentation of informed consent?**

10.2.1. No ☒

10.2.2. Yes; provide justification. ☐

10.2.2.1. An IRB may **waive the requirement for the investigator to obtain a signed consent** form for some or all subjects if it finds either:

- ☐ 1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- ☐ 2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

R. **Compensation**

1. **Summarize any financial compensation that will be offered to subjects.** Please see Table 3 below for details on the financial compensation.

2. **Provide the schedule for compensation.** The schedule of pro-rated compensation will involve one payment for completion of the baseline assessments measures, weekly compensation for the each of the study visits over 8 weeks, and for the 2 post-study visits at 3 months and 6 months.
   2.1. **Per study visit or session.** The specific details of the payments are shown in Table 3
   2.2. **Total amount for entire participation.** $750.

3. **Explain how compensation will be provided via cash, voucher, gift card, etc.** Patient will be given a voucher that may be exchanged for cash at the agent cashier of CMCVAMC, similar to that done for prior studies.

4. **If financial compensation will be prorated, explain the process.** See Table 3 below for details.

5. Not Applicable - ☐

Table 3: Suggested Pro-rated Financial Compensation Involved with

Missing Assessments	Baseline Assessments	Week 1-7	Week 8	F/U (in 3 & 6 months)
None	$150	$50	$100	$75
Incomplete Actigraphy	$125	$25	$75	$40
Incomplete forms	$125	$25	$75	$50
≥ 2 Rating Scales	$125	$20	$70	$40
Polysomnogram	$100	-	$50	-
Any combination of above	$50	$15	$15	$40
No blood sample	$100	-	-	-

S. **Withdrawal/Early Withdrawal**

1. **Describe how and when a subject may withdrawal from the study.** Once the subject completes the first session of the CBT-I, he will not be dropped from the study, unless they specifically request that they not be contacted, or the subject cannot be located for assessment by the 8-week follow-up. The subject may voluntarily withdraw from the study at any point in time. Subjects who are discontinued from the cognitive behavioral therapy intervention will continue to be followed in the study until the completion of the 8 weeks of intervention and the post-study follow-up at 3 and 6 months. The reason the subject is discontinued from the study and any referrals that are made are documented in the appropriate section of the subject's casebooks.

2. **Provide procedures for the orderly termination of participation by the participant and if any consequences would result from early withdrawal from the study.** The subject may be terminated from the research study by the investigator, without regard to his/her consent, under certain conditions. These conditions may include, if s/he does not comply with the recommendations of the research staff, including compliance with study related procedures on ≥3 consecutive office appointments; s/he reports ideas of harm to self or to anybody else with any intent and/or a plan. S/he will additionally be referred to the outpatient treatment program at the Addiction Recovery Unit of the CMCVAMC. Alternatively patient will be withdrawn from the study on successful completion of their study participation.

   Subjects will be discontinued/withdrawn from the study if any of the following events occur:

   - Any condition which the study psychiatrist finds CBT-I to be a hazard to the subject (i.e. patient seen to be agitated, onset of increasing paranoia, inability to follow through with recommendations and/or homework)
   - Participant screens positive at baseline for moderate to severe obstructive sleep apnea (as seen baseline screening portable sleep monitor data), and is currently on not treatment for the obstructive sleep apnea
   - Relapse to sustained heavy drinking during treatment as quantified at ≥ 5 standard drinks for men and ≥ 4 standard drinks for women less than 70 years of age, or a total of 14 drinks/ week in men and 7 drinks per week in women for ≥4 days a week and >1 week;

- Development of an inter-current medical illness or condition that requires a new hospital admission
- Emergence of another substance abuse problem which necessitates inpatient admission or a more aggressive treatment than provided by the protocol.
- Subject is incarcerated for more than a week.

Study participation can be restarted after consultation with the research physician for subjects who 1) return to treatment after a period of brief absence of less than 3 weeks, or 2) return to treatment after brief inpatient hospitalization of less than 2 weeks or additional outpatient treatment. Restarting study procedures is contingent upon clinical need and continuing to meet inclusion and exclusion criteria.

3. **Explain if survival data is required. If so, clarify how data will be obtained.** We will not be assessing for survival data in this pilot study. However we may consider looking at the survival data if there are a significant number of drop out of subjects from the study, with the end point of the survival analysis being the drop out date (i.e. total duration of participation in the study).

4. Not Applicable; subjects not recruited; chart review. ☐

T. Risk/Benefit Assessment

1. Potential Study Risks

1.1. Describe and assess all of the following risks that may be associated with the research:

1.1.1. Physical a. Portable Sleep Apnea Monitoring: there may be discomfort associated with the use of nasal cannulas and sensors on the chest/abdomen; b. Overnight Polysomnography: Sleeping in the CMCVAMC sleep laboratory with adhesive leads on the body may be associated with physical discomfort;

1.1.2. Psychological a. Sleep Restriction: patients may experience an increase in the daytime sequelae of insomnia as a result of this intervention (the scheduling of time in bed so as to equal average total sleep time). In the first few days of treatment this is likely to entail some sleep deprivation (~1 hour less sleep than is normal for the individual) and result in a transient increase in daytime sleepiness, fatigue, concentration problems, and irritability; b. Data Collection during the Study: there may be discomfort associated with talking about family history of alcoholism, psychiatric issues and addiction-related issues. Furthermore, in some cases, the use of the sleep diaries and actigraphs may lead to (or be perceived as causing) a transient worsening of insomnia symptoms at home; c. Relapse to Alcohol: there is a possibility that the transient "side effects" of CBT-I may lead some individuals to resort to occasional alcohol use and that such behavior may also lead to relapse (heavy drinking); d. Use of Other Drugs: there is a possibility that the transient "side effects" of CBT-I may lead some individuals to start using other drugs while taking part in the study-related procedures; e. Suicidal/Homicidal Ideation. While there is no evidence that CBT-I increases suicidal or homicidal ideation, it is a possible consequence of the transient sleep deprivation that occurs with CBT-I. That is, sleep deprivation may lead to decreased inhibition in the frontal brain areas, which may, in turn, lead to a failure to inhibit or cope with such thoughts, especially in vulnerable populations like those who suffer from alcoholism.

1.1.3. Social. A decreased interest in affiliating with other people because of persisting insomnia or a transient increase in the insomnia secondary to the sleep restriction associated with the CBT-I.

1.1.4. Economic. Time spent participating in the study may interfere with the subject's ability to seek employment or participate at his job.

1.1.5. Monetary. May be secondary to loss of time spent in participating in the study.
1.1.6. Legal. An increase in the drowsiness may lead to potential risk of a motor vehicle accident.
1.1.7. Loss of confidentiality a. there is a possibility that the subject's identifying data and/or study information may be viewed by non-study personnel.
1.1.8. Assess the likelihood and seriousness of such risks. Although the risks associated with drowsy driving are serious, the likelihood of this risk is low. The likelihood of the other risks are variable, between a low to a moderate level, and specific to the Veteran's individual situation.
1.1.9. Other. N/A

1.2. Specify what steps will be taken to minimize these risks.

a. Portable Sleep Apnea Monitoring: While the use of nasal cannulas and sensors on the stomach and abdomen are required for this screening, subjects that experience discomfort during orientation will be provided (where possible) the opportunity to select from different types of cannulas and sensors .

c. Sleep Restriction: As noted above, this behavioral procedure is not without side effects (sleep loss and increases in the daytime symptoms of sleepiness, fatigue, concentration problems, and irritability). The subject will be made aware that "things will [and must] get worse before they get better" and that the transient worsening of symptoms is in the service of long-term gains. This said, in the rare cases where the procedure is viewed by the patient as intolerable, the protocol will be to either 1) re-assess the patient's basal sleep ability (conduct a second baseline assessment) or to substitute sleep compression[54] for sleep restriction. In addition, similar to our clinical care, we will counsel and monitor subjects at each of the follow-up visits for any excessive daytime drowsiness leading to drowsy driving, a risk factor for a motor vehicle accident, and we will review tips to avoid drowsy driving. If the patient does not wish to engage in these alternatives or the accommodations above do not increase the tolerability of the intervention, then the subject is (as always) free to withdraw from the study.

d. Data Collection during Initial Evaluation. Every attempt will be made to minimize the discomfort associated with disclosure of personal data. All of our staff are accustomed to and have a high degree of facility with the acquisition of sensitive information (e.g., drinking history). If, despite our staff's best efforts, the patient is unable to discuss issues that bear on their family and/or clinical history, they are free to not disclose this information and they are free to withdraw from the study. Further, if the patient's reluctance to share information precludes the acquisition of data that are critical to the conduct of the study, they will, at the PI's discretion, be asked to withdraw from the study. In the event that the subject feels they cannot tolerate completing daily sleep diaries or wearing the study actigraph, they will be told that such effects tend to be very transient. If the subject continues to find the collection of such data intolerable and/or is non-compliant, they will initially be assisted by the study-related staff in being compliant with the data collection through frequent reminders (as these data are central to the study). Despite frequent reminders, if they continue to remain non-compliant and at the PI's discretion, they may be asked to withdraw from the study.

e. Confidentiality: During the participation in this study, the patient will be assigned a 4-digit unique identification number. This number will not be derived from PHI of any sort (e.g., DOB, SSN, etc.) and will simply represent the study and the subject's recruitment number (e.g., 1001). Study numbers will be linked to subject identifiers in one spreadsheet that will be stored on the PI's password-protected VA online drive. These efforts make it very unlikely that the subject's identifying data and/or study

information may be viewed by non-study personnel. The data will now be captured and stored within the VA Redcap and stored in the secured VA servers.

f. Relapse to the Drinking. All drinking behavior will be monitored. Monitoring will be based upon self-report items on the daily sleep diaries and clinical interviews by the principal investigator during the outpatient visits. These variables will be monitored for both research and clinical purposes. The research purpose is to determine how alcohol use varies with treatment for insomnia. The clinical purpose is to be able to determine if there has been a resumption of heavy drinking (four standard alcoholic drinks on any day or ≥ 14 drinks a week). If there is a resumption of sustained heavy drinking and this sustained heavy drinking places the subject at risk of medical, psychological or physical harm, then he will be withdrawn from the study, and a referral to the ARU or the inpatient unit, as deemed necessary for further treatment, will be offered to the participant

g. Use of Other Street Drugs. Patients will be evaluated for the use of other street drugs through structured assessment instruments. Further, if there is a history of regular drug use, the subject will be regularly monitored with standard urine tests (note: this will be a condition for admittance into the study). If regular drug use is detected, the subject will be withdrawn from the study, and a referral to the ARU for further treatment will be offered to the participant.

h. Suicidal/Homicidal Ideation. If the participant reports suicidal ideation with intent to hurt themself, or if on evaluation, s/he is seen to be a danger to themself or others, s/he will be referred immediately from the office to the Emergency Department of the CMCVAMC (CMCVAMC -ER). If s/he reports passive suicidal ideation, s/he will be monitored for any change during visits. S/he will also be offered a referral to the Addiction Recovery Unit of the CMCVAMC for further evaluation at the end of the study.

1.3. **If methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.** In the extreme situation where the risks cannot be mitigated with the above steps, and risk of participation in the study are considered to be greater than non-participation, the P.I. may withdraw the subject from the study and monitor him till the end of the study duration, along with any other additional clinical care that may be warranted.

1.4. **If chart review, breach of confidentiality is always a concern. Specify what steps will be taken to minimize these risks.** These will include the following: restriction of chart review to the P.I. and the study coordinator; storing the identifying information in locked drawers in locked office spaces; use of any of the 17-HIPAAA identifiers to communicate with research staff either over the phone or using the "do not forward" option of the VA email system; and discarding the patient related information into the designated shredding bins within the VA promptly after the information is reviewed or communicated with staff or the specific Veteran.

2. **Potential Study Benefits**

2.1. **Assess the potential benefits to be gained by the individual subject, as well as benefits that may accrue to society in general as a result of the planned work.** It is possible that the patients will not obtain any benefit from participation in this study. However, it is also possible that some of the participants may have an improvement in their insomnia after completion of their participation in the study. Some potential participants who screen positive for moderate to severe obstructive sleep apnea will be referred to the CMCVAMC Sleep Center for further evaluation and treatment for the

disorder. In addition, as seen in our past Quetiapine Sleep Study and our current CBT-I pilot study in the recovering alcoholics, some of the subjects, by virtue of their participation in this study, may obtain a better understanding of their insomnia and available treatments after the end of the study. This understanding will therefore help them make better choices for their future insomnia treatment.

3. **Alternate Procedures**

3.1 **Describe the alternatives available to the subject outside the research context.** Alternatives available to the participant include the following: to not participate in the research study at all, taking a sedating psychotropic medication for their insomnia as prescribed by the patient's care provider, or enrolling for CBT-I treatment at the CMCVAMC sleep center.

U. **Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)**

1. **Will an independent DSMB or DMC oversee the project?** ☒YES ☐NO ☐N/A

1.1. If yes, please provide contact information for the DSMB or DMC or Coordinating Center Representative and attach a copy of the charter.

Name: **Tamara Paine** Phone Number: 708-202-5785

Title: Project Manager E-mail: Tamara.Paine@va.gov

2. **If a DSMB or DMC will not monitor this study, who will monitor this study? Check all that apply.**

☐ Principal Investigator
☐ Sponsor
☐ VA Cooperative Studies Program
☐ Safety monitoring committee

V. **Data Monitoring**

1. **Describe the data monitoring plan.** A monitor, independent of the study team will regularly inspect the accuracy of data entered. S/he will randomly pick out the source documents and ensuring that the study is adhering to the study protocol with the applicable research regulations and CMCVAMC requirements.

2. **Describe how protocol deviations, adverse events, serious adverse events, breaches of confidentiality, unanticipated adverse device effect (UADE), and unanticipated or unexpected problems will be reported to the** CMCVAMC **IRB and sponsor**. Protocol deviations, adverse events, and unanticipated/unexpected problems will be notified in writing to the CMCVAMC IRB as per CMCVAMC R & D regulations and to the DMC. Serious adverse events and unanticipated adverse events will be reported to the IRB within 5 days of knowledge of the event. Adverse events will be reported in the continuing review as per regulations.

2.1. Describe the management of information obtained that might be relevant to participant protections such as:

2.1.1. **Unanticipated problems involving risks to subjects or others.** The unanticipated problems involving risks to the subjects or the others will be notified to the CMCVAMC -IRB. In addition, subjects will be individually notified of the unanticipated problems and the associated risks and benefits of continued participation will be furnished – this will help the Veteran make an informed decision on the need for continued participation.

2.1.2. **Interim results.** N/A.

2.1.3. **Protocol modifications.** The protocol modifications will be implemented after authorization from the CMCVAMC -IRB. Where ever applicable, the subject will

need to sign an updated consent form, if the changes in the protocol involve him and occur while he is participating in the research study-related procedures.

3. **If applicable, define the plan for subjects if research shows results such as:**
   3.1. Depression - depressive symptoms are common in those complaining of insomnia as well in Veterans during early recovery. Depressive symptoms will be monitored through the study.
   3.2. Suicide - In the unusual situation the participant is seen to develop severe depressive disorder with inability to function with his daily activities or seen to have the onset of suicidal ideation with intent and/or plan, the veteran patient will be referred to the CMCVAMC – ER for further evaluation and treatment.
   3.3. Abuse – If participant is seen to abuse another drug excluding cannabis and nicotine through the study, s/he will be monitored and at the end of the study, s/he will be recommended a referral back to the ARU. If s/he is currently in treatment in the ARU, her/his treatment team will be notified of the clinical progress in the research study as well as the new substance use. In case the patient is discovered to have dependence to another drug e.g. a sedative-hypnotic or opiates s/he will be monitored through the active study and follow up, educated about her/his drug dependence, urged to abstain from the drug use and if s/he consents, referred to the ARU for active treatment and will also be simultaneously follow up by our research staff, till the end of the study related follow up visits.

4. **Statistical Analysis**
   4.1. **Include statistical power calculations and the assumptions made in making these calculations.** The following power calculations for Aims 1-3 assume the availability of 86 subjects who are eligible for randomization into one of two groups (n=43 per group). We assume a range of intra-class correlation of 0.1-0.5 and up to 10 follow-up measures per participant. The sample size is inflated to accommodate a 30% missing or dropout rate by 6 months based on rates over a similar period of time in previous studies[55]. We consider a conservative adjustment in the two-sided level of significance, 0.025, to account for two hypothesis tests per Aim (3-month and 6-month outcome). Table 4 presents the detectable effect size based on the above assumptions for 90% and 80% power. The study will have 80% power to detect a moderate effect size of 0.50 standard deviations of a continuous outcome measure at 6 months assuming an intra-class correlation of 0.3. Table 5 presents the detectable effect in units applicable to each outcome based on the observed standard deviation from studies in the literature.

Table 4. Detectable effect size for the 3- & 6-month outcome at varying levels of power and intra-class correlation

Power	Intra-class Correlation	Detectable effect size	
		3 months	6 months
80%	**0.1**	0.35	0.40
	0.3	0.48	0.50
	0.5	0.58	0.61
90%	**0.1**	0.40	0.41
	0.3	0.55	0.57
	0.5	0.66	0.70

(Assumptions: power=80%; n=30 per group after 30% attrition; 2-sided=0.05)
[a] Standard Deviation
[b] Insomnia Se
[c] Quality of Life
[d] Pooled within group standard deviation
[e] Pooled within group standard deviation (estimated from presented data)
[f] Pooled within group standard deviation for general health

Table 5. Minimum detectable difference between groups (two-sided $\alpha = .05$, 80% power)

Outcome	Pre-Post S.D.[a]	Detectable Difference
ISI[b]	3.809[d]	1.90 points
Abstinent Days	15.96[e]	7.98 %
Health Related QOL[c]	9.15[f]	4.58 points

4.2. **Define plans for data and statistical analysis, including key elements of the statistical plan, stopping rules and endpoints.** *Overview*: Our study proposes a longitudinal repeated-measures parallel-group design. This powerful design, with a baseline measurement and up to ten follow-up measures per participant over 6 months, allows for comparisons within each participant over time as well as across participants (treatment groups). The main analysis will look at differences between intervention groups in the changes in outcomes over time (i.e. insomnia severity, alcoholism-related outcomes and daily functioning). *Randomization*: Patients will be recruited and randomized as individuals. Allocation will be uniform across the two groups after suitable blocking and stratification on family history of alcoholism to ensure optimal balance of participant characteristics and to observe relationships between groups with and without a family history of alcoholism in the Exploratory Aim. Participants are randomly assigned to the CBT-I group, or the QDT group. The study biostatistician will create randomization sequences by family history of alcoholism (separate sequences) using a pseudo-random number generator with block sizes of 4. Two boxes of sequentially numbered, sealed, opaque envelopes will be prepared using the randomization sequences and labeled "Family History" and "No Family History". At the time of randomization, the first envelope, in sequential order, is pulled from the appropriate box and opened to reveal the group assignment. All the staff conducting assessments will be blinded to the allocation of treatment arm with the exception of Dr. Findley, the BSM treatment provider, Ms. Barilla the person overseeing treatment allocation, and Dr. Harb, the monitor for BSM treatment for the study. *Preliminary Analyses*: All data, regardless of the format, will first be assessed by Dr. Chakravorty and his mentors for missing data, distributions of all observed measures, and out-of-range values by means of conventional descriptive tables. SAS v9.3 will be our primary tool for these analyses as the software is both mature and well-documented[56]. Next, we will employ raw and smoothed plots to visualize the individual and average trajectories of all repeated measures over time according to assigned treatment and by participant characteristics. All questions of data quality and integrity will be investigated before any statistical modeling, since complete and accurate data are essential for unbiased estimates and confidence intervals. We will compare all baseline variables across groups to check the adequacy of randomization. The baseline comparisons will be based on: 1) t-test or Wilcoxon rank sum tests for continuous variables depending on the symmetry of the distributions; 2) on logistic regression for binary or ordinal variables; and 3) on Poisson log-linear regression for count data. If imbalances are found at baseline, then the relevant variables will be treated as confounders in the analysis.

Specific Aims 1-3: The analysis for the specific aims 1-3 is based upon the intent-to-treat principle; all randomized participants will be included in the analysis regardless of whether they drop out of the intervention or study. The analysis will involve the comparison of the insomnia severity (Aim 1), abstinence from drinking (Aim 2), and quality of life (Aim 3) across the intervention groups in order to allow for different trajectories of the outcome measures and to afford flexibility in making contrasts within participants over time and across participants while simultaneously controlling for potential confounding factors, we propose the participant-specific or *mixed effects* linear

model. In this model, the mean ISI depends on fixed covariates and random effects [57]. The fixed covariates of interest include time, treatment assignment, the interaction between time and treatment assignment, adjusting for family history of alcoholism and confounding variables identified in the preliminary analysis. The random effects represent the unobserved factors that lead to variation of the individual participant's outcome. Random intercepts for each participant permit modeling of natural variation across participants at baseline in the outcome of interest. In addition, random slopes or random effects for the trajectory of each participant over time allow for variation of each participant about a mean, overall trajectory across all participants. Estimates of the random effect for an individual participant also permit far more focused investigations of those individuals who depart from the mean over time and experience either better or worse than average change in outcome. Thus, the mixed effects longitudinal model permits both comparisons of groups as well as contrasts of individuals. Although less robust to model misspecification, the mixed effects paradigm offers special flexibility in longitudinal data when exposures vary over time and when dropout and missed visits lead to unbalanced groups. ISI and quality of life are continuous measures and most likely follow a symmetric or approximately normal distribution. Therefore the linear mixed regression model is appropriate. If departures from normality are found, we will consider transformations or other distributional forms that may better fit the data. The alcoholism-related outcome measures are counts (e.g. number of days abstinent, number of heavy drinking days, etc.) but will be summarized as percentages (e.g. percent abstinent days) and will also most likely follow a normal distribution. The target of inference is the participant-specific response to treatment over time. Specifically we are interested in the efficacy at the end of treatment (8 weeks) and durability after 3 and 6 months of follow-up. At each time point of interest, we will estimate from the fitted model the difference from baseline in the outcome for each treatment group and test the difference between these differences. The treatment effects will be the contrasts that represent the difference of differences from baseline in outcome across treatment groups at 3 and 6 months. Both univariate and multivariate results will be reported in terms of Wald test, point estimates, and 95% confidence intervals.

Exploratory Aim 4: We will examine whether family history of alcoholism modifies the effect of the intervention on outcomes. Effect modification or moderators of the intervention will be tested and estimated with 3- and 2-way interactions among the treatment factor, potential moderator, and time in the ITT models described above. Because the hypotheses relating to effect modification will be exploratory, we will use p=0.1 to declare significance of such interactions. The analyses will be followed with stratified analyses corresponding to the effect modification hypotheses.

Regarding missing data and drop-out, we will assess the relationship of missing data patterns with dependent and independent variables. Specifically, we will use logistic regression with missingness as the binary outcome and dependent and independent variables under each Aim as covariates for the missing data model. If there are significant associations, we will perform multiple imputations with PROC MI in SAS, and take weighted averages of parameter estimates and standard errors from the longitudinal regressions across the multiple imputation iterations.

W. Privacy and Confidentiality

1. **Indicate the type of data that will be received by the Principal Investigator. Check all that apply.**
   1.1. ☐ De-identified – Without any identifiers that could link the data to a specific participant. (Contact Privacy Officer for assistance. *If data is coded, it is not considered de-identified.)*

1.2. ☐ Identified – Linked to a specific participant by identifiers sufficient to identify participants. (See HIPAA and Common Rule Criteria for list of identifiers.)

1.3. ☒ Coded – Linked to a specific subject by a code rather than a direct identifier. If coded is checked, specify:

1.3.1 **Explain who will maintain the link or code.** The principal investigator and the research assistant will have access to the codes, which will be stored in a locked filing cabinet in room #228 or in the locked cabinet in Dr. Chakravorty's office (TBA). In addition, the code will also be stored in a back-up file in the password protected online drive of the principal investigator on the MIRECC drive (\\vhaphifpcmirecc\Research Studies\Chakravorty – CBT-I) or the K: drive of the PI/\\vhaphiclunas11s (K:).

1.3.2 **Describe who will have access to the link or code.** P.I., and/or the study coordinator.

1.3.3 **Provide exact details for how the data is coded.** The participant will be assigned a 4-digit unique identifying number for this study. This 4-digit identification number will not be related to the last 4 digits of his social security number or a 4-digit number generated by scrambling his social security number. The link between the 4-digit coded identification number and the participant's name and social security number will be stored on paper in a locked cabinet in room #228 B, or in the locked cabinet in Dr. Chakravorty's office (Room # 218, Bldg 3), as well as backed up electronically in the password protected VA online MIRECC drive (\\vhaphifpcmirecc\Research Studies\Chakravorty – CBT-I) or the K: drive of the PI/\\vhaphiclunas11s (K:).

2. **Does the project require the use of existing Protected Health Information (PHI) from a database, medical records, or research records?** ☒YES ☐NO ☐N/A

2.1. If yes,

2.1.1. **Specify the source of the existing PHI**. The CMCVAMC medical records in CPRS.

2.1.2. **Indicate the specific data elements/identifiers (e.g., name, address, phone numbers, etc.) on the below table.** We will collect personal information such as name, address (street address, city, county, precinct, ZIP code), dates directly related to you (including birth date, admission date, discharge date), telephone number for you as well as for a designated contact person (in case we cannot contact you), electronic mail address, social security number, HIV and infectious disease diagnoses results and treatment records, information related to the diagnoses and treatments related alcohol and/or other drug use disorder/s, results of sleep disorder evaluation and/or any sleep related studies, any radiological studies, prior laboratory tests for medical disorders (including and not related to liver function tests, thyroid function tests, hyperlipidemia, diabetes), current medications, and the results of prior history and physical examinations.

2.2. If the study uses an existing database/data warehouse,

2.2.1. **Provide a description of the database/data warehouse.** The patient's clinical chart, CPRS will be used to prescreen subjects and subsequently we will contact the Veterans' practitioner regarding the possibility of discussing this study with the Veterans.

2.2.2. **Make clear who is responsible for maintaining it.** N/A

2.2.3. **Cite any relevant Standard Operating Procedures (SOP) for the database/data warehouse.** N/A

2.2.4. Provide a copy of the SOP.

3. Will PHI be collected prior to obtaining informed consent? ☒YES ☐NO ☐N/A

4. HIPAA Identifiers - Indicate the PHI that will be collected from project participants directly or indirectly.

4.1. ☒ Name

4.2. ☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census

4.3. ☒ All elements of dates (except year) for dates directly related to an individual, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.

4.3.1. ☐ Birth Date ☐ Date of Death

4.3.2. ☐ Discharge date ☐ Admission date

4.3.3. ☐ Appointment Dates ☐ Other Dates (e.g. lab tests, x-rays, MRI, etc.)

4.4. ☒ Telephone numbers

4.5. ☐ Fax numbers

4.6. ☒ Electronic mail addresses

4.7. ☒ Social Security Number

4.8. ☐ Medical record numbers

4.9. ☐ Health plan beneficiary numbers

4.10. ☐ Account Numbers

4.11. ☐ Certificate/license numbers

4.12. ☐ Vehicle identifiers and serial numbers, including license plate numbers

4.13. ☐ Device identifiers and serial numbers

4.14. ☐ Web universal resource locators (URLS)

4.15. ☐ Internet protocol (IP) address numbers

4.16. ☐ Biometric identifiers, including fingerprints, voiceprints, audio recordings

4.17. ☐ Full-face photographic images and any comparable images

4.18. ☐ Any other unique identifying number, characteristic, or code

4.19. ☒ Personal and Family History

4.20. ☒ History and Physical Examination ☒ Progress Notes

4.21. ☒ Discharge Summary(ies) ☐ Photographs, videotapes, other images

4.22. ☐ X-Ray ☐ HIV (testing or infectious disease) records

4.23. ☒ Diagnostic/Laboratory tests ☐ Sickle cell anemia

4.24. ☒ Drug Abuse Information ☒ Behavioral Health notes

4.25. ☒ Alcoholism or Alcohol Use ☒ Operative Reports

4.26. ☐ Billing records ☒ Medication List

4.27. ☒ Health Summary Reports ☐ Anatomic Pathology Report

4.28. ☒Other Records: Any prior sleep studies or treatment outside the VA health system for sleep disorders

5. Will participants be contacted from existing PHI? ☒YES ☐NO ☐N/A

5.1. If yes, clearly explain how participants will be contacted. We will contact the prospective participants who have been identified by their providers after expressing willingness regarding the study or alternatively, if the participant contacts us directly regarding the study. In addition, providers of patients identified by review of records will be contacted by the study related staff to discuss the study briefly with the patients.

6. Provide the titles of the exact individuals who will have access to the collected data. See section 6.1 below for details.

6.1. Explain why these individual will have access to this data.

1. The principal investigator – he may conduct any of the procedures, as may be necessary
2. Research Assistant – coordinate the study related visits and procedures.

3. Psychologist associated with the study (Certified Behavioral Sleep Medicine Specialist, TBA) – to assess, and answer any questions that the participant may have, especially if he is non-compliant with a study related visit.
4. The regulatory agencies including the IRB at the CMCVAMC, DMC, and the grant funding organization VA CS R & D. They will have access to the information in order to conduct their regulatory activities.
5. The genetic data will be stored in the freezer space designated by the CMCVAMC R & D services and will reside there with the coded identification numbers and without any of the 17 HIPAA identifiers. Once all the samples have been collected and we are ready to commence the genetic analyses, we will request CMCVAMC -IRB approval to transfer the blood samples to the designated laboratory at the University of Pennsylvania for further analyses of the samples. After the analyses the blood samples will be destroyed.

X. **Information Security**

Provide the precise plan how data is to be collected or acquired (repeat the same information as listed under "Data Collection" section of this form. (Section 2). Most of the assessment measures will involve interviews (e.g. for the SCID form, or for the initial CBT-I session). The only exceptions to this rule are for actigraphs and portable sleep monitors. Actigraphs will be worn on the wrist for a few days at a stretch and the Veteran will be maintaining a sleep diary for the sleep-wake schedule. The monitor has sensors attached to the body recording oxygen saturation, airflow (nasal pressure), thoracic movements, snoring, body position and the heart rate. The apparatus measures nasal pressure, which is an accepted surrogate marker of air flow (instead of using oro-nasal thermistors, used in the earlier portable monitors). Please see Table 1 for specific details on the assessment measures and the time frames of their assessments.

2. **Provide a listing of the exact research data that will be stored, including but not limited to signed, original informed consent and HIPAA authorization forms, case report forms, etc.** Data including but not limited to signed, original informed consent and HIPAA authorization forms, case report forms, genetic analysis in the future, and results of the urine drug screen.

2.1 Indicate how project's research data (original and all copies) will be stored and provide corresponding security systems. a) Original assessment measure on paper and pencil – in the locked drawers of the locked office spaces of the MIRECC (room 228 B). Some of the data may be stored in the Principal Investigator's locked drawer in his locked office (Room # 218, Bldg 3); we will transition data collection and storage to the VA Redcap from the paper forms; b) Original Actigraphic data – in the desktop in the locked drawers of the locked office space of the study coordinator within the MIRECC (room 228 B) or in the Principal Investigator's locked drawer in his locked office (Room # 218, Bldg 3); c) Electronic data with identifying information within the electronic servers of the CMCVAMC (MIRECC server (\\vhaphifpcmirecc\Research Studies\Chakravorty – CBT-I) or the K: drive of the PI/\\vhaphiclunas11s (K:)).); d) Electronic coded data without the HIPAA identifiers for statistical analyses – password protected computer within the University of Pennsylvania; e) Electronic data captured in the VA Redcap: a secure web application and back-end database model, developed at Vanderbilt University with collaboration from a consortium of institutional partners. Approved study staff will enter data directly into REDCap, which obviates the need for transferring written data into electronic form; this significantly improves the quality of data. The VA has licensed its own version of REDCap housed on VA servers located within a VA data center inside the VA firewall and therefore afforded the same network protections as all VA sensitive clinical data. REDCap was developed specifically around HIPAA

Security guidelines and is recommended to Penn Medicine researchers by our Office of Human Research. Relevant HIPAA-compliant features include password-protected access to the system, restriction of access to specific clinical trial data to designated users, audit trails of access and data updates, and built-in de-identification functions that can be used when exporting data for analysis. REDCap has been disseminated for use locally at other institutions and currently supports 170 academic/non-profit consortium partners on six continents and 13,000 research end-users (www.project-redcap.org). Approved study staff can access REDCap through a web-based interface and securely input data from any location at the time of data collection minimizing the need for travelling with either electronic or paper versions of sensitive information.

VA REDCap database administrators will have control over electronic access rights to REDCap databases. Only VA IRB approved individuals will be granted access to this database. This database keeps time-stamped information on people accessing, inputting, and altering data in the database.

3. **Provide exact location where research data (original and all copies) will be stored and secured.**

a. Original assessment measure on paper and pencil – in the locked drawers of the locked office spaces of the MIRECC (room 228 B); some of the data may be stored in the Principal Investigator's locked drawer in his locked office (Room # 218, Bldg 3);

b. Original Actigraphic data – in the desktop in the locked drawers of the locked office space of the study coordinator within the MIRECC (room 228 B) or in the Principal Investigator's locked drawer in his locked office (Room # 218, Bldg 3);

c. Electronic data with identifying information within the electronic servers of the CMCVAMC (MIRECC server drive (\\vhaphifpcmirecc\Research Studies\Chakravorty – CBT-I), or the K: drive of the PI /\\vhaphiclunas11s (K:));

d. Electronic coded data without the 17 HIPAA identifiers for statistical analyses – password protected computer within the University of Pennsylvania;

e. The blood samples for the genetic analyses will be stored at a freezer within the CMCVAMC. When all the samples have been collected and samples are ready for analyses we will transfer the samples with the coded identifier (and without any of the 17 HIPAA identifiers) from the CMCVAMC to the designated laboratory at the University of Pennsylvania after obtaining the required CMCVAMC -IRB authorization. The samples will be destroyed at the University of Pennsylvania after the genetic tests have been conducted;

f. Redcap: a secure web application and back-end database model, developed at Vanderbilt University with collaboration from a consortium of institutional partners. Approved study staff will enter data directly into REDCap, which obviates the need for transferring written data into electronic form; this significantly improves the quality of data. The VA has licensed its own version of REDCap housed on VA servers located within a VA data center inside the VA firewall and therefore afforded the same network protections as all VA sensitive clinical data. REDCap was developed specifically around HIPAA Security guidelines and is recommended to Penn Medicine researchers by our Office of Human Research. Relevant HIPAA-compliant features include password-protected access to the system, restriction of access to specific clinical trial data to designated users, audit trails of access and data updates, and built-in de-identification functions that can be used when exporting data for analysis. REDCap has been disseminated for use locally at other institutions and currently supports 170

academic/non-profit consortium partners on six continents and 13,000 research end-users (www.project-redcap.org). Approved study staff can access REDCap through a web-based interface and securely input data from any location at the time of data collection minimizing the need for travelling with either electronic or paper versions of sensitive information.

VA REDCap database administrators will have control over electronic access rights to REDCap databases. Only VA IRB approved individuals will be granted access to this database. This database keeps time-stamped information on people accessing, inputting, and altering data in the database.

4. **Explain how data is to be transported or transmitted from one location to another.** The coded data (without the HIPAA identifiers) will be transferred using encrypted discs which will be hand-carried by Dr. Chakravorty to Dr. Morales's office at the University of Pennsylvania.
   - 4.1. Informed Consent discloses PHI transported or transmitted off-site. ☐YES ☒NO ☐N/A
   - 4.2. HIPAA Authorization discloses entities to whom PHI will be transported or transmitted. ☐ YES ☒NO ☐N/A
     - 4.2.1. **List all entities or individuals outside** CMCVAMC **to whom data is to be disclosed, and the justification for such disclosure and the authority.** Dr. Knashawn Morales and her staff at the Center for Clinical Epidemiology and Biostatistics of the University of Pennsylvania. She and her staff will conduct the statistical analyses of the coded research data without the HIPAA identifiers.
   - 4.3. If yes, list the exact data that will be transmitted. **Coded data from all the assessment instruments and measures.**
   - 4.4. If yes, explain how data will be protected during transmission outside of CMCVAMC. **The data will be hand carried in encrypted compact disc/s by the Principal Investigator to her office within the University of Pennsylvania.**
   - 4.5. Off-site, provide exact location coded data without the 17 HIPAA identifiers will be transferred for statistical analyses to the Center for Clinical Epidemiology and Biostatistics, at the University of Pennsylvania.
     - 4.5.1. Data Use/Transfer Agreement ☒YES ☐NO ☐N/A
     - 4.5.2. Off-Site Storage/Transfer of Research Data ☒YES ☐NO ☐N/A
     - 4.5.3. Memorandum of Understanding ☐YES ☒NO ☐N/A

5. **List who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security).** 1. Principal Investigator – source documents, electronic spreadsheets, and compact discs with backed up data; 2. Study Coordinator - source documents, electronic spreadsheets, and compact discs with backed up data; 3. Statistician (Dr. Morales) – electronic coded data without the 17 HIPAA identifiers; 4. CMCVAMC -IRB – data as deemed necessary; e) VA CS R & D, the grant funding agency – data as deemed necessary.

6. **Describe who is to have access and be responsible for the security of the information.** The staff members who will have access to the information will include the following: a) Principal Investigator, Dr. Chakravorty; b) The Study Coordinator, Mr. He; c) Statistician at the University of Pennsylvania, Dr. Morales (she will have access to the coded data without the 17 HIPAA identifiers); d) CMCVAMC -IRB; e) DMC; f) VA CS R & D, the grant funding agency. The security of the information will be responsibility of everybody involved with the study and having privileges of access to the study-related data.

7. **Provide mechanisms used to account for the information.** The study related staff will follow the guideline of keeping the identifiable health information in locked drawers or on the online

password protected electronic drives of the CMCVAMC. The source documents will be maintained in the locked office space of the MIRECC in room # 228 or in the locked clinic office of Dr. Chakravorty (Room # 218, Bldg 3). We will migrate over to the VA version of Redcap for future data entry and the data will be stored within the VA VIRECC servers as mentioned previously. The coded data without the 17-HIPAA identifiers will be transferred in encrypted compact discs by the investigator himself to the statistician's office at the University of Pennsylvania. The statistician will store the coded data with the HIPAA identifiers in the password protected computer in her office. Once the data analysis is completed the coded data will be destroyed from the statistician's computer.

8. **Give security measures that must be in place to protect individually identifiable information if collected or used.** Identifiable information will be stored in locked office spaces of the MIRECC (room 228), and in the Principal Investigator's locked office space (exact location TBA). Electronic data with identifiable information will be stored in the password protected online servers of the CMCVAMC and VIRECC, and the on the password protected desktops of the Study Coordinator and the Principal Investigator.

9. **How and to whom a suspected or confirmed loss of VA information is to be reported.**
   9.1. The Investigator will notify the Information Security Officer, Privacy Officer, IRB, Associate Chief of Staff for Research and Research Compliance Officer within one hour of a suspected or confirmed loss of VA information.

10. **Identify any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence, and describe appropriate actions to provide such safeguards.**
    The subjects will be reminded of the voluntary nature of the study during the initial screening, during the informed consent session, as well as tested in the informed consent quiz.

11. Electronic PHI will be stored on the following:
    11.1. CMCVAMC desktop computer with password protection and/or encryption. ☒YES ☐NO ☐N/A
        12.1.1. If yes, identify where the desktop is located. **Study coordinator's desktop in room 228 of the MIRECC and the Principal Investigator's desktop in a locked office space (exact room location TBA).**
    11.2. CMCVAMC secure server. ☒YES ☐NO ☐N/A
        11.2.1. If yes, identify the CMCVAMC server. **The MIRECC server (\\vhaphifpcmirecc\Research Studies\Chakravorty – CBT-I), the Principal Investigator's folder in the K: drive/\\vhaphiclunas1fs(K:)).**
        11.2.2. External drive that is password protected and/or encrypted. ☐YES ☐NO ☒ N/A
            11.2.2.1. If yes, identify the external drive.
    11.3. Off-Site server ☐YES ☒NO ☐N/A (If off-site, attach at least one of the following.)
        11.3.1. Provide exact location and the name of the off-site server. 1) secure VA VIRECC server that houses the data from the VA Redcap; 2) Coded data without the HIPAA identifiers will be transferred for statistical analyses to the Center for Clinical Epidemiology and Biostatistics, at the University of Pennsylvania.
        11.3.2. Data Use/Transfer Agreement ☒YES ☐NO ☐N/A
        11.3.3. Off-Site Storage/Transfer of Research Data ☒YES ☐NO ☐N/A
        11.3.4. Memorandum of Understanding ☐YES ☒NO ☐N/A

12. **Explain how data is to be transported or transmitted from one location to another.** The VA Redcap data will be entered into the VA Redcap using desktops with CMCVAMC onto the password protected account for the study. The actigraph will be returned by the subject in-person to the study coordinator or mailed out to the study coordinator in prepaid mailing envelopes. They will be hand carried in compact discs by the study coordinator from the CMCVAMC sleep center to room 228 (MIRECC). The blood samples for the genetic analyses will be stored in a freezer within the CMCVAMC. When all the samples have been collected and samples are ready for analyses we will transfer the samples with the coded identifier (and without any of the HIPAA identifiers) from the CMCVAMC to the designated laboratory at the University of Pennsylvania after obtaining the required CMCVAMC -IRB authorization. The samples will be destroyed at the University of Pennsylvania after the genetic tests have been conducted.

13. **Informed Consent discloses PHI transported or transmitted off-site.** ☐YES ☒NO ☐N/A

14. **HIPAA Authorization discloses entities to whom PHI will be transported or transmitted.**
☒YES ☐NO ☐N/A

15. **List all entities or individuals outside** CMCVAMC **to whom data is to be disclosed, and the justification for such disclosure and the authority.** The data will be disclosed to the following entities or individuals: a) CMCVAMC -IRB as required for regulatory purposes; b) VA CSR & D, the grant funding agency as deemed necessary; c) Dr. Knashawn Morales – the designated statistician associated with the study at the Center for Clinical Epidemiology and Biostatistics of the University of Pennsylvania. Dr. Morales will receive the coded data without the 17 HIPAA identifiers, which will be hand carried by the principal investigator on a compact disc to her office within the University of Pennsylvania.

16. **Clarify what protection exists for a database.** The tracking database with the demographic identifiers will reside within the password protected electronic servers of the CMCVAMC. In addition, the polysomnographic data with the identifiers will be stored in the case report forms within the locked MIRECC space of CMCVAMC. The electronic databases with the coded data relating to the study will exist in password protected electronic servers of the CMCVAMC and the VA Redcap-related VIRECC servers. The coded electronic polysomnographic data will be stored within the password protected electronic servers of the CMCVAMC. The actigraphic data will be stored in the hard drive of the password-protected desktops of the study coordinator and the principal investigator. The electronic actigraphic data will be stored in compact discs in the locked desk drawers of the desks of the study coordinator and the principal investigator. The coded data for statistical analyses at Dr. Morales's office will be stored in the password-protected computer in the University of Pennsylvania.

16.1. Data is stored:

16.1.1. With identifiers - ☒YES ☐NO

16.1.2. Coded - ☒YES ☐NO

16.1.3. De-Identified - ☐YES ☒NO

16.1.4. **Provide the <u>exact</u> list of identifiers that will be stored.** The database will be stored in the password protected online drives of the CMCVAMC. The tracking database will have the study identification number, subjects full name, age, race, date of birth, the last 4 of his/her social security number, the contact telephone numbers, date of telephone screening and date of informed consent process, reason for ineligibility (if applicable). The other forms including the actigraphic data will be coded (with the unique 4-digit identification number) and without the HIPAA identifiers. They will however have dates of the conduct of study procedures.

17. **Describe the plan for protecting research data from improper use or disclosure.** The participant will be assigned a 4-digit unique identifying number for this study. This 4-digit identification number will not be related to the last 4 digits of his social security number or a 4-digit number generated by scrambling his social security number. The link between the 4-digit coded identification number and the participant's name and social security number will be stored on paper in a locked cabinet in room # 228 B or in a locked cabinet in the Dr. Chakravorty's locked room and also backed up electronically in the password protected VA online drives. Data on paper will be stored in locked cabinets and locked desk drawers in the MIRECC office space in room number 228 B. Electronic data will either be stored on the password protected online drive of the CMCVAMC. The actigraphic data will be stored on the research assistant's password protected desktop, the principal investigators desktop, and backed up on a compact disc as recommended by the manufacturer and as is being done in our current CBT-I pilot study. All the discs will be stored in the principal investigators locked office space with restricted access (room # TBA), in a locked cabinet. CMCVAMC Information Security Officer and Privacy Officer will be notified within one hour of the improper use or disclosure, as well as the IRB, Associate Chief of Staff for Research (ACOS/R) and Research Compliance Officer.

17.1. The Investigator must notify the Information Security Officer, Privacy Officer, IRB, Associate Chief of Staff for Research and Research Compliance Officer within one hour of the improper use or disclosure.

18. Is there a plan to apply for a Certificate of Confidentiality? ☐YES ☒NO ☐N/A

18.1. If yes, provide a copy of the certificate with this application or to the IRB Office as soon as received.

19. **Record Retention**:

19.1. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). VHA Handbook 1200.05 §26.h

19.2. Until a schedule for local research records is published, ALL records including identifiers must be retained." ORO/ORD Guidance on Informed Consent Form Modifications Addressing VA Record Retention Requirements (July 23, 2009)

19.3. If there are additional procedures for record retention, explain further. **N/A**

Y. Qualification of the Investigators

1. Provide a description of the qualifications of each investigator/co-investigator and their specific role in the study.

(i) Dr. Subhajit Chakravorty – is the principle investigator for this study. He is a staff physician here at the Philadelphia Veterans Affairs Medical Center, a researcher associated with the MIRECC, and a faculty member of the Penn Sleep Center. He is certified in Psychiatry and with sub-specialty certifications in Sleep Medicine and Addiction Medicine. He will be a backup provider for the CBT-I; in addition, he will be a backup staff for all the duties associated with the study from answering questions from prospective participants to scheduling appointments for veterans in clinic at the end of the study.

(ii) Sean He/alternative Study Coordinator – will coordinate the study. S/he will conduct the following obligations associated with the study; a) Answering telephone calls for potential participants; b) Screening participants for inclusion-exclusion criteria; c) Coordination of study visit procedures; d) drawing and processing the blood samples; e) Uploading data onto online servers; f) Communication with the IRB; g) Any other required study-related documentation.

(iii) Certified Behavioral Sleep Medicine Specialist (Dr. James Findley) – s/he will conduct the cognitive behavioral therapy for insomnia and the Quasi-Desensitization Therapy

(QDT) along for the participants in the study; Dr. Chakravorty will function as the back-up behavioral sleep medicine specialist for this study

2. **If applicable, the Principal Investigator must identify a qualified clinician to be responsible for all study related healthcare decisions.** Dr. Chakravorty will be the clinician involved in making the study related healthcare decisions for the subjects. The designated Behavioral Sleep Medicine specialist will function as a backup to Dr. Chakravorty in making health care decisions for the Veterans in the study.
3. PI should submit a current, dated CV with each new initial review.

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