Protocol Number: 18-CC-0079

Protocol Title: Pilot RCT of web-based behavioral sleep intervention for individuals with alcohol use disorder

Abbreviated Title: RCT of sleep intervention for AUD

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Précis: Alcohol use disorder (AUD) is characterized by problematic drinking that becomes severe (NIAAA, 2017). The prevalence of insomnia in individuals with alcohol dependence is estimated to be between 36-91% and after two weeks of alcohol detoxification, as many as 65% of these individuals still experience "sleep problems." Cognitive behavioral therapy for insomnia (CBT-I) is an efficacious non-pharmacological treatment for insomnia (Morin, et al., 2006) and is recommended as a first-line treatment for adults with chronic insomnia disorder (Qaseem, Kansagara, Forciea, Cooke, Denberg et al., 2016). CBT-I has been associated with more rapid and "durable" improvement in sleep outcomes, even when compared with other nonpharmacological treatments (Garland et al., 2014). Internet-based CBT-I (ICBT-I or eCBT-I for "electronic") could play a key role in the dissemination of this behavioral sleep intervention, given the paucity of trained clinicians able to provide CBT-I in person and other logistical/cost concerns. SHUTi (Sleep Healthy Using The Internet) is the most tested and empirically-sound internet intervention for insomnia. The SHUTi program tailors specific recommendations based on participant responses to sleep diaries and other input within the program. Despite the promise of internet-based CBT-I interventions, very little is known about their effectiveness among individuals with AUD (Brooks & Wallen, 2014): to date, no RCTs exist examining the feasibility/effectiveness of an internet-based CBT-I program among individuals recovering from AUD. This is a two-phase randomized controlled trial assessing feasibility/acceptability and effectiveness of the SHUTi program for research participants at the NIH Clinical Center. Phase I will be focused on assessing feasibility and effectiveness of program delivery and data collection (n=10). Phase II will be a pilot RCT powered to examine intervention effectiveness (n=20 per group). All participants enrolled in this study will first be admitted under the screening and assessment protocol on the 1SE clinic (14-AA-0181), which includes adults over 18 years of age seeking treatment for alcohol rehabilitation. Participants for this study must also meet criteria for "mild to severe" insomnia. Individuals randomized to the intervention group will receive six sessions of the SHUTi intervention (one completed while inpatient, the rest while outpatient) and individuals randomized to the control group will receive an educational web-based program. The goals of the study are as follows: 1) assess the feasibility and acceptability of Internet-based CBT-I among individuals with AUD in recovery with insomnia (Phase I), 2) compare the efficacy of CBT-I versus control group with respect to primary and secondary outcome variables (Phase II), and 3) explore specific domains associated with improved outcomes: e.g. demographic, psychiatric, and/or drinking-related factors (Phase II). Primary outcome measures include changes in insomnia severity over time and changes in actigraphy-recorded sleep efficiency over time.

CONTENTS

1 Background:

Alcohol and sleep disturbances. Alcohol use disorder (AUD) is characterized by problematic drinking that becomes severe (NIAAA, 2017). To be diagnosed with severe AUD, individuals must meet six or more of the 11 criteria outlined in the Diagnostic and Statistical Manual (current edition: DSM-5). This was referred to as "alcohol dependence" in previous versions of the DSM; thus, some researchers and clinicians still use the term "dependence." Alcohol dependence is associated with insomnia and a myriad of other sleep-related disorders (Chakravorty, Chaudhary, Brower, 2016; Stein & Friedmann, 2005; Brower KJ, 2001). Insomnia in individuals who are alcohol-dependent who are actively drinking may aggravate existing psychosocial problems (Chaudhary, Kampman, Kranzler, Grander, & Debbarma, 2015). The prevalence of insomnia in individuals with alcohol dependence is estimated to be between 36-91% and after two weeks of alcohol detoxification, as many as 65% of these individuals still experience "sleep problems" (Chakravorty, et al., 2016). Data on insomnia in the patient population on the 1SE inpatient treatment unit at the NIH Clinical Center is not currently being collected, but the prevalence of sleep disturbance is relatively high throughout the course of treatment (Wallen & Brooks, 2014; Brooks, Wallen, et al., 2016). Pilot data from research participants on 1SE demonstrated a prevalence of sleep disturbances among an inpatient sample of individuals in recovery: 90% of participants reported sleep disturbances at baseline and sleep disturbances remain in around 50% of patients even at the end of the inpatient treatment period (Wallen, et al., 2014). Ongoing outpatient studies demonstrate that these sleep disturbances continue post-discharge (Brooks et al., 2016).

Evidence supporting Cognitive Behavioral Therapy for Insomnia (CBT-I) as a first-line treatment for insomnia. CBT-I is an efficacious non-pharmacological treatment for insomnia (Morin, et al., 2006) and is recommended as a first-line treatment for adults with chronic insomnia disorder (Qaseem et al., 2016). It is also effective for those with posttraumatic stress disorder (PTSD) and depression, which are common co-morbidities among those with AUD (Talbot et al., 2014; Siebern & Manber, 2011). While pharmacological intervention of insomnia in addition to CBT-I can produce added benefits acutely, it is recommended that medications should ultimately be discontinued for long-term outcomes during "maintenance" CBT-I (Morin et al., 2009). CBT-I has been associated with more rapid and "durable" improvement in sleep outcomes, even when compared with other non-pharmacologic treatments (Garland, et al., 2014).

Effectiveness of internet-delivered CBT-I. Internet-based CBT-I (ICBT-I or eCBT-I for "electronic") could play a key role in the dissemination of behavioral sleep interventions, given the paucity of trained clinicians able to provide CBT-I in-person and other logistical/cost concerns. This method of delivery is of particular interest to researchers and clinicians working with individuals with alcohol use disorders (Brooks & Wallen, 2014). A recent systematic review and meta-analysis of 11 randomized controlled trials (total of 1460 participants) revealed that eCBT-I improved insomnia severity, sleep efficiency, subjective sleep quality, wake after sleep onset, sleep onset latency, total sleep time, and number of nocturnal awakenings with effect sizes comparable to face-to-face CBT-I (Zacharie, Lyby, Ritterband, O'Toole, 2015). Another meta-analysis showed that ICBT-I significantly improved comorbid anxiety and depression (Ye et al., 2015). The most recent meta-analysis of 15 studies showed improved sleep efficiency, insomnia severity, total sleep time, and depression severity that was maintained from 4-48 weeks after post-treatment assessment (Seyffert et al., 2016).

Description of Sleep Health Using the Internet (SHUTi) program for CBT-I. The SHUTi program is an automated, interactive, internet-based intervention based on well-established face-to-face CBT-I components including sleep restriction, stimulus control, sleep hygiene, cognitive restructuring, and relapse prevention. It consists of six core areas of focus that include interactive educational content and case studies about insomnia and its precipitating factors. These cores are designed to parallel traditional (in-person) CBT-I sessions and are "metered;" that is, new cores are available seven days after completion of the previous core. The program includes a variety of interactive features, including goal-setting, feedback based on user-identified symptoms, animations, quizzes, vignettes, and video-based expert explanations. SHUTi was developed based on the Model for Internet Interventions (a-Ritterband, et al., 2009). SHUTi users must fill out at least five daily sleep diaries for each core in seven days in order to access subsequent cores. Sleep diary input is crucial in the customization of the program based on individual situations.

SHUTi is considered a NSR IDE device as it is **not** being used in the indications as set forth:

- as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject".

Effectiveness of SHUTi program. In adults with primary insomnia, SHUTi significantly improved insomnia severity index (ISI) scores and these improvements were sustained at a 6-month follow-up. Additionally, there were significant decreases in wake after sleep onset (WASO) and increases in sleep efficiency compared to a wait-list control group (a -Ritterband et al., 2009), with similar effects in adult cancer survivors (Ritterband et al., 2012) Evaluation of co-occurring symptoms in those trials showed that SHUTi also significantly improved psychological symptoms, mental health-related quality of life, and fatigue (Thorndike et al., 2013). More recently, researchers established long-term (one year follow-up) effectiveness in a representative sample with chronic insomnia and a range of comorbid conditions via randomized controlled trial (Ritterband et al., 2016). Finally, the program has significantly lowered depressive symptoms among those with both insomnia and depression symptoms (without major depressive disorder) compared to time- and attention-matched controls (Christensen et al., 2016).

Gap in the literature: Despite the established efficacy of CBT-I in the community and in those with AUD, very little is known about the effectiveness of this internet based CBT-I among individuals with AUD (Brooks & Wallen, 2014). To date, no RCTs exist examining the feasibility/effectiveness of an internet-based CBT-I program among individuals recovering from AUD.

1.1 Theoretical framework

This study will examine sleep-related beliefs and behaviors in the context of the Social Cognitive Theory (SCT; Bandura, 1986). Self-efficacy is perhaps the most well-established construct in the SCT and was an important predictor of sleep quality in our pilot work (Brooks et al., *Under Review*). We anticipate that the SHUTi program will directly impact personal, environmental, and behavioral factors for participants, and the theory includes all three as potential predictors of outcomes (insomnia severity and ultimately relapse).

1.2 Study Objectives:

1. *Phase I:* Assess the feasibility and acceptability of Internet-based CBT-I among individuals with AUD in recovery

2. *Phase II:* Compare the efficacy of CBT-I versus an education-only control group with respect to primary and secondary outcome variables
    a. Primary outcome variables include: changes in insomnia severity over time, changes in actigraphy-recorded sleep efficiency over time
    b. Secondary outcome variables include actigraphy-related (objective) variables, alcohol consumed (post-discharge), alcohol craving (post-discharge), sleep disturbance, daytime sleepiness, anxiety/depression, fatigue, self-efficacy for sleep, dysfunctional beliefs about sleep, and functional outcomes
    c. Explore specific domains associated with improved outcomes: e.g. demographic, psychiatric, and/or drinking-related factors

2 Study design and methods

This is a two-phase study. Phase I will be focused on assessing feasibility and effectiveness of program delivery and data collection (n=10). Phase II will be a pilot RCT powered to examine intervention

effectiveness in the target population (n=20 per group). All study participants will receive a handheld tablet to access the SHUTi or education-only program.

2.1 Phase I

In Phase I, all participants will be given access to the SHUTi intervention. Phase I will assess the feasibility and acceptability of the intervention and ensure that our data collection processes are functioning as they should be. As data become available to the research team, we will assess patterns based on participant feedback and may make modifications to the program. If this is the case, we will amend the protocol prior to beginning Phase II. Participants will receive training from a member of the research team on accessing the program and using the handheld tablets provided as part of study participation. Individuals who participate in Phase I of this study and are re-admitted to 1SE will not be eligible for participation in Phase II, as they will have already experienced the intervention.

2.2 Phase II

Randomization will be achieved using a random number generator, assigning equal numbers of participants to each of the two conditions. The PI and AIs will remain blind to the randomization scheme until each study participant is deemed eligible and signs the consent form.

Intervention/control groups (Phase II only):**

1. **Intervention group:** 6 sessions ("modules") of SHUTi intervention (at least one module completed while inpatient, the rest while outpatient): In SHUTi, customization is based on multiple variables, including sleep diary responses. The SHUTi program tailors specific recommendations based on sleep diary responses or other input within the program (e.g., responses on the Dysfunctional Beliefs and Attitude Scale trigger recommendations for specific cognitive restructuring strategies).

2. **Control group:** education/monitor only (insomnia education web-based program that participants access and read at their own pace – contains no customization of program based on sleep diary responses). Participants in the control group are given educational information (like they might see on WebMD or National Sleep Foundation websites), but are left to apply it themselves.

**Participants who are randomly assigned to the intervention condition will be granted access to the program free of charge for up to six months from the start of the program. Participants who are randomly assigned to the education-only condition will be given access to the full SHUTi program three months after discharge upon request. Similarly, participants who are randomly assigned to the intervention condition will be granted access to the education materials provided to the education-only condition participants three months after discharge upon request.

All participants enrolled in this study will first be admitted under the screening and assessment protocol on the 1SE clinic (14-AA-0181), which includes adults at least 18 years of age seeking treatment for alcohol use disorders. Once consented and enrolled into the inpatient treatment, screening, and research protocol, participants are screened and recruited enrollment in additional studies for which they meet eligibility criteria (including the study described herein). Study participants will be asked to

come back to the Clinical Center post-discharge for a follow-up visit to complete a face-to-face semi-structured interview (Phase I participants only) and questionnaires (Phases I and II participants). If participants are unable to return for the follow-up visit, we will attempt to conduct the surveys and interview via phone.

2.3 Screening Measures

Insomnia Severity Index (ISI). The ISI is a seven-item global index of self-reported insomnia symptom severity. Seyffert and colleagues (2016) categorized insomnia severity by scores as follows: 0-7 = no clinically significant insomnia, 8-14 = subthreshold insomnia, 15-21 = moderate insomnia, and 22-28 = severe insomnia. The Veterans' Administration (VA) is currently using this questionnaire as a clinical assessment tool to provide VA healthcare providers information about their patients' sleeping difficulty and its effects on daytime functioning (Veterans Administration, 2017). We will be using the ISI to determine if potential participants are eligible to be enrolled in this study and will only consider individuals with an ISI score ≥ 10 for inclusion in the study.

Objective measure of Apnea Hypopnea Index (presence/severity of obstructive sleep apnea): the WatchPAT. We will utilize the WatchPAT, which is a portable diagnostic medical device, to detect presence/severity of obstructive sleep apnea (OSA). The research participant will wear the WatchPAT on his or her wrist and finger when he or she goes to bed at night for one night during their inpatient stay as part of the screening prior to randomization. The WatchPAT works by using a Peripheral Arterial Tone (PAT) technology that allows for non-invasive and portable detection of sleep apnea. The data collected from the WatchPAT will be uploaded into a proprietary computer software program which uses validated algorithms to analyze two indices, Apnea-Hypopnea Index (AHI) and Respiratory Disturbance Index (RDI), to determine the total Apnea Hypopnea Index and provide an indication of presence and severity of sleep apnea. While polysomnography remains the "gold standard" diagnostic tool, clinical studies have shown that the WatchPAT has a high degree of correlation with polysomnography studies (r = 0.85-0.96) in detecting respiratory events during sleep (Itamar Medical, 2016). Interpretation of the WatchPAT results will be supervised by a physician at the University of Pennsylvania with expertise in sleep medicine (Dr. Subhajit Chakravorty, who is also an AI on the study). If a participant has more than 15 "events" per hour of sleep, they will be ineligible for participation in the study. The results of the WatchPAT study will be reviewed with the patient and the clinical care team. If the patient is seen to have mild obstructive sleep apnea (5-14.9 events/hour of sleep), we will recommend him/her to work on losing weight (if they are overweight or obese), avoid alcohol use, and follow up with a primary care provider. In the case that they are found to have moderate to severe OSA (score of 15 or higher), we will provide the patient with a patient education handout that explains what OSA is, the risks associated withA untreated OSA, and the treatment options available. We will urge the patient to seek evaluation and treatment through a primary care provider or directly from a sleep medicine clinic, as is appropriate for them.

2.4 Study Measures

Feasibility and acceptability measures. Participants enrolled during Phase I will be asked to start the SHUTi modules prior to being discharged from inpatient treatment. They will be invited to participate in a short interview after they complete the first SHUTi module in order to gather additional information on program delivery and acceptability in the population. We will also utilize the Internet Evaluation and Utility Questionnaire (Ritterband et al.,2008) at the pre-discharge interview, which is a 16-item measure

designed to assess usability, likeability, usefulness, understandability, and convenience of the intervention. We will also implement an exit assessment for Phase I *and* II participants. At the exit assessment, we will use the Internet Impact and Effectiveness Questionnaire, the Internet Evaluation and Utility Questionnaire, and the Internet Intervention Adherence Questionnaire (Ritterband et al., 2008). The Intervention Impact and Effectiveness Questionnaire is a 14-item measure designed to assess perceptions of the impact of the program. Responses on all questionnaires related to utility and impact are rated on 5-point Likert scales from 0 ("not at all") to 4 ("very"). Participants will complete these assessments with a member of the research team who will take notes on participants' comments for each question. Open-ended questions (used in Phase I only) will be audio recorded and the entire session (including the questionnaires) are expected to last between 20-60 minutes, depending on the participant's responses. Additional measures of program adherence (in the experimental group, for both Phases I and II) will be measured by three variables: login count (goal of two per week), completed diary count (minimum of five per week), and number of "cores" completed out of a possible six cores.

Insomnia Severity Index (ISI). The ISI is a seven-item global index of self-reported insomnia symptom severity. It is valid, reliable, sensitive to changes in insomnia treatment (Bastien, Vallieres, & Morin, 2001; Morin, Belleville, Belanger, & Ivers, 2011) and validated for online use (Thorndike et al., 2011). Seyffert and colleagues (2016) categorized insomnia severity by scores as follows: 0-7 = no clinically significant insomnia, 8-14 = subthreshold insomnia, 15-21 = moderate insomnia, and 22-28 = severe insomnia. Changes in the ISI over time will be a primary outcome measure. The ISI is collected within the SHUTi intervention program at the beginning of each core, but participants in both Phase I and Phase II will also complete a paper version of the ISI during the pre-, mid-point, and post-test assessments.

Daily sleep and symptom diaries. Prospectively collected sleep diaries are a proven method for assessing insomnia and track treatment effects (Carney, et al., 2012; Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006) and have been used for other sleep studies among patients on 1SE (inpatient and outpatient). Participants will be asked to complete at least five out of every seven days of daily sleep and symptom diaries. These diaries will include sleep/wake times, time in bed, sleep onset latency, number and duration of awakenings, sleep quality, naps, alcohol consumption, any over-the-counter of prescription medications used to help with sleep (participants will be instructed to include any marijuana use in this section), and open-ended comments. For the experimental group, diaries will be used to assess adherence to their "sleep window," based on actual time in bed as a proportion of prescribed time in bed. We will cross-validate diary-reported sleep duration with actigraphy data when possible. Secondary outcome measures captured in the diaries will include a categorical measure of relapse (i.e. whether the participant reports any drinking post-discharge) as well as quantity and frequency of drinking, which will be calculated in the case of relapse, as well as all other diary variables.

Penn Alcohol Craving Sale (PACS). The PACS is a clinical tool for practitioners to measure alcohol craving. It is a five-item self-administered instrument that measures frequency, intensity, and duration of thoughts about drinking along with ability to resist drinking. The final item asks the responder to provide an average rating of his or her craving over the course of the past week. The PACS has excellent internal consistency (Cronbach's alpa = 0.92). Construct, predictive, and discriminant validity has also been established. This assessment takes between two and five minutes to complete (Flannery, Volpicelli, & Pettinati, 1999). The PACS will be administered as part of the post-test assessment.

Functional Outcomes of Sleep Questionnaire (FOSQ-10). The FOSQ-10 is a 10-item abbreviated version of the original 30 item instrument used to evaluate quality of life in relation to daytime sleepiness. The 30-

item questionnaire measures difficulty in performing tasks from five domains due to sleepiness or tiredness: General Productivity, Activity Level, Vigilance, Social Outcome, and Intimacy and Sexual Relationships (Weaver et al., 1997). The FOSQ-10 consists of two questions from General Productivity subscale, three from Activity Level, three from Vigilance, and one each from Social Outcome and the Intimacy and Sexual Relationships subscales. The 10-item version demonstrates high internal consistency similar to that of the original instrument (Cronbach's alpha = 0.87), high correlation with the 30-item version of the scale, and the ability to detect a wide range of functional limitations (Chasens, Kampman, & Weaver, 2009). To obtain the total score for the FOSQ-10, the mean-weighted item score is calculated for each subscale. These subscale scores are then averaged and the mean was multiplied by five. Lower scores are indicative of higher levels of dysfunction. The FOSQ-10 will be administered at pre- and post-test time points.

Objective measure of sleep: actigraphy. "Actiwatches" are small wristband data loggers that record digitally-integrated measures of gross motor activity. These devices contain accelerometers and light sensors in order to objectively assess sleep. Prior studies have demonstrated actigraphy's high sensitivity with moderate accuracy for detecting sleep in populations with normal and disturbed sleep when compared to polysomnography (Kushida et al., 2001; Paquet et al., 2007). The *Actiwatch Spectrum Plus* (Philips Respironics) has been used in previous studies with patients on 1SE in both inpatient and outpatient settings. The watch is worn on the non-dominant wrist. Study participants will be asked to wear an actiwatch for 4 days, 3 nights (Phase I only) and for at least 1 week (Phase II only) at three study time points (Pre SHUT-i®/Education-Only initiation, 3-4 weeks after SHUT-i®/Education-Only initiation and Post SHUT-i®/Education-Only program completion). Participants will return the actiwatches either in person (if the participant will be returning to the Clinical Center) or by mail after each study time point so that the research team can download the data and return the watch to the participant (with the exception of the last study time point). The main outcome of interest will be improvements in sleep efficiency from baseline to follow-up assessment periods. The watch also provides measures of total sleep time (TST), wake after sleep onset (WASO), sleep onset latency (SOL), number of awakenings (NWAK), and time in bed (TIB).

Pittsburgh Sleep Quality Index (PSQI). The Pittsburgh Sleep Quality Index (PSQI) is a 19-item, self-rated questionnaire used to measure sleep quality and disturbances over a 30-day time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global summation score of five or higher is indicative of poor sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI has been validated in populations with insomnia and other sleep disorders, with psychiatric patients, and in normal populations (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002; Doi, Minowa, Uchiyama, Okawa, Kim, Shibui, & Kamei, 2000). There exists some early evidence of validity in alcohol-dependent populations (Brooks, Krumlauf, Whiting, Clark, & Wallen, 2012; Wallen et al., 2014). The PSQI has internal consistency and a reliability coefficient ranging from 0.80 to 0.83 for its seven components (Buysee, et al. , 1989; Carpenter & Andrykowski, 1998). It takes approximately five minutes to complete. Phase I and II participants will complete the PSQI at the pre- mid-point, and post-test.

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). The MFSI-SF (Stein 2004), which is a 30-item measure, was used in the 2012 study by Ritterband and colleagues that demonstrated the efficacy of internet-delivered CBT-I for cancer survivors. This measure has also been used in relation to insomnia and internet-based delivery of CBT-I by Thorndike and colleagues in 2013. A

review by Donovan and colleagues (2015) reported that the measure has been used in a variety of study designs, including longitudinal, cross-sectional, and randomized control trials, with acceptable psychometric properties.

Epworth Sleepiness Scale (ESS). The Epworth Sleepiness Scale (ESS) is an eight-item self-administered questionnaire that provides a measure of an individual's general level of excessive daytime sleepiness over a one week time period (Johns, 1991). Individuals are asked to rate their usual chances of dozing off or falling asleep on a four-point scale in eight distinct situations or activities that most people engage in during their daily lives. Higher scores are indicative of higher levels of daytime sleepiness. An alpha coefficient between 0.70 to 0.88 has been documented and numerous studies support high validity and reliability (Spira, Beaudreau, Stone, et al., 2012; Johns, 1992). A score higher than ten is indicative of *excessive* daytime sleepiness (Johns, 1993). Completing the ESS generally takes two to three minutes.

Self-Efficacy for Sleep Scale (SE-S). The SE-S includes nine items used to measure the level of confidence a person has in performing behaviors that might be helpful in initiating sleep. Each item is scored on a five-point Likert scale from 1 representing "not confident" to 5 representing "very confident." The total score ranges from nine to 45, with higher scores indicative of greater confidence. Concurrent validity of the scale was established by comparison with PSQI, sleep diaries, and objective measures of sleep (Edinger, Wohlgemuth, Radtke, Coffman, & Carney, 2007). The scale has excellent internal reliability (Cronbach's alpha of 0.71-0.86; Edinger, et al., 2007**;** Rutledge, La Guardia, & Bluestein, 2013). Test-retest reliability has also been established (Fichten, Libman, Creti, Amsel, Sabourin, Brender, & Bailes, 2001). The SE-S was shown to be a significant predictor of sleep quality (unpublished data); increased self-efficacy for sleep was associated with better sleep quality (Brooks et al., unpublished data).

Dysfunctional Beliefs and Attitudes about Sleep (brief version; DBAS-16). The DBAS-16 is a 16-item questionnaire that assesses sleep-related cognitions including faulty beliefs and appraisals, unrealistic expectations, and perceptual and attention bias. The DBAS-16 has adequate internal consistency (Cronbach's alpha = 0.77 for clinical and 0.79 for research samples) and temporal stability (r = 0.83). Factor structure is similar to the original 30-item version of the questionnaire and includes perceived consequences of insomnia, worry/helplessness about insomnia, sleep expectations, and medication. Domains include expectations about sleep requirements and issues with being worried or feeling helpless about insomnia (Morin, Vallieres, & Ivers, 2007). The scoring of the DBAS-16 is the average score of all items.

Inventory of Depressive Symptoms (IDS; 30-item self-rated version). The IDS is a 30 item measure that can be used to screen for depression or measures symptom severity using the nine symptom domains used to define a major depressive episode. The IDS has high internal consistency (Cronbach's alpha = 0.90; Trivedi et al., 2004). Administration of the IDS takes approximately 10-15 minutes and scores are calculated by summing responses the 28 of the items for a score ranging from 0 to 84. A higher score indicates higher severity of depressive symptoms, with 49-84 indicating very severe symptoms (Rush et al, 2003, Trivedi et al, 2004).

Trait Anxiety Inventory. The Trait Anxiety Inventory is a 20-item measure of anxiety (Spielberger et al., 1983). The Trait Anxiety Inventory differs from the State Anxiety Inventory by asking questions on how respondents "generally feel" (Trait Anxiety), while the State Anxiety questionnaire asks how respondents feel "at this moment." Responses to each statement is rated on a four point scale, ranging from "almost never" to "almost always". The Trait Anxiety Inventory demonstrates high internal

consistency (Cronbach's alpha > 0.86) (Barnes, Harp, & Jung, 2002). Higher scores on the STAI indicates higher levels of anxiety.

Composite Scale of Morningness (CSM). The Composite Scale of Morningness is a 13-item scale (Smith, Reilly, & Midkiff 1989). Questions address topics like morning affect, preferred sleep/wake times, and peak cognitive performance, with scores ranging from 13 (reflecting "eveningness") to 55 (reflecting "morningness"). The CSM typically shows relatively high internal consistency (Cronbach's alpha > 0.8) (Di Milia, Adan, Natale, & Randler 2013).

We will pull additional data from the screening/treatment protocol to characterize our sample and conduct exploratory analysis based on the aforementioned aims, including but not limited to:

- Childhood Trauma Questionnaire (CTQ)
- Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-5) (SCID)
- Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar)
- Comprehensive Psychopathological Rating Scale (CPRS)

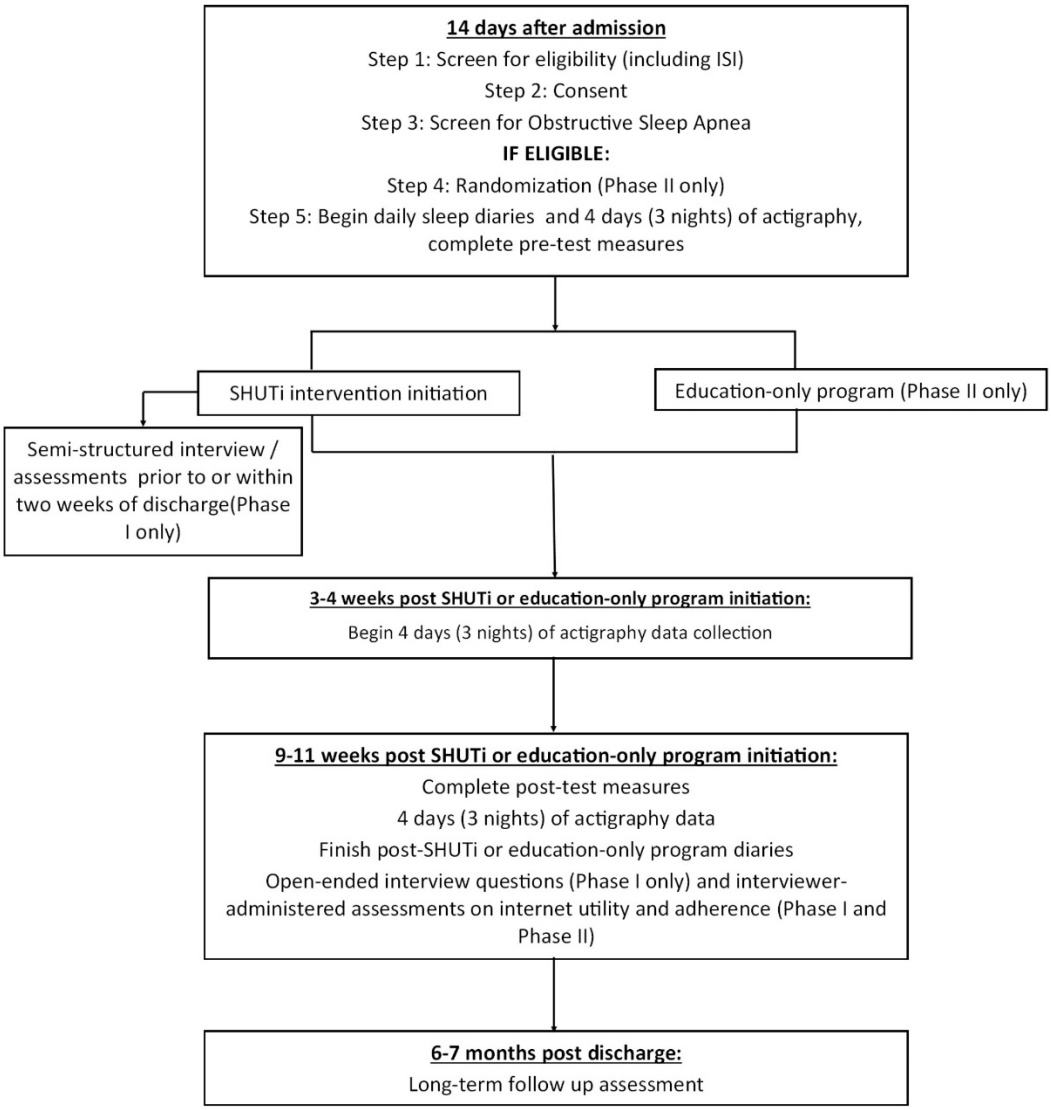

Figure 1: *Study flow chart*

Participants will be screened for eligibility on or after day 14 of inpatient treatment. Days 14-21 will be when the participant is consented, screened for OSA (after consent), randomized (if they meet inclusion requirements), and begin daily diary assessments as a baseline measure. If they are discharged before they are deemed eligible for continue study participation and randomized to a group, they will be removed from the study.

Table of Measures						
	Inpatient			Outpatient		
	Pre-Test (Before SHUT-i® Intervention or Education only program initiation)	**Start SHUT-i® Intervention or Education only program**	**Prior to or within 2 weeks of Discharge**	**3-4 weeks after SHUT-i® Intervention or Education only program initiation**	**Post-Test (After SHUT-i® Intervention or Education only program completion)**	**6-7 months post-discharge (clinic visit or by phone)**
ISI				X		X
PACS					X	X
PSQI	X			X	X	
DBAS-16	X				X	
FOSQ-10	X				X	
SE-S	X				X	
IDS	X				X	
ESS	X				X	
Trait Anxiety Inventory	X				X	
CSM	X					
MFSI-SF	X				X	
At least 4 days, 3 nights (Phase I)/1 week (Phase II) of actigraphy assessment	X			X	X	
Sleep Diaries	X			X	X	
Start SHUTi (Phase I and II) or education only (Phase II only) program		X				
Abbreviated Internet Evaluation and Utility Questionnaire (Phase I only)			X			

Internet Impact and Effectiveness Questionnaire, Internet Evaluation and Utility Questionnaire, and the Internet Intervention Adherence Questionnaire (Phase I and II)					X	
Exit interview regarding experience with SHUTi program (Phase I only)					X	
Dichotomous Yes/No Relapse Assessment						X (If YES, TLFB will be administered)
TLFB						X

2.5 Inclusion and Exclusion Criteria

2.5.1 Participants will be eligible for this study if they:

- Are 18 – 65 years old
- A score of 10 or higher on the Insomnia Severity Index*
- Are admitted as a treatment-seeking inpatient on 1SE under protocol 14-AA-0181 (signing both the clinical and research consent)
- Have been inpatient for at least 14 days prior to consent/screening
- Can speak, understand, and write in English
- Are able to comply with study requirements (including ability to access the Internet at least 2x per week)

2.5.2 Participants will be ineligible for this study if they:

- Are pregnant
- Are a prisoner
- Report a physician diagnosis of moderate to severe obstructive sleep apnea (OSA) OR test positive for moderate to severe OSA as documented with an Apnea Hypopnea Index of 15 events/hour based on WatchPAT testing results
- Have irregular sleep schedules that prevent the ability to follow treatment recommendations (i.e. usual bedtimes outside of 8:00 pm to 2:00 am or arising times outside of 4:00 am to 10:00 am)
- Meet SCID-5/DSM-5 criteria for opioid use disorder in the past year
- Meet SCID-5/DSM-5 criteria for severe cocaine use disorder and/or severe cannabis use disorder in the past year
- Meet diagnostic criteria for an unstable or serious psychiatric condition (schizophrenia, bipolar, major depressive disorder not currently in remission) - based on diagnosis from the SCID for DSM-5
- Are participating in any experimental pharmacological intervention study
- Presence of unstable or serious medical/neurologic illness at PI and MAI discretion

2.5.3 Justification for certain inclusion/exclusion criteria

*Morin, Belleville, Bélanger, and Ivers (2011) recommend an ISI cutoff score of at least 10 in detecting clinical insomnia while preserving very good specificity and sensitivity in a population-based or clinical trial sample.

One of SHUT-I's potential side effects from its sleep restriction phase is increased daytime sleepiness. Increased daytime sleepiness is associated with increased frequency of falls in the elderly (individuals >65 years old) (Helbig et al., 2013), thus we are excluding individuals over the age of 65.

Among individuals who are alcohol-dependent with untreated moderate-severe OSA, sleep restriction may further increase sympathetic and stress response, leading to an increased risk of cardiovascular adverse events (Irwin & Ziegler, 2005). Severe OSA is associated with increased daytime sleepiness, motor vehicle crashes, depression, cardiovascular and cerebral morbidity and mortality, cognitive and metabolic dysfunction (Peppard & Hagen, 2017). Thus, we are excluding individuals with untreated moderate-severe OSA.

A study by Pacek, Herrmann, Smith, and Vandrey (2017) reported that participants reported sleep difficulties with abstinence from cannabis and resulted in the relapse in cannabis use at a later time. It is unclear whether sleep difficulty symptoms improve with relapse, but the authors also point out that cannabis use contributes to observed sleep difficulties. Whether or not disordered sleep contributes to long-term cannabis use is unclear (Pacek, Herrmann, Smith, & Vandrey, 2017). Finally, cannabis is independently associated with impairment of sleep continuity (Pacek et al., 2017). Thus, we are excluding participants who meet the criteria SCID-5/DSM-5 criteria for severe cannabis use disorder.

Cocaine is a stimulant that can disrupt sleep and sleep architecture in both humans and animals (Angarita, Emadi, Hodges, & Morgan, 2016; Cortes et al., 2016; Irwin, Bjurstrom, & Olmstead, 2016). Increased arousal is the most common effect of cocaine use with regards to sleep and animal models showed that the level of arousal is dose dependent (Chakravorty, Vandrey, He, & Stein, 2018; Cortes et al., 2016). Individuals who are diagnosed with cocaine use diorder (CoUD) have an underlying sleep disturbance that may persist even after abstinence for several weeks, although recent evidence suggests that improving sleep may increase the likelihood of sustained abstinence from cocaine (Angarita et al., 2016; Hodges, Pittman, & Morgan, 2017; Winhusen, Theobald, & Lewis, 2019). CoUD as well as other substance use disorders are commonly comorbid with AUD (Chakravorty et al., 2018). For this study, we will only exclude participants who meet the DSM-5 criteria for severe CoUD. During analysis, we will attempt to control for any comorbid substance use disorders.

Opioids are associated with a more complex picture of sleep disorders that includes insomnia, obstructive sleep apnea, and complex sleep apnea (Hassamal, Miotto, Wang, & Saxon, 2016). Patients who are diagnosed with opioid use disorder are usually treated with oral naltrexone. “Oral naltrexone is capable of inducing fatigue, nausea, sleepiness, restlessness, and dysphoria in nonopiate users during the first few hours acutely post-ingestion” (Mysels, Cheng, Nunes, & Sullivan, 2011, p.22). Insomnia also transiently worsened with naltrexone treatment, but it is purported to be associated with subacute opiate withdrawal (Mysels et al., 2011). Thus, we are exluding participants who meet the SCID-5/DSM-5 criteria for opioid use disorder regardless of severity.

A previous study on predictors of dropout in a CBT-I program indicated a drop-out rate of around 34%. Based on potential dropout of those individuals who are eligible and are randomized in Phase II (conservative estimate: 40%), and a target of 20 individuals per group, we have adjusted our accrual ceiling to 67 (plus 12 for Phase I). We will submit an amendment to adjust this number if we discover the prevalence and severity of OSA in the population is higher than our estimate based on results from the WatchPAT screening.

Any experimental pharmacological agent may affect the data collected for this study and its effect on sleep will be largely unknown. As a result, our research team decided on excluding participants that are enrolled in any experimental pharmacological study.

Study measures have only been validated in English.

Additional note: after enrollment in the study, the management of sedatives/hypnotics for individuals who have been prescribed either will be done by a clinician who is blind to the treatment condition.

3 Statistical analysis:

Qualitative analysis (Phase I participants only). Each audio-recorded interview will be transcribed verbatim. A codebook will be developed based on themes from the interviews. Each code will be accompanied by an operational definition that will allow for clarity and consistency in the coding process. Evidence of each code or theme will be assessed using quotes from the interviews. A team of coders will independently review all transcripts. Discordant coding will be discussed until consensus among the coding team is achieved. Once the iterative process of consensus building is complete, an intramural expert in qualitative methodology will validate the final themes and coding. After data are coded, NVivo will be utilized for further qualitative analysis and data management.

Quantitative analyses (Phase II only). The first step in quantitative data analysis will be running baseline "diagnostics" to check for outliers and normal distribution of all continuous variables. If the assumptions of normality are not violated, we will proceed with parametric testing. If the assumptions of normality are violated, non-parametric tests will be utilized. For quantitative analyses, statistical significance will be considered at $p < 0.05$.

Descriptive data will include frequencies for categorical variables and range, mean, and standard deviation for continuous variables. Patterns of missing data will be examined thoroughly to assess whether any questions were systematically skipped by all participants or any sub-group of participants. Initial analyses will be descriptive and exploratory in nature to any changes in insomnia severity (as measured by the ISI) over time. Relationships between variables will be examined with bivariate correlation coefficients (for two continuous variables), Chi-squares (for two categorical variables), and t-tests or ANOVA (for one categorical and one continuous variable).

Actigraphy analyses. After device removal and data download, raw data from the *Actiwatch Spectrums* will be analyzed using the Philips Respironics computerized sleep scoring software, which scores each epoch based on a threshold method algorithm. Investigators will review each sleep period prior to analysis to screen for malfunctioning watches, corrupt data, and required adjustments using bedtimes and wake times from self-reported diary data when necessary.

Power analysis: In studies of CBT-I, the effect sizes for improvements in insomnia severity ranged from d=0.2 (Ritterband et al., 2016) to d=2.24 (Ritterband et al., 2012), with the sample sizes ranging from 29 (Ritterband et al., 2012) to 300 individuals (Ritterband et al., 2016). One such study also provided effect sizes for improvements in several other sleep-related variables, including wake after sleep onset (d=0.74), sleep onset latency (d=0.26), and sleep efficiency (d=0.68; b - Ritterband et al. 2009).

Phase I: 10 participants – the qualitative phase is not meant to infer, generalize, or generate statements about the population as a whole. Thus, our sample size is based on the concept of *saturation*, which describes the number of participants at which no new themes are being generated. It is expected that 12 patients will be screened to achieve 10 “completers” (i.e. individuals providing pre- and post-test assessment data).

Phase II: 60 participants - the total sample size for phase II of this study will test the primary hypotheses associated with the analysis plan. With insomnia severity as the primary outcome, we will use a two-sided alternative hypothesis that the rate of change will be different between the intervention group and the control group. Assuming a correlation of 0.6 between the two time points, an alpha level of 0.05, a power level of 0.8, and an estimated attrition rate of 40 percent, we will be able to detect an effect size of 0.84 with 60 participants (Fitzmaurice, Laird, & Ware, 2012). Permuted block randomization with block size of four will be used to equally assign participants in each group. The statistician, who will not have any contact with participants, will prepare the randomization sequences and give out the allocation assignment after each participants is consented.

Mixed model for repeated measure with group, time, and the interaction of group by time will be used to test the changes of insomnia severity in two groups. Mixed model for repeated measures will also be used to test the secondary objectives with potential covariates in the model. Demographic, psychiatric, and/or drinking-related factors significantly related to the outcomes listed in the secondary objectives will be entered in the model. Aikake information criterion and the Bayesian information criterion will be used to select best-fitting models. A potential dosing effect analysis including the number of cores completed as a covariate will be conducted for the treatment group only. With the linear mixed model approach, all available data points will be included in the analyses. Under missing completely at random and missing at random assumptions, linear mixed model with restricted maximum likelihood estimation can produce unbiased estimators (Salim, Mackinnon et al. 2008).

Investigator Conflicts: NIH guidelines on conflict of interest have been distributed to all investigators. NIH guidelines on conflict of interest have been distributed to all investigators.

Technology Transfer: No technology transfer agreement is in place for this protocol.

4 Rationale for subject selection

This study will be open to both males and females of all racial and ethnic groups, without targeting any specific group. We anticipate the target enrollment of participants to reflect the racial/ethnic distribution of residents in the greater Washington DC metropolitan area.

5 Recruitment plan

Following IRB approval, all eligible participants admitted to the Clinical Center alcohol rehabilitation unit (1SE) who sign the clinical and research consents for 14-AA-0181 will be approached for participation in this study. The PI or a designee will explain the study objectives, time commitment, expectations, and processes for assessments.

5.1 Informed Consent Process and Procedures

All eligible participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. Qualified staff (PI or a designee) will review and discuss the consent form with the volunteer at the study visit, as well as answer any questions that volunteers might have concerning the study procedures and/or other aspects of the consent form. The original signed consent form will be placed in the medical record and a copy will be given to the individual. The participant will

be informed that a patient rights representative is available to volunteers. After providing written informed consent, screening and all research procedures will be completed.

5.2 Rationale for involvement of vulnerable populations

Not applicable.

5.3 Justification for exclusion of vulnerable populations

Vulnerable populations (including individuals who are pregnant, cognitively impaired, children, and prisoners) will not be enrolled in this study as they are ineligible for admission under the screening and assessment protocol (14-AA-0181).

6 Evaluation of Risks/Discomforts and Benefits ratio:

a. **Benefits:** This study will provide pilot data on the feasibility, acceptability, and efficacy of an internet-based CBT-I program undergoing inpatient treatment AUD. The program may represent an efficacious non-pharmacologic intervention for insomnia in this population, potentially decreasing medication intervention. It is possible that there may be no direct benefit to the participant. However, based on prior literature, we anticipate alleviation or decrease in insomnia in some study participants.

b. **Risks:** It is possible that answering some of the questionnaires may cause discomfort to participants. Participants may feel uncomfortable wearing the WatchPAT device or the actiwatch device to sleep. Participants may potentially experience a rash and/or pruritus in wearing the WatchPAT or actiwatch. During WatchPAT testing, participants might also experience slight pressure around their finger that is being used for the test. After WatchPAT testing, participants might notice proximal nail fold redness and a few may experience proximal nail fold blister on the finger that is being tested. These side effects will usually resolve within 24-48 hours after the test. Participants will be instructed to report any untoward side effects from WatchPAT testing to the 1SE inpatient unit's clinical staff and to the research team. 1SE clinical staff will monitor the progression of these side effects and treat as necessary. Participants will also be made aware that they can always stop the WatchPAT testing at any time for any reason. Participants in Phase I and those assigned to the SHUTi condition in Phase II may experience daytime sleepiness (and potentially impaired daytime functioning) during the sleep restriction part of the program, particularly if they are taking medications with side effects of drowsiness during the study period.

c. **Alternative treatments and procedures:** The alternative to participating in this study is not to participate and obtain treatment as usual.

d. **Procedures for protecting/minimizing risk:** Every effort will be made to address and minimize participant discomfort including scheduling a repeat session or postponing study procedures if a participant becomes uncomfortable. Confidentiality and information technology standards are in place at the intramural programs of the NIH campus to protect electronic repositories of patient data. We selected a minimally-

invasive diagnostic tool to assess for OSA, requiring only one night of sleeping with the device. It is reasonably expected that these safeguards will protect participants' medical and personal health information, ensuring their privacy. Participants exhibiting excessive sleepiness will be counseled to avoid activities (e.g. drowsy driving and/or using the stove) that will jeopardize their safety and the safety of others.

e. **Provisions for ensuring that necessary medical or professional intervention is available in the case of adverse events to the subjects:** The MAI will be made aware of any adverse events to participants directly related to this protocol.

6.1 Protection of Participants' Privacy and Confidentiality

Participants will complete surveys and interviews behind closed doors for privacy. Data will be de-identified where possible through the use of non-identifiable codes. Any personally-identifiable information that participants mention during the interview (specifically their names) will be removed from transcripts and excluded from all data sets and any publications. The key to the code will be kept securely and separate from data and samples. Participant information will be maintained in secure databases and computers in locked files within a locked office. Paper records will be maintained in locked files and a locked office. Access to samples and data will be limited to authorized study personnel. We will be provided with a Certificate of Confidentiality in order to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except in certain circumstances which are clearly outlined in the consent forms.

6.2 Study Agents/Interventions

A description of the SHUTi program is outlined in the background and methods (under "intervention").

7 Reporting Procedures

Patients participating in this study may experience side effects, toxicities, and adverse events associated with completion of study procedures. Adverse events reported under this protocol will be limited to those events which are possibly, probably or definitely related to the research described in this protocol. The clinical care team overseeing the primary screening protocol will report any adverse events that are related to the screening protocol (14-AA-0181). An adverse event is defined as any untoward medical occurrences that 1) result in death, 2) are life-threatening, 3) require hospitalization, 4) cause persistent or significant disability / incapacity, 5) result in congenital anomalies or birth defects, 6) are other conditions which in the judgment of the investigators represent significant hazards. All events will be reported to the IRB in accordance with NIH Human Research Protection Program Policy #801 (Reporting Research Events).The PI will provide continuous, close monitoring of data and side effects, toxicities, and adverse events to identify trends. The PI will be responsible for revising the protocol as needed to maintain safety. All adverse events will be reported in aggregate at the time of continuing review, unless otherwise granted waiver by the IRB. If it is determined from the review of the aggregate data than an event is occurring at a greater frequency or level of severity than previously expected, it constitutes an unanticipated problem (UP) and will be reported in accordance with the reporting requirements outlined in the NIH Human Research Protection Program Policy #801.

8 Data Safety and Monitoring Plan

Data and safety monitoring will be performed annually by the Principal Investigator and Medical Advisory Investigator. The PI will distinguish serious adverse events (SAEs) from non-serious adverse events (AEs) and provide attributions. All SAEs, AEs, and unanticipated problems will be managed consisted with IRB guidelines. The PI will continuously evaluate implementation of the protocol for any unusual or unpredicted complications that occur and will review the data for accuracy and completeness. Monitoring will consist of evaluating the recruitment, retention and enrollment of participants to ensure consistency with the diversity plan as outlined in the protocol as well as evaluation of data and external factors that may impact the safety of the participants. Should evaluation of the data demonstrate that that participation in the protocol places the subjects at unnecessary risk, study activities may be temporarily halted until reviewed by the IRB. The NIH Clinical Center's Quality Assurance Program will conduct study monitoring at least annually or more frequently as required for open studies. Monitoring visits will include a review of patient consent documents, primary outcome results will be monitored, correct dating, and agreement between case report forms and source documents. All regulatory reports, reviews and amendments, adverse events and problem reports related to the study, along with investigator credentials, training records, and the delegation of responsibility log will be reviewed during monitoring visits. Any major findings will be summarized in writing and reported to the study PI who will be responsible for submitting the monitoring report to the IRB. Annually, 20% of the protocols closed to accrual and in data analysis will be randomly selected to be audited. Principal investigators for selected protocols will be queried, at least bi-annually, to determine if data analysis activities have occurred in the time since the last monitoring visit. A limited monitoring visit will be conducted if investigators have been engaged in data analyses. The monitoring will include a review of the study status, IRB records, protocol adherence specific to previously approved data analysis plan, and compliance with investigator training requirements for human subjects' research. Findings will be summarized in writing and reported to the study PI who will be responsible for submitting the monitoring report to the IRB.

9 Clinical Monitoring Plan

Clinical monitoring will be conducted in accordance with the Clinical Center (CC) Monitoring Policy. In brief, protocols will be submitted to the CC Quality Assurance Coordinator who will determine the frequency and complexity of monitoring based on the IRB assigned risk and patient populations. Monitoring will be performed by the CC Quality Assurance Coordinator.

Participants will be discontinued/withdrawn from the study if any of the following events occur: participant requests to be removed from study, participant is admitted to an addiction inpatient treatment program at the NIH or elsewhere within 9 weeks of discharge from 1SE (upon PI discretion), participant exhibits any condition which the MAI finds CBT-I to be a hazard to the participant (i.e. participant seems agitated, onset of increasing paranoia) participant is unable to comply with study-related procedures (i.e. SHUTi program recommendations and/or "homework), and/or participant develops a medical illness or condition that requires a new hospital admission.

10 Data/Records Management

The PI will be responsible for assuring that all investigators follow the plan for protecting the confidentiality of information and data provided by research participants. Assessments collected via paper-and-pencil questionnaires will be de-identified through the use of non-identifiable codes. The key to the code will be kept securely and separate from data and samples. Participant information will be

maintained in secured databases and computers in locked files and a locked office. Paper records will be maintained in locked files and a locked office. Access to samples and data will be limited to authorized study personnel. The PI will be responsible for overseeing entry of the data (quantitative and interview transcripts) into a password protected electronic system and ensuring data accuracy, consistency, and timeliness.

Information to be collected via the internet-based insomnia treatment program, SHUTi, will include participants' responses to individual questions within the program and the dates and times questions are modules were completed. Personnel at the University of Virginia (where the servers are located) will periodically download this data, which contains no PII and is identified only by user ID and forwarded to research personnel. Participants will not be asked to provide any PII in the course of their engagement in the SHUTi intervention and/or education-only programs. At the initial meeting for consenting and baseline assessment, participants will be provided with a unique user login ID and a temporary password. The participant will be required to change the password at initial logon to the website to a personal one that he or she will recall. Only the participant and the study staff will have the authority to access the participant's responses to the components of the intervention. All baseline and follow-up assessments not part of the SHUTi program will be completed in person or over the phone with paper-and-pencil questionnaires and will be administered by a member of the research team.

The SHUTi program has the ability to send automated pre-developed introductory, reminder, congratulatory, and (insomnia) relapse prevention emails to participants, which serve to enhance engagement and clinical outcomes. The content of each email is included in the appendices. The e-mails are automatically sent by the program and not manually by an individual. The e-mail content explicitly states that participants should not respond to the e-mail. No PII or protected health information is sent in the e-mails. In this project, all participant interaction with the program will be de-identified. Several other projects that have tested the SHUTi program have used an "e-mail exchange" to separate participant's real email address from the SHUTi program. An e-mail exchange is a set of dummy email address set up though a common e-mail provider such as "g-mail." The SHUTi program will e-mail a dummy email address. The dummy address will then forward the e-mail to the participants' real e-mail address. Only study personnel will have access to the document linking the dummy e-mail with the participants' e-mail, which will be accessible only to authorized study personnel as with other PII. Participants will be informed of this process during informed consent procedures. Data will be stored in locked cabinets and a password-protected database, in accordance with NIH records management policies, until it is no longer of scientific value.

10.1 Data sharing plan

Data may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases if consent for sharing was obtained (if applicable: or under waiver of informed consent as described below). Repositories receiving data from this protocol may be open-access or restricted access. Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data and samples may be shared with investigators and institutions with an FWA or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB

approval. Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.

10.2 Study closure

Study closure will be handled according to Policy 205 Requirements for IRB Submissions. At the time of study closure, the PI will submit an *Intramural Clinical Protocol Study Closure Application.* Research records will be maintained by the PI in accordance with record retention policies of the CC. Research records shall be made available for inspection and copying by authorized representatives of OHRP at reasonable times and in a reasonable manner. Premature study closure is not anticipated, but if necessary the PI will work with the IRB to inform currently-enrolled subjects about the closure.

11 Compensation

Participants will be compensated for research-related discomfort and inconveniences in accordance with NIH guidelines. If participants are unable to finish the study, they will be paid only for those parts completed. Payment will be made via check or direct deposit based on Clinical Research Volunteer Program (CRVP) guidelines. Because participants will need access to a tablet or laptop to complete the program, we will provide tablets to all participants (capable of Wifi connectivity). Participants will be able to keep the study-provided tablets.

- OSA screening: $30.00

If participant meets criteria for inclusion:

- Pre- and post-test assessments: $50.00
- Wearing actiwatch as instructed and returning at end of study: $50.00
- Completing sleep diaries as part of SHUTi or education-only group: $30.00
- Completing follow-up assessments in-person or by phone (6 months post-discharge): $30.00
  Tablet (approximate value: $135)
  Total possible compensation: $190 (+ tablet, estimated at $135)

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