1.0 TITLE PAGE

Puget Sound Psychiatry Center
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"A Randomized, Open Label, Sleep Hygiene Controlled 6-Week Study to Compare the Efficacy of four (CBT-I, FOA, Combined CBT-I and FOA and Sleep Hygiene) Different Behavioral Approaches for the Treatment of Adult Subjects with Insomnia"

PSPC-17-01
NCT- 03461666

Protocol Date: 02-12-2018
Version 1.2

Confidentiality Statement:

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study PSPC-17-01	
Study Number	PSPC-17-01
Title of Study	A Randomized Open Label, Sleep Hygiene Controlled 6-Week Study to Compare the Efficacy of four (CBT-I, FOA, Combined CBT-I and FOA and Sleep Hygiene) different Behavioral Approaches for the Treatment of Adult Subjects with Insomnia.
Study Center (Country)	Puget Sound Psychiatric Center, Bothell, WA 98011(**United States**)
Development Phase	Prospective Study
Objective	The current study seeks to evaluate and compare the effectiveness of (1) cognitive behavior therapy for insomnia [CBT-I], (2) focus of attention [FOA], (3) a combination of cognitive behavior therapy for insomnia and focus of attention, and (4) a sleep hygiene control intervention.
Methodology	Allocation: Randomized (1; 1; 1; 1) Intervention Model: Parallel Assignment Primary Purpose: Treatment
Number of Patients	40/group or 160 totals. It is estimated that 320 prospects will need to be screened in order to have 40 per group for a total of 160 participants.

Diagnosis and Main Criteria for Inclusion.	Male and female outpatients who are 18 or older to 72 years. Insomnia Severity Index > or = 10 Meet diagnostic criteria for Insomnia Disorder per DSM-5 Willing and able to sign Informed consent form Not planning on moving away from the area for the subsequent 12 weeks.
Exclusion Criteria	Participants who answer "yes" to any of the following will be excluded: Females who are lactating or who are pregnant Night shift workers, and individuals who nap 3 or more times per week over the preceding month Consumption of caffeine beverages (i.e. tea, coffee, or cola) comprising usually more than 5 cups or glasses per day Participation in another trial for insomnia Persons unable to complete the study questionnaires and psychological tests Persons who are unable to participate for the entire duration of the study, or in the opinion of the investigators, are likely to be non-compliant with the obligations inherent in the trial participation Persons self-describing with severe anxiety or severe depression (BDI score of 29 or higher) or severe anxiety (BAI score of 36 or higher). Persons with a history of epilepsy, seizures, or dementia Any significant, severe or unstable, acute or chronically progressive medical or surgical condition Serious head injury or stroke within the past year Current alcohol or substance abuse/dependence (must have >90 days of sobriety) Presence of other neurological disorders (e.g., multiple sclerosis, Parkinson's Disease) Presence of an untreated or unstable medical or psychiatric comorbid condition (e.g., major depressive disorder or psychotic disorder requiring admission within the last two years). People using psychotropic medication, hypnotic or sedative medications may be included if they are on a stable dosage for the last 2 months prior to the study, if the dose remains stable throughout the study, and if the medication is judged to not interfere with the study outcomes. Currently on medications known to produce insomnia (e.g., stimulants) Sleep apnea (AHI >15) or previous diagnosis of sleep apnea??? **Study participants who use a continuous positive airway pressure (CPAP) device for sleep apnea will be eligible for participation if they are below the apnea/hypopnea cutoff while using CPAP and agree to use the device during study participation.**

Test Product, Dosage, and Mode of Administration	Behavioral intervention, Six sessions, one hour each. In person.
Duration of Treatment	Treatment involves six consecutive weekly sessions. The study also includes 3 month, 6 month and 12 month follow-up assessment.
Reference Therapy, Dosage, and Mode of Administration	Cognitive Behavior Therapy for Insomnia (CBT-I) Focus of Attention (FOA) Combined CBT-I and FOA Sleep Hygiene Six sessions, one hour each, in person.
Criteria for Evaluation	
Primary Endpoint	The primary end point is completion of 6 treatment sessions and completion of the 3 month, 6 month and 12 month follow-up assessment. Improvement of insomnia outcome is measured by Self Report Sleep Measures (SRSM).
Key Secondary Endpoint	The Secondary end point is improvement outcomes.
Additional Endpoints	**Safety Population:** will include all randomized subjects who meet eligibility criteria and meet with their treatment provider for session 1. **Intent-to-Treat Population:** will include all subjects who meet with their treatment provider for session 1 and for whom the treatment provider determines the subject meets diagnostic criteria for 780.52 Insomnia Disorder. **Pre-Protocol (PP) Population:** will include all subjects who complete the 6 sessions of treatment as well as the 3 month, 6 month and 12 month follow up assessment. It is estimated that 80% of those who complete session 1 will complete session 6. It is estimated that 80% of those who complete session 6 will complete the 3 month, 6 month and 12 month follow up assessments. This will result in 25 participants who will have completed the entire study

Pharmacogenetics Sampling	There are no pharmacogenetics samplings.
Health Outcomes	
Safety Measures	In general the potential risks for participants are minimal. The treatment approaches involved in related studies have been shown to be a safe procedure and in most of the published studies people who underwent these procedures did not report any harmful effects. It is nonetheless possible participant (s) may experience some discomforts during the treatment. These may include temporary decrease in time asleep and accompanying daytime drowsiness. Some people may become anxious while initially following the treatment procedures, with increased worry about their sleep difficulty. Anxiety and worry about sleep difficulty are in fact common among persons with insomnia. Therefore identifying and addressing these possibilities will be directly addressed during the treatment, and participants will be given guidance about what to expect and **how to manage should these discomforts occur.** Persons with certain medical illnesses, certain psychiatric illnesses or other sleep disorders may be at increased potential risk of exacerbation of that illness. This is a possibility for participants with epilepsy, bipolar depression, parasomnia, obstructive sleep apnea or other illnesses which have excessive daytime sleepiness as a feature of the parent disorder. The participant may (or may not) be assigned to a treatment which involves sleep restriction. Sleep loss through sleep restriction may 1) lower the threshold for seizures in persons with epilepsy; 2) precipitate mania in bipolar participants; 3) exacerbate parasomnias; prevent adequate ventilation in patients with obstructive sleep apnea; and/or aggravate the day time somnolence to the point where it is no longer safe for the participant to drive, operate machinery and/or make judgments that adequately promote their own and/or the safety and well-being of others. The risk is generally higher when these illnesses are untreated. Prospective participants treated for any of these illnesses and interested in participating must have the written approval of their treatment provider in order to be eligible. Prospective participants will be screened and informed of these potential risks. If any of these risks (1-5 above) occur during the study, the participant will be asked to immediately discontinue the sleep restriction, and an alternative treatment not involving sleep

	restriction will be offered. The participant will also have the option of discontinuing the treatment if they prefer this to proceeding with the alternative treatment which does not involve sleep restriction.
Pharmacokinetic Sampling	There are no pharmacokinetic samplings.
Statistical Analysis	Repeated measures analysis of variance (ANOVA) will be used to test Hypotheses 1, 2 and 3. Chi square will be used to test Hypothesis 4.

SCHEDULE OF EVALUATIONS: Study PSPC-17-01

	Screening	Randomized, Open label, sleep Hygiene Controlled 6 Week study						EOT/ ET (1 week F/U)	Safety Follow up Period		
Visit #	**1**	**(BV)/ 2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Study Day Weeks/Months	**up to 14 days**	**1W**	**2W**	**3W**	**4W**	**5W**	**6W**	**7W**	**3M**	**6M**	**12M**
Informed consent	x										
Review of Histories	x										
Medication History +Concomitant Medications	x										
Inclusion/ Exclusion	x	X	x	X	x	x	x	x	x	x	x
Randomization Assessment		X									
Questionnaire & Inventories GMS/GMS-I	x										
ISI x								x	x	x	x
BDI	x							x	x	x	x
BAI	x							x	x	x	x
SRSM	x	x	x	x	x	x	x	x	x	x	x
WSL								x	x	x	x
CGI-I	x	x	x	x	x	x	x	x	x	x	x
CGI-S	x	x	x	x	x	x	x	x	x	x	x
Q-LES	x							x			
DSM-5 diagnostic Interview	x										
C-SSRS	x	x	x	x	x	x	x	x	x	x	x

(GMS) Goal Motivation Scale; (GMS-I) Goal Motivation Scale-Insomnia, Beck Depression Inventory (BDI); Beck Anxiety Inventory (BAI); Insomnia Severity Index (ISI); Self Report Sleep Measures (SRSM); Weekly Sleep Log (WSL);
Clinical Global Impression - Improvement (CGI-I), Clinical Global Impression – Severity scale (CGI-S)
Quality of Life Enjoyment and Satisfaction (Q-LES), End of Treatment (EOT)/Early Termination (One week F/U): (ET)
Columbia suicide severity rating scale (C-SSRS); Baseline Visit (BV)

3.0 TABLE OF CONTENTS

4.0 LIST OF ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ET	Early termination
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
PSPC	Puget Sound Psychiatry Center
SD	Standard deviation
SAEs/AEs	Serious adverse events/Adverse Events
ANOVA	Analysis of Variance
PN	Participant Number
eCRFs	Electronic Case Report Forms
MDC	Manual Data Capture
ECG	Electro Cardiogram
BDI	Beck Depression Inventory
BAI	Beck Anxiety Inventory
ISI)	Insomnia Severity Index
SRSM	Self Report Sleep Measures
WSL	Weekly Sleep Log
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity scale
Q-LES	Quality of Life Enjoyment and Satisfaction
EOT/ET	End of Treatment/Early Termination
C-SSRS	Columbia suicide severity rating scale
BV	Baseline Visit
CBT	Cognitive behavioral therapy
CBT-I	Cognitive Behavior Therapy for Insomnia
FOA	Focus of Attention
SAS	Software; Statistical Analysis System
DSMB	Data and Safety Monitoring Board

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

Approval by the local IRB/PSPC Ethical Committee, before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to the Sponsor-PSPC, along with a roster of IRB members. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with the US CFR, Title21, Part 56.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997).

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study and before participating in any study procedures, each patient must provide written informed consent in compliance with 21 CFR, Parts 50 and give HIPAA authorization.

Each patient will read and sign an ICF and/or other authorization form as per local regulations; each patient will be made aware that he or she may withdraw from the study at any time.

The ICF contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF and the HIPAA or other locally applicable form will be given to the patient, and both documents will be placed in the Investigator‘s study files.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at Puget Sound Psychiatry Center (PSPC) Bothell WA, in the United States. The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator‘s care; and for the control of investigational products under investigation. An investigator shall obtain the informed consent for each patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at Puget Sound Psychiatry Center (PSPC) must meet his or her obligations to the patients, ethics committee, Sponsor, and regulatory authorities by maintaining oversight and control of the study‘s conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of staff capabilities and performance is consistent with the study investigational plan. The Investigator at Puget Sound Psychiatry Center (PSPC) will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

REVIEW OF RELATED LITERATURE: BEHAVIORAL TREATMENT OF INSOMNIA DISORDER

The annual prevalence of insomnia symptoms in the general adult population ranges from 35% to 50% (Walsh, Coulouvrat & Hajak et al, 2011). To distinguish chronic from acute insomnia, which may occur in anyone at one time or another, varied definitions for chronic insomnia have been utilized from study to study, with minimum durations ranging from 30 days to as long as 6 months (National Institutes of Health, 2005). The prevalence of insomnia disorder ranges from 12% to 20% (Morin, LeBlanc, Belanger, Ivers, Merette, & Savard J. 2011; Roth, Coulouvrat, & Hajak et al. 2011).

Insomnia Disorder involves a predominant complaint of dissatisfaction with sleep quantity or quality, associated with one or more of the following symptoms: (1) difficulty initiating sleep, (2) difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings; (3) early morning awakening with inability to return to sleep (American Psychiatric Association, 2013). Sedative hypnotics or antidepressant drugs are the most common treatments offered patients who meet clinical criteria for Insomnia Disorder (Walsh & Schweitzer, 1999). Numerous negative side effects accompany traditional hypnotics, e.g., benzodiazepines. In addition, these drugs provide only symptomatic relief because they do not address underlying mechanisms which sustain primary insomnia. As a result, upon termination of the sleep medications, patients very commonly experience a full return of their insomnia symptoms. Given the prevalence of insomnia and the limited effectiveness of medication for the treatment of insomnia disorder, there is a need for non-pharmaceutical behavioral treatment approaches.

COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA:

Cognitive behavioral therapy for insomnia (CBT-I) is the most prominent non-pharmacologic treatment for insomnia disorder (Wu, Appleman, Salazar & Ong, 2015). Early in the development of what is now "CBT-I", first generation behavioral interventions were designed to target presumed perpetuating mechanisms involved in primary insomnia. The approach aimed to correct sleep disrupting habits using stimulus control and to reduce bedtime arousal using relaxation training, for example. Over time cognitive behavior therapy for insomnia has adopted a multi-component approach to treatment.

As noted by Perlis et al (2008), the clinical practices which constitute the primary or first line components are to some extent debated. However, most clinical practices and clinical trial protocols now include (1) stimulus control therapy and (2) sleep restriction therapy along with (3) sleep hygiene education, (4) cognitive therapy to identify and reduce negative sleep thoughts, and often (5) relaxation strategies such as progressive muscle relaxation and bedtime rituals that facilitate calming, especially as bedtime approaches. (1) Stimulus control is a set of instructions originally developed by Richard Bootzin that address conditioned arousal. These instructions strengthen the bed and bedroom as a cue for sleep and weaken the bed and bedroom as a cue for wakefulness. (2) Sleep restriction therapy or "sleep consolidation training" is a procedure originally designed by Arthur Spielman to eliminate prolonged awakenings in the middle of the night. The procedure can also help with difficulty initiating asleep at the beginning of the night. This step-wise procedure aims to first improve sleep quality and later worry about sleep quantity. The time spent in bed is initially restricted to the currently feasible amount of sleep. Time spent in bed is gradually increased in subsequent steps. (3) Sleep hygiene education commonly lists best practices in sleep hygiene (get up at the same time each day, cut down on all caffeine products, make sure your bedroom is at a comfortable temperature during the night, etc.). Typically this involves education, then identifying specific sleep hygiene practices for improvement, identifying goals and follow up. (4) Cognitive therapy and (5) relaxation therapy are often included on an as needed basis to bolster incomplete treatment responses and address predisposing and precipitating factors thought to still be substantially contributory (Perlis et al, p.

17). The cognitive therapy component identifies negative sleep talk such as "I can't stand it that I'm not getting to sleep" or "If I don't get 8 hours of sleep tonight, I'll do poorly at work and I could get fired". Some cognitive therapists have a didactic focus. Others use a variety of cognitive restructuring procedures. While the therapies differ in approach, all are based on the observation that persons with insomnia have negative thoughts and beliefs about their condition and its consequences (Perlis, p. 18). Relaxation therapy focuses on managing stress, muscle relaxation and bedtime rituals that facilitate calming [https://stanfordhealthcare.org/medical-treatments/c/cognitive-behavioral-therapy-insomnia.html].

EFFECTIVENESS OF CBT-I:

The results using CBT-I among subjects with primary insomnia reporting sleep onset problems have been moderately effective for treating sleep onset problems. In a meta-analysis of 37 studies, Wu, Appleman, Salazar and Ong (2015) reported 36% of CBT-I patients were in remission from insomnia and no longer met diagnostic criteria for Insomnia Disorder at post-treatment evaluation compared to 16.9% in comparison conditions.

Key quantitative measures include sleep latency, the amount of time it takes person to initiate sleep upon retiring to bed; wake time after sleep onset (WASO); total sleep time (TST); and sleep efficiency, the percentage of sleep period during which person is actually asleep. In their review of the results of five randomized clinical trials which compared CBT-I to medications among patients with primary insomnia, Mitchell, Gehman, Perlis and Umscheid (2012) report sleep efficiency improved 8 to 16 percent with CBT-I. CBT-I generally led to improvement of 30 to 45 minutes in sleep latency and 30 to 60 minutes in total sleep time. Note that TST is not only an outcome variable but is manipulated as part of CBT-I using the restriction of time spent in bed. Sleep restriction therapy requires that time in bed be reduced to a time interval equal to the patient's 'sleep ability' by measuring average TST with a sleep log during a baseline period. As noted by Mitchell, Gehrman, Perlis and Umscheid, "The net result of this, after completion of CBT-I, is that many patients do not recover their baseline TST but are nevertheless substantially improved with respect to other aspects of sleep" (p. 6).

LIMITATIONS OF COGNITIVE BEHAVIOR THERAPY FOR INSOMNIA:

According to Mitchell et al "There are two main disadvantages to CBT-I. First, during the first few week of treatment there is often an acute reduction in total sleep time that can lead to the side effect of increased daytime sleepiness which, for some, is enough to lead them to drop out of treatment. Second, improvements from CBT-I are typically not seen until 3-4 weeks into treatment" (p. 3 of 18). Also noteworthy is the emotional response of patients upon learning their sleep will be restricted, commonly with a markedly later bedtime during the implementation of sleep restriction. Although apparently no research to date has assessed patient satisfaction and/or distress during treatment implementation, this may be a factor related to dropout rate with CBT-I. Among ten randomized controlled trials of CBT-I for primary insomnia reporting dropout rate and involving sleep restriction, dropout rates ranged from 0% to 33%. Specifically, 4 studies reported 0% dropout; 1 study reported 7% dropout; 2 studies reported 8% dropout; and dropout rates of 11%, 18% and 33% were each reported in one study (Table 1, Okajima, Komada & Inque, 2011). In addition, while 36% remission of insomnia disorder is better than 16.9% (comparison group), this means 64% of those completing CBT-I continued to meet diagnostic criteria for Insomnia Disorder (Wu, Appleman, Salazar and Ong, 2015). With all due respect for the major contribution of CBT-I in assisting those with insomnia, there is room for improvement as evidenced by 64% still having Insomnia Disorder upon completion of treatment.

Another potential limitation of CBT-I relates to the mechanism of change and may lead to a means to improve upon the efficacy of behavioral treatment(s) for insomnia. "Research by Gregg D. Jacobs, Ph.D. and colleagues has established that insomniacs have faster brain wave patterns in bed than good sleepers which is consonant with heightened mental activity." (Jacobs, 2000, p. 22). The faster brain wave pattern is only partially addressed in CBT-I which focuses on negative sleep talk. However, the emphasis in CBT-I is upon reality testing and/or challenging negative sleep talk, not upon slowing the faster brain wave pattern itself. A behavioral treatment approach which targets the actual here-and-now brain wave frequency

with the goal of slowing the brain wave frequency in the moment at the time when the person wants to go to sleep may further improve their ability to do so.

BRAIN WAVE FREQUENCY AND SLEEP:

The human brain is composed of neurons that are interconnected to each other in networks. These neurons receive inputs from other areas of the brain. Electrical activity in the form of nerve impulses is always present in the form of nerve impulses being sent and received, even during sleep. The electrical activity reflects both intrinsic activity of neurons in the cerebral cortex (an internal process, i.e., thinking) and information sent to it by the body and sensory receptors (input from sight, sound, smell, touch). This composite activity is measured with an electroencephalogram or EEG. An EEG mainly detects the activity of the brain region just under it, the cerebral cortex. Nevertheless, the electrodes receive the activity from thousands of neurons. In fact, one square millimeter of cortex has more than 100,000 neurons.

Frequency range	**Name**	**Usually associated with:**
13–39 Hz	Beta waves	Active, busy or anxious thinking and active concentration, arousal, cognition, and or paranoia
7–13 Hz	Alpha waves	Relaxation (while awake), pre-sleep and pre-wake drowsiness, REM sleep, Dreams
4–7 Hz	Theta waves	Deep meditation/relaxation, NREM sleep
< 4 Hz	Delta waves	Deep dreamless sleep, loss of body awareness

(Precise boundaries between ranges vary among definitions; there is no universally accepted standard). The dominant frequency determines one's current state. For example, if alpha waves are dominating, the person is in the alpha state. This happens when one is relaxed but awake. However, other frequencies will also be present, although with smaller amplitudes. Falling asleep for a waking state begins with Stage 1 (non-REM) which is the stage between wakefulness and sleep, sometimes referred to as somnolence or drowsy sleep, in which the muscles are still quite active and the eyes roll around slowly and may open and close from time to time. In more scientific terms, stage 1 is the period of transition from relatively unsynchronized beta and gamma brain waves (with a frequency of 12-30 Hz and 25-100 Hz respectively), which is the normal range for the awake state, to more synchronized but slower alpha waves with a frequency of 8-13 Hz, and then to theta waves with a frequency of 4-7 Hz. It is difficult to pinpoint the actual point of sleep onset (falling asleep), as the process is a continuum as brain wave activity gradually slows down (http://www.howsleepworks.com/types_nonrem.html).

In short, a predominant lower brain wave frequency is associated with sleep, and a predominant higher brain wave frequency is associated with busy or anxious thinking and arousal. Therefore shifting the predominant brain wave frequency to a lower frequency should be associated with increased ability to initiate sleep. How can lower brain wave frequencies be increased when a person wants to sleep? A potential answer to this question and an associated treatment approach for insomnia comes primarily from the literature on meditation with ancillary guidance from the literature on brain entrainment.

MEDITATION:

Meditation's effect on the brain can be put into two categories: state changes and trait changes, respectively alterations in brain activities during the act of meditating and changes that are the outcome of long-term

practice. The former is of interest as relates to lowering the predominant brain wave frequency to increase ability to initiate sleep. Assessed in a review by Cahn and Polich (2006), many studies on meditation have linked frequency alpha (8-13 Hz) and theta (4-7 Hz) waves to meditation (Cahn & Polich, 2006). A much older study reports more specific findings, such as decreased alpha blocking and increased frontal lobe specific theta activity. Alpha blocking is a phenomenon where the active brain, normally presenting beta wave activity, cannot as easily switch to alpha wave activity (Kasamatsu & Hirai, 1966).

Envision a person is in bed, head on the pillow, sheet and blanket covering them, eyes closed, and wanting to go to sleep. If the person does not go to sleep, they are very likely thinking about things. For example, they might think about what a family member said or something they have to do tomorrow. In any event, thinking about things activates the brain, and the brain activation maintains a higher predominant brain wave frequency which is associated with being awake. In essence, that upon which the person focuses their attention stimulates a certain brain wave frequency. Imagine falling out a window several stories above street level, for example, and notice how anxiety immediately increases. Think of the possibility a loved one's flight tomorrow will crash, and anxiety level will again immediately increase. These examples illustrate how focus of attention relates to brain wave frequency: anxiety reflects a higher predominant brain wave frequency at the moment. In short, a person's focus of attention relates to their predominant brain wave frequency.

When in bed and wanting to initiate sleep, "thinking about things" reflects the mind focused on activating thoughts. These activating thoughts relate to higher brain wave frequency. Thus the person has difficulty initiating sleep, a phenomenon associated with a lower brain wave frequency. With the focus on something less activating, it is reasonable to believe the predominant brain wave frequency will be lower. Meditation eliminates background mental noise, commonly by focusing attention on the breathe (yoga, for example), a mantra (transcendental meditation), a calming image (guided imagery), or non-judgmental observation of one's own thinking (mindfulness). As relates to facilitating sleep, the sound of the breath and a mantra are of particular interest as steady, unmoving auditory processes. Imagery involves the visual brain, and it is the auditory brain which is activated while "thinking about things". Mindfulness meditation focuses on observing one's own thinking process, which is itself an ever shifting phenomenon and therefore at least mildly activating. While in bed trying to sleep, the act of thinking "Oh, I have to remember to pay the rent tomorrow" involves auditory activation. A much less activating auditory stimulus is the sound of one's breathing. Shifting and then maintaining the focus of attention on listening to the sound of here-and-now breathing shifts the auditory brain to a less activating auditory stimulus, thereby lowering the predominant brain wave frequency. One tends to become bored with continued listening to the sound of one's own breath. Boredom reflects less activation. Similarly, repeating a non-stimulating mantra again and again in one's mind shifts the focus to a less activating auditory stimulus, thereby lowering the predominant brain wave frequency.

Lower brain wave frequency is associated with relaxation, deep meditation and sleep. Therefore, meditative practices which increase the predominance of lower brain waves appear fitting as a means of increasing the ability to initiate sleep. The first author has been using specific meditative strategies with outpatient clients whose therapy goals include increased ability to initiate sleep. The meditation strategies are (1) listening to the sound of one's own breathing; (2) using a mantra to slow and quell thinking; and (3) guided imagery linking breathing with focus on calming during exhalation. With an explanation of the approaches and specific directions for focusing attention on listening to the sound of their own breathing, clients whose overall anxiety level is low to moderate often report the next week, "It works." However, clients whose overall anxiety level is moderate to high often report the next week, "It works a little." "Some nights it worked. Some nights I just couldn't stop thinking about things." As follow up, when these more anxious clients are then given an explanation and specific directions for using a mantra, these clients often report the next week, "It works." As follow up with more anxious clients reporting considerable body activation, specific directions are given for guided imagery to link the calming body sensation with breathing out. Listening in the moment to the sound of the breath is a more passive activity, presumably with less brain activation than actively repeating a mantra. If in fact manta-based meditation is more effective in slowing the brain of the more anxious person, brain entrainment provides one possible explanation. Here is a

synopsis on brain entrainment, followed by a working hypothesis regarding the differential effectiveness of the two meditative strategies.

BRAIN ENTRAINMENT:

Human subjects rarely hear frequencies below 20 Hz, which is exactly the range of Delta, Theta, Alpha, , and low to mid Beta brainwaves. Among the methods by which some investigations have sought to induce lower brain wave frequencies is to have subjects listen to binaural beats. A binaural beat is an auditory illusion perceived when two different pure-tone sine waves, both with frequencies lower than 1500 Hz, with less than a 40 Hz difference between them, are presented to a listener, one through each ear. For example, if a 530 Hz pure tone is presented to a subject's right ear, while a 520 Hz pure tone is presented to the subject's left ear, the listener will perceive the auditory illusion of a third tone, in addition to the two pure-tones presented to each ear. The third sound is called a binaural beat, and in this example would have a perceived pitch correlating to a frequency of 10 Hz, that being the difference between the 530 Hz and 520 Hz pure tones presented to each ear (Draganova, Ross, Wollbrink & Pantev, 2008).

Listening to binaural beats has been shown to precipitate auditory driving by which ensembles of cortical neurons entrain their frequencies to that of the binaural beat, with associated changes in self-reported subjective experience of emotional and cognitive state (Becher, Höhne, Axmacher, Chaieb, Elger & Fell, 2015; Pratt, Starr, Michalewski, Dimitrijevic, Bleich & Mittelman, 2009; Karino, Yumoto, Itoh, Uno, Yamakawa, Sekimoto & Kaga, 2006; McConnell, Froeliger, Garland, Ives & Sforzo, 2014). The brain entraining is more effective if the entraining frequency is close to the user's starting dominant frequency. Therefore, it is suggested to start with a frequency near to one's current dominant frequency (likely to be about 20 Hz or less for a waking person) and then slowly decrease or increase it towards the desired frequency.

IMPLICATIONS FOR MEDITATION PRACTICES FOR INSOMNIA:

While brain entrainment provides a means of stimulating a particular brain wave frequency, the approach requires expensive equipment not commonly available and to date untested in the treatment of insomnia. It nonetheless provides guidance in the process of shifting the brain wave frequency. Specifically, a strategy that increases the frequency slightly lower than the predominant brain wave frequency at hour of sleep may be more effective than a strategy that increases a frequency markedly lower than the predominant frequency at that moment.

SUMMARY:

The prevalence of insomnia disorder ranges from 12% to 20%. The most prominent non-pharmacologic treatment for insomnia disorder is cognitive behavioral therapy for insomnia (CBT-I). Meta-analysis indicates 36% remission of insomnia disorder upon completion of CBT-I vs. 16.9% in the comparison group(s). This means 64% of those completing CBT-I continued to meet diagnostic criteria for Insomnia Disorder. While CB-I has made a major contribution in assisting those with insomnia, there is room for improvement as evidenced by 64% still having Insomnia Disorder upon completion of treatment with CBT-I.

Research has established that insomniacs have faster brain wave patterns in bed than good sleepers which is consonant with heightened mental activity. The mechanisms of action for CBT-I do not directly address the faster brain wave patterns. Assessed in a review by Cahn and Polich (2006), many studies on meditation have linked frequency alpha (8-13 Hz) and theta (4-7 Hz) waves to meditation (Cahn & Polich, 2006). A predominance of these lower brain wave frequencies has been found to be directly related to relaxation and sleep. The first author's clinical use of meditation techniques to increase clients' ability to initiate sleep has met with frequent client feedback that "It works". This approach, called "focus of attention" appears promising. However, "It works" is not sufficient. A clinical trial is needed in order to assess the relative efficacy of (a) cognitive behavior therapy for insomnia, (b) focus of attention [FOA], (c) a combination of CBT-I and FOA and (d) a comparison group.

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8.0 STUDY OBJECTIVES

The objectives of this study seeks to evaluate and compare the effectiveness of (1) cognitive behavior therapy for insomnia [CBT-I], (2) focus of attention [FOA], (3) a combination of cognitive behavior therapy for insomnia and focus of attention, and (4) a sleep hygiene control intervention.

PRIMARY OBJECTIVE The primary objective is completion of 6 treatment sessions and completion of the 3 months, 6 months and 12 months follow-up assessment. Improvement of insomnia outcome is measured by Self Report Sleep Measures (SRSM).

SECONDRY OBJECTIVE The Secondary objective is improvement outcomes.

SAFETY AND TOLERABILITY END POINTS

In general the potential risks for participants are minimal. The treatment approaches involved in related studies have been shown to be a safe procedure and in most of the published studies people who underwent these procedures did not report any harmful effects. It is nonetheless possible participant(s) may experience some discomforts during the treatment. These may include temporary decrease in time asleep and accompanying daytime drowsiness. Some people may become anxious while initially following the treatment procedures, with increased worry about their sleep difficulty. Anxiety and worry about sleep difficulty are in fact common among persons with insomnia. Therefore identifying and addressing these possibilities will be directly addressed during the treatment, and participants will be given guidance about what to expect and how to manage should these discomforts occur. Persons with certain medical illnesses, certain psychiatric illnesses or other sleep disorders may be at increased potential risk of exacerbation of that illness. This is a possibility for participants with epilepsy, bipolar depression, parasomnia, obstructive sleep apnea or other illnesses which have excessive daytime sleepiness as a feature of the parent disorder. The participant may (or may not) be assigned to a treatment which involves sleep restriction. Sleep loss through sleep restriction may

1) Lower the threshold for seizures in persons with epilepsy;
2) Precipitate mania in bipolar participants;
3) Exacerbate parasomnias;
4) Prevent adequate ventilation in patients with obstructive sleep apnea; and/or
5) Aggravate the day time somnolence to the point where it is no longer safe for the participant to drive, operate machinery and/or make judgments that adequately promote their own and/or the safety and well-being of others.

The risk is generally higher when these illnesses are untreated. Prospective participants treated for any of these illnesses and interested in participating must have the written approval of their treatment provider in order to be eligible. Prospective participants will be screened and informed of these potential risks.
If any of these risks (1-5 above) occur during the study, the participant will be asked to immediately discontinue the sleep restriction, and an alternative treatment not involving sleep restriction will be offered. The participant will also have the option of discontinuing the treatment if they prefer this to proceeding with the alternative treatment which does not involve sleep restriction.

SAMPLE SIZE

It is estimated that 320 prospects will need to be screened in order to have 40 per group for a total of 160 participants.

ANALYSIS POPULATIONS

Safety Population: will include all randomized subjects who meet eligibility criteria and meet with their treatment provider for session 1.

Intent-to-Treat Population: will include all subjects who meet with their treatment provider for session 1 and for whom the treatment provider determines the subject meets diagnostic criteria for 780.52 Insomnia Disorder.

Pre-Protocol (PP) Population: will include all subjects who complete the 6 sessions of treatment as well as the 3 month, 6 month and 12 month follow up assessment. It is estimated that 80% of those who complete session 1 will complete session 6. It is estimated that 80% of those who complete session 6 will complete the 3 month, 6 month and 12 month follow up assessments. This will result in 25 participants who will have completed the entire study.

HYPOTHESES

Hypothesis 1: Treatment Effect on Subjective Measures from Weekly Sleep Log

There will be no statistically significant overall post-treatment minus pre-treatment differences across the four treatment groups in subjective sleep measures using standardized sum scores across the four measures of self-report data from Weekly Sleep Log. If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:

Hypothesis 1a. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in the mean number of minutes to initiate sleep (SL);

Hypothesis 1b. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in the mean number of minutes to return to sleep upon awakening after sleep onset (WASO);

Hypothesis 1c. There will be no statistically significant post-treatment differences across the four treatment groups in the mean total number of minutes of sleep (TST);

Hypothesis 1d. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep divided by the total number of minutes in bed (SE).

Hypothesis 2: Treatment Effect on Objective Measures of Sleep

There will be no statistically significant overall post-treatment minus pre-treatment differences across the four treatment groups in overall objective sleep measures using standardized sum scores for data from subjects wearing an ActiWatch 2. If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:

Hypothesis 2a. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in the mean number of minutes to initiate sleep (SL);

Hypothesis 2b. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in the mean number of minutes to return to sleep upon awakening after sleep onset (WASO);

Hypothesis 2c. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep (TST);

Hypothesis 2d. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep divided by the total number of minutes in bed (SE).

Hypothesis 3: Treatment Effect on Insomnia Severity

There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in insomnia severity as measured by the Insomnia Severity Index (ISI).

Hypothesis 4: Treatment Effect on Insomnia Diagnosis
There will be no statistically significant (chi square) post-treatment minus pre-treatment mean differences across the four treatment groups in the percentage of subjects who meet DSM-5 criteria for 780.52 Insomnia Disorder across time (pre-treatment; post-treatment).

Hypothesis 5: Treatment Effect on Self Report Sleep Satisfaction Measures
There will be no statistically significant overall post-treatment minus pre-treatment differences across the four treatment groups in overall satisfaction/dissatisfaction with sleep using standardized sum scores for data from subjects across the five likert scale measures of satisfaction/dissatisfaction on the Self Report Sleep Measures.
If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:
Hypothesis 5a. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to get to sleep at bedtime;
Hypothesis 5b. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with frequency of awakenings after having initiated sleep;
Hypothesis 5c. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to return to sleep after awakenings during the night;
Hypothesis 5d. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with average quantity of sleep;
Hypothesis 5e. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with overall quality of sleep.

Hypothesis 6: Treatment Effect on Subjective Sleep Distress
There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of distress with sleep difficulty.

Hypothesis 7: Treatment Effect on Subjective Report of Impairment
There will be no statistically significant overall post-treatment minus pre-treatment differences across the four treatment groups in overall self-report of impairment due to sleep difficulty measures using standardized sum scores across the three measures. If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:
Hypothesis 7a. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of social impairment due to sleep difficulty;
Hypothesis 7b. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of occupational impairment due to sleep difficulty;
Hypothesis 7c. There will be no statistically significant post-treatment minus pre-treatment mean differences across the four treatment groups in self report of extent of academic impairment due to sleep difficulty.

Hypothesis 8: Endurance of Treatment Effect on Subjective Measures from Weekly Sleep Log
There will be no statistically significant overall 12 month follow up minus pre-treatment differences across the four treatment groups in subjective sleep measures using standardized sum scores across the four measures of self-report data from Weekly Sleep Log. If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:

Hypothesis 8a. There will be no statistically significant 12 month follow up minus pre-treatment mean differences across the four treatment groups in the mean number of minutes to initiate sleep (SL);
Hypothesis 8b. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean number of minutes to return to sleep upon awakening after sleep onset (WASO);
Hypothesis 8c. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep (TST);
Hypothesis 8d. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep divided by the total number of minutes in bed (SE).

Hypothesis 9: Endurance of Treatment Effect on Objective Measures
There will be no statistically significant overall significant overall 12 month follow up minus pre-treatment differences across the four treatment groups in overall objective sleep measures using standardized sum scores for data from subjects wearing an ActiWatch 2.
If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:
Hypothesis 9a. There will be no statistically significant post-treatment minus pre-treatment differences across the four treatment groups in each of the following objective sleep measures using data from subjects wearing an ActiWatch 2:
Hypothesis 9b. There will be no statistically significant 12 month follow up minus pre-treatment mean differences across the four treatment groups in the mean number of minutes to initiate sleep (SL);
Hypothesis 9c. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean number of minutes to return to sleep upon awakening after sleep onset (WASO);
Hypothesis 9d. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep (TST);
Hypothesis 9e. There will be no statistically significant 12 month follow up minus pre-treatment differences across the four treatment groups in the mean total number of minutes of sleep divided by the total number of minutes in bed (SE).

Hypothesis 10: Endurance of Treatment Effect on Insomnia Severity
There will be no statistically significant 12 months follow up minus pre-treatment mean differences across the four treatment groups in insomnia severity as measured by the Insomnia Severity Index (ISI).

Hypothesis 11: Endurance of Treatment Effect on Insomnia Diagnosis
There will be no statistically significant chi square 12 month follow up minus pre-treatment mean differences across the four treatment groups in the percentage of subjects who meet DSM-5 criteria for 780.52 Insomnia Disorder across time (pre-treatment; post-treatment; 12 month follow-up).

Hypothesis 12: Endurance of Treatment Effect on Sleep Satisfaction Measures
There will be no statistically significant overall 12 month follow up minus post-treatment differences across the four treatment groups in overall satisfaction/ dissatisfaction with sleep using standardized sum scores for data from subjects across the five likert scale measures of satisfaction/dissatisfaction on the Self Report Sleep Measures.
If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:
Hypothesis 12a. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to get to sleep at bedtime;
Hypothesis 12b. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with frequency of awakenings after having initiated sleep;

Hypothesis 12c. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to return to sleep after awakenings during the night;
Hypothesis 12d. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with average quantity of sleep;
Hypothesis 12e. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with overall quality of sleep.

Hypothesis 13: Endurance of Treatment Effect on Subjective Sleep Distress
There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of distress with sleep difficulty.

Hypothesis 14: Endurance of Self Report Sleep Satisfaction Measures
There will be no statistically significant overall 12 month follow up minus post-treatment differences across the four treatment groups in overall satisfaction/ dissatisfaction with sleep using standardized sum scores for data from subjects across the five likert scale measures of satisfaction/dissatisfaction on the Self Report Sleep Measures.
If ANOVA indicates a significant overall difference, pairwise t-tests will test the following hypotheses:
Hypothesis 14a. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to get to sleep at bedtime;
Hypothesis 14b. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with frequency of awakenings after having initiated sleep;
Hypothesis 14c. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with ability to return to sleep after awakenings during the night;
Hypothesis 14d. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with average quantity of sleep;
Hypothesis 14e. There will be no statistically significant 12 month follow up minus post-treatment mean differences across the four treatment groups in self report of extent of satisfaction or dissatisfaction with overall quality of sleep.

Hypothesis 15: Satisfaction with Treatment
There will be no statistically significant differences across treatment types in post-treatment reported overall level of satisfaction with the treatment received as measured with a 5-point Likert Scale on the FEEDBACK QUESTIONNAIRE.

Hypothesis 16: Likelihood to Recommend to Others
There will be no statistically significant differences across treatment types in post-treatment reported level of likelihood to recommend to others the treatment received as measured with a 5-point Likert Scale on the FEEDBACK QUESTIONNAIRE.

MISSING DATA

All data measures will be reviewed upon receipt to ensure no data is missing. Subjects who have not completed the data measures and/or specific items will be asked to do so immediately upon the review having identified missing data. In any situations in which important missing data cannot be gathered, the subject will be eliminated from the study. It is anticipated that in effect 5-10% of subjects will not

complete 12 month follow-up. These subjects will then be eliminated as relates to analyses involving 12 month follow-up data. Statistical analyses will be conducted to determine whether those with missing data differ significantly from those without missing data using t test comparing the two groups on total scores on Insomnia Severity Index at pre-treatment as well as post-treatment.

STATISTICS

Repeated measures analysis of variance (2 X 4 ANOVA) will be used to test the Hypotheses 1-3, 5-10 and 11-16. Any statistically significant ANOVAs will be followed by pairwise t-test comparisons to identify between group differences. Chi square will be used to test Hypotheses 4 and 11.

SAFETY ANALYSIS

In general the potential risks for participants are minimal. The treatment approaches involved in related studies have been shown to be a safe procedure and in most of the published studies people who underwent these procedures did not report any harmful effects.
Prospective participants will be informed that it is nonetheless possible you may experience some discomforts during the treatment. These may include temporary decrease in time asleep and accompanying daytime drowsiness. Some people may become anxious while initially following the treatment procedures, with increased worry about their sleep difficulty. Anxiety and worry about sleep difficulty are in fact common among persons with insomnia. Therefore identifying and addressing these possibilities will be directly addressed during the treatment, and participants will be given guidance about what to expect and how to manage should these discomforts occur. Prospective participants will also be informed that persons with certain medical illnesses, certain psychiatric illnesses or other sleep disorders may be at increased potential risk of exacerbation of that illness. This is a possibility for participants with epilepsy, bipolar depression, parasomnia, obstructive sleep apnea or other illnesses which have excessive daytime sleepiness as a feature of the parent disorder. The participant may (or may not) be assigned to a treatment which involves sleep restriction. Sleep loss through sleep restriction may

1) Lower the threshold for seizures in persons with epilepsy;
2) Precipitate mania in bipolar participants;
3) Exacerbate parasomnias;
4) Prevent adequate ventilation in patients with obstructive sleep apnea; and/or
5) Aggravate the day time somnolence to the point where it is no longer safe for the participant to drive, operate machinery and/or make judgments that adequately promote their own and/or the safety and well-being of others.

The risk is generally higher when these illnesses are untreated. Prospective participants treated for any of these illnesses and interested in participating must have the written approval of their treatment provider in order to be eligible. If any of these risks (1-5 above) occur during the study, the participant will be asked to immediately discontinue the sleep restriction, and an alternative treatment not involving sleep restriction will be offered. The participant will also have the option of discontinuing the treatment if they prefer this to proceeding with the alternative treatment which does not involve sleep restriction.

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

TELEPHONE PRE-SCREENING

A) Provide information about the study, what to expect and what is required if participating. Use Informed Consent form as an outline and a reference. Ask if the person has any questions.

B) Assess: Inclusion and Exclusion Criteria
The definition of insomnia will be that of DSM-5.

9.1.1 IN PERSON SCREENING AND DATA GATHERING

Complete diagnostic interview per DSM-5. To be eligible, the person must meet the DSM-5 diagnostic criteria for 780.52 Insomnia Disorder. This includes a cumulative minimum average sum of 30 minutes or more of time spent, adding number of minutes of inability to initiate or return to sleep plus number of minutes of early morning awakening with inability to return to sleep.

If the person does not meet diagnostic criteria, thank them for their interest and inform the person that they are not eligible. Provide the specific reason for ineligibility. For example, the person may not meet one or more required aspect of the diagnostic criteria for Insomnia Disorder per DSM-5.

If the person meets eligibility criteria and DSM-5 diagnostic criteria for insomnia disorder, provide the person with a copy of the Informed Consent form. Have the person follow along as you read the form aloud in their presence.

At the end of this process, if the person is still interested in participating, go through the **Informed Consent Form (ICF) for Participants in Insomnia Study** with the participant.

9.1.2 DSM-5 DIAGNOSTIC SCREENING INTERVIEW

Once the Informed Consent form has been completed, the next step involves a diagnostic interview to assess for Insomnia Disorder. The Research Coordinator reads the bold print script to the prospective participant. See DSM-5 Diagnostic Assessment Interview.

QUESTIONNAIRE AND INVENTORIES

Since this is a clinical research trial, we have a questionnaire and some inventories for you to complete as part of the initial data gathering.

Here is the first one. Give the person the Sleep Measures (SM) questionnaire.

I recommend you use a pencil so you can erase if you make an error. Do you need a pencil?
Be sure the person has a comfortable place to write (a table top, for example).

This is the first one. Go ahead. Take a few minutes to complete it. I'm here if you have any questions.
When the participant has completed the Sleep Measures (SM) questionnaire, check to ensure that all questions have been answered. Be sure questions with numerous options (a-f; -3 to +3; etc.) are clearly answered.

Ask the person to complete the **Insomnia Severity Index (ISI).**

This will give us important information about your insomnia.
When the participant has completed the inventory, check to ensure that all questions have been answered clearly. Check for ISI > or = 10. If not, the person is not eligible. If still eligible, record their score.

Ask the person to complete the **Beck Depression Inventory (BDI).**

Depression may or may not be a factor for you. However, this is a research study, and the researchers want to be able to assess whether the treatment effect differs by level of depression.
When the participant has completed the BDI, check to ensure that all questions have been answered clearly. Check for BDI > or = 29. If so, the person is not eligible. If still eligible, record their score.

Similarly explain and ask the person to complete the **Beck Anxiety Inventory (BAI).** When the participant has completed the BAI, check to ensure that all questions have been answered clearly. Check for BAI > or = 36. If so, the person is not eligible. If still eligible, record their score.

1. **Goal Motivation Scale (GMS)**
2. **Goal Motivation Scale-Insomnia (GMS-I)**
3. **Self-Report Sleep Measures (SRSM)**
4. **Clinical Global Impression (CGI)**
5. **Clinical Global Impression – Severity scale (CGI-S)**
6. **Quality of Life Enjoyment and Satisfaction (Q-LES)**
7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

Give the person an ActiWatch. Ask them to read and sign the ActiWatch Liability Agreement. Ask them to return the Actiwatch on the day of their first scheduled session with their treatment provider.

Explain the treatment scheduling to the participant. Read the following aloud.
It is after your initial meeting with the treatment provider that we will make a final decision about your eligibility. This depends on the ActiWatch data and the opinion of the treatment provider whether you do or do not meet the diagnostic criteria for Insomnia Disorder. I am not a clinician, and therefore I am not qualified to give a diagnosis.

As a participant, if you are eligible after the first session, you will be expected to participate in five additional treatment sessions scheduled weekly on the same day of the week and at the same time each week as was your first session with the treatment provider.

It will be very important that you arrive on time for each of the treatment sessions. If you miss one of the scheduled sessions for any reason, you must reschedule that session with your treatment provider for later that day or on the next day. If not, you will be discontinued from the study. The treatment provider may only be available at certain times, and you will be expected to flex to make up for the session you missed. Only one such rescheduling is allowed.

ASSIGNMENT TO TREATMENT AND SCHEDUILNG
Each participant will be assigned a "Participant Number" (PN). The first seven digits will identify the participant with date of birth followed by the first letter in their first name (given at birth). Digits the first three digits will identify the participant. The first participant assigned a PN will be 001. The second participant assigned a PN will be 002, etc. The 4th digit will identify the participant's gender (M/F). The 5th digit will identify the participant's treatment type [1 = Focus of Attention (FOA); 2 = Cognitive

Behavior Therapy for Insomnia (CBT-I); 3 = Combination of FOA and CBT-I (Combined); and 4 = Placebo (Sleep Hygiene only). Digits 5-6 will identify the primary study staff delivering the treatment. An example might be 01 = Brie Everard.

The Research Coordinator will determine the scheduling.

If you participate, your time commitment will include six one hour appointments with your study staff. These appointments will be on a weekday day, at 11:00am, 12:00 noon or 2:00pm. As a participant, you will be assigned to on weekday for a one hour appointment for six consecutive weeks. Please put an X beside each time that works for you on each day.

Monday @	___ 11:00am;	____ 12:00 noon;	____ 2:00pm
Tuesday @	____ 11:00am;	____ 12:00 noon;	____ 2:00pm
Wednesday @	____ 11:00am;	____ 12:00 noon;	____ 2:00pm
Thursday @	____ 11:00am;	____ 12:00 noon;	____ 2:00p

Treatment providers will be required to declare at least one and preferably two of these times (11am, noon and/or 2pm) as times they will be available to delivery treatment, given two week notice of a participant being assigned. The Research Coordinator will make effort to inform each provider when it is likely they will be assigned a new participant.

The Research Coordinator will inform the treatment provider one week in advance of a probably participant being assigned, also informing the treatment provider of the treatment to be utilized (FOA, CBT-I, Combined and Sleep Hygiene).

The Research Coordinator will keep an Excel spread sheet in order to systematically assign subjects (participants) to treatment. Participants will be randomly assigned to treatment and then assigned to the next treatment provider in a systematic, non-biased manner. The first four treatment providers will be randomly designated by the Research Coordinator as the first, second, third or fourth treatment provider to be assigned the participant. The first participant in the clinical trial will go to the provider declared first to be assigned. The second participant in the clinical trial will go to the provider declared second to be assigned. Similarly for assignment of a participant to the third and fourth provider. The fifth participant will be assigned to the provider who had been randomly designated as the first to be assigned a participant. The assignment will proceed, sixth participant to the provider who had been assigned the second participant in the study, etc. The Research Coordinator will use Excel spread sheet in order to determine which treatment provider is next to be assigned a participant.

At the end of the In Person Screening and Data Gathering, the Research Coordinator will inform the participant of the time and date of their first treatment session and the name of the treatment provider.

The Research Coordinator will direct the participant to arrive a few minutes early and to check in at the front desk in the first floor reception area. The participant will be told to tell the receptionist their name, the name of their treatment provider, and that they are receiving treatment for insomnia in the Insomnia Clinical Research Trial.

The Research Coordinator will schedule the participant with one of the treatment providers. The treatment will be at either 11:00am, 12 noon or 2:00pm depending on which one hour block of time that treatment provider has reserved for treatment delivery. The Research Coordinator will schedule the initial session in Practice Fusion with 5 weekly repeats. The Research Coordinator will then send an email to the treatment provider indicating the name of the client, the time and date on which the first session is scheduled, and the treatment the provider is to deliver (FOA, CBT-I, Combined and Sleep Hygiene).

CLINICAL PROCEDURES

The study staff will follow the six session protocol for treatment delivery. Each of the six sessions is scripted so as to provide standardization, and the study staff will generally be reading the script. The first session is identical across all four treatments. For specifics, see file folders entitled CBT-I, FOA, Combo and Sleep Hygiene.

DATA GATHERING DURING TREATMENT

Ongoing self-report data pertaining to the participant's sleep using a Weekly Sleep Log. Weekly Sleep Logs will be completed by the participant and brought to each treatment session. At the beginning of each session, the study staff will review the Weekly Sleep Log for completion. After the treatment session has ended and during the same day, the study staff will forward the Weekly Sleep Log to the Research Coordinator.

The Research Coordinator will enter the following information onto the DATA SHEET:

1. **SL; Sleep Latency (time to fall asleep in minutes)**
2. **NOA: Number of Awakenings**
3. **WASO: Wake After Sleep Onset (in minutes)**
4. **SL + WASO (in minutes)**
5. **TOB: Total Time Out of Bed in minutes**
6. **TST: Total Sleep Time (in minutes)**
7. **TIB: Time In Bed (total, in minutes)**
8. **SE: Sleep Efficiency = TST/TIB (as a decimal)**

9.1.3 SAFETY FOLLOW UP PERIOD

Coordinated and administered by Research Coordinator. Completed after last treatment session; can be on that day but not before the treatment session; must be no later than one week after that date.

FEEDBACK QUESTIONNAIRE:

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self-Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Quality of Life Enjoyment and Satisfaction (Q-LES)**
8. **Columbia Suicide Severity Rating Scale (C-SSRS)**

THREE MONTH FOLLOW UP:

WEEKLY SLEEP LOG (WSL)

Data entry completed for one week at each administration [At in person intake, each week during treatment and at 3, 6 and 12 months]

[Each of the following is needed for data entry as an average for the last 7 nights]

1. **SL; Sleep Latency (time to fall asleep in minutes)**
2. **NOA: Number of Awakenings**
3. **WASO: Wake After Sleep Onset (in minutes)**
4. **SL + WASO (in minutes)**
5. **TOB: Total Time Out of Bed in minutes**
6. **WASO: Waking Time After Sleep Onset in minutes**
7. **TST: Total Sleep Time (in minutes)**

8. **TIB: Time In Bed (total, in minutes)**
9. **SE: Sleep Efficiency = TST/TIB (as a percentage)**
10. **Beck Depression Inventory (BDI)**
11. **Beck Anxiety Inventory (BAI)**
12. **Insomnia Severity Index (ISI)**
13. **Self-Report Sleep Measures (SRSM)**
14. **Clinical Global Impression (CGI)**
15. **Clinical Global Impression – Severity scale (CGI-S)**
16. **Columbia Suicide Severity Rating Scale (C-SSRS)**

SIX MONTH FOLLOW UP:

This is the same as the THREE MONTH FOLLOW UP except that the following three are added.

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self-Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

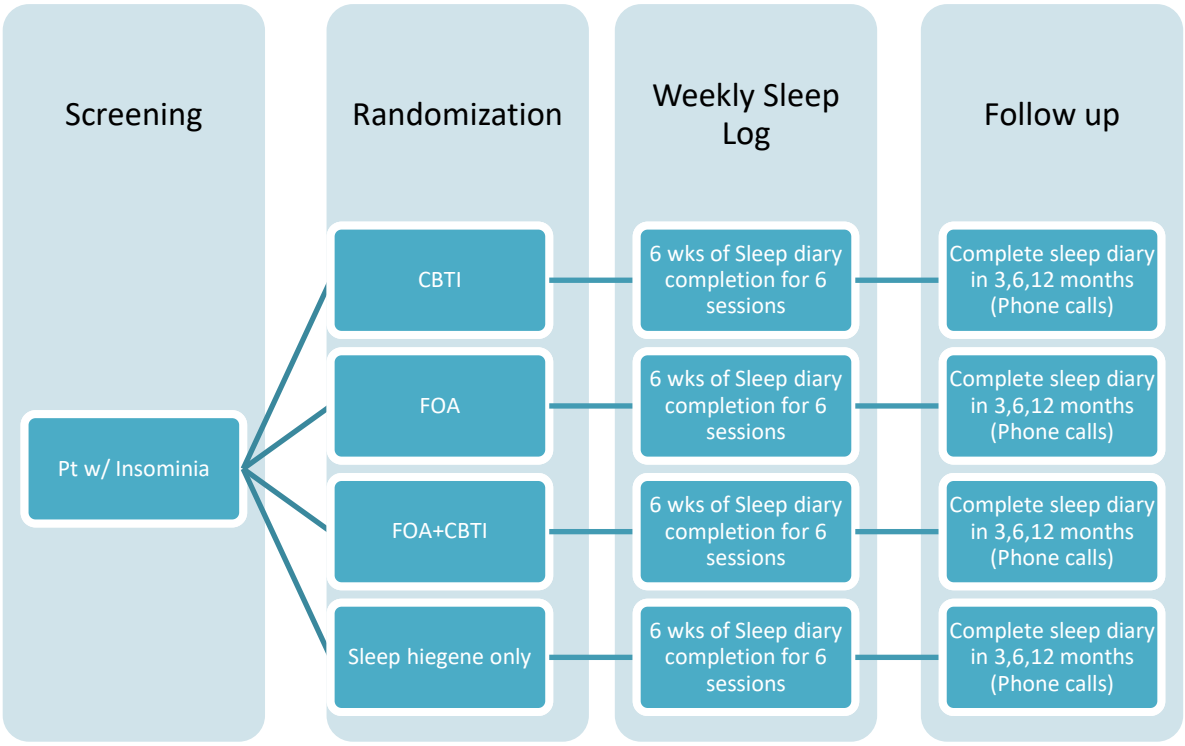
TWELVE MONTH FOLLOW UP:

This is the same as the SIX MONTH FOLLOW UP adding the Feedback Questionnaire.

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self-Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

A schematic of the study design is presented in Figure9.1-1. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit can be found in Section 9.5.6.

FIDURE 9.1-1 **STUDY DESIGN**



9.2 DISCUSSION OF STUDY DESIGN

This is a randomized, open label, sleep hygiene, controlled, 6-week study to compare the efficacy of four (CBT-I, FOA, Combined CBT-I and FOA and Sleep Hygiene) different behavioral approaches for the treatment of adult subjects with insomnia. In this study, investigators will enroll patients, male and female, who are 18 or older to 72 years. Insomnia Severity Index > or = 10 and meet diagnostic criteria for Insomnia Disorder per DSM-5 willing and able to sign Informed consent form not planning on moving away from the area for the subsequent 12 weeks. In this study, safety and efficacy assessments are included during every visit to determine adequacy of response, safety, and tolerability.

9.3 SLECTION OF STUDY POPULATIONS

Inclusion/Exclusion criteria to be assessed at Screening (Visit 1) and Every Visit (Visit 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11)

9.3.1 INCLUSION CRITERIA

All potential participants must meet these inclusion criteria:

1. Both genders
2. Age ≥ 18 to 72 years
3. Insomnia Severity Index > or = 10
4. Meet diagnostic criteria for Insomnia Disorder per DSM-5
5. Be willing and able to sign Informed consent form
6. Not planning on moving away from the area for the subsequent 12 weeks.

9.3.2 EXCLUSION CRITERIA

Participants who answer "yes" to any of the following will be excluded:

1. Females who are lactating or who are pregnant
2. Night shift workers, and individuals who nap 3 or more times per week over the preceding month
3. Consumption of caffeine beverages (i.e. tea, coffee, or cola) comprising usually more than 5 cups or glasses per day
4. Participation in another trial for insomnia
5. Persons unable to complete the study questionnaires and psychological tests
6. Persons who are unable to participate for the entire duration of the study, or in the opinion of the investigators, are likely to be non-compliant with the obligations inherent in the trial participation
7. Persons self-describing with severe anxiety or severe depression
    a. (BDI score of 29 or higher) or severe anxiety (BAI score of 36 or higher).
8. Persons with a history of epilepsy, seizures, or dementia
9. Any significant, severe or unstable, acute or chronically progressive medical or surgical condition
10. Serious head injury or stroke within the past year
11. Current alcohol or substance abuse/dependence (must have >90 days of sobriety)
12. Presence of other neurological disorders (e.g., multiple sclerosis, Parkinson's Disease)
13. Presence of an untreated or unstable medical or psychiatric comorbid condition (e.g., major depressive disorder or psychotic disorder requiring admission within the last two years). People using psychotropic medication, hypnotic or sedative medications may be included if they are on a stable dosage for the last 2 months prior to the study, if the dose remains stable throughout the study, and if the medication is judged to not interfere with the study outcomes.
14. Currently on medications known to produce insomnia (e.g., stimulants)
15. Sleep apnea (AHI >15) or previous diagnosis of. Study participants who use a continuous positive airway pressure (CPAP) device for sleep apnea will be eligible for participation if they are below the apnea/hypopnea cutoff while using CPAP and agree to use the device during study participation.
16. **If the person not eligible** per inclusion and exclusion criteria, thank the person for their interest and inform them that they are not eligible. Also inform the person that regardless, they still have

the option of seeing a health care provider at their own initiative and under whatever financial agreement they may establish with that health care provider (insurance or otherwise).

17. **If the person is eligible** and is interested in being considered, schedule the initial in person screening interview and data gathering.

9.3.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study visits and procedures. Patients can be prematurely discontinued from the study after careful consideration for one of the following reasons:

1. Screen failure (failure to meet inclusion/exclusion criteria or pregnancy)
2. Pregnancy
3. Withdrawal of consent
4. Lack of efficacy
5. Protocol violation
6. Noncompliance with treatment plan
7. Lost to follow-up
8. Study terminated by Sponsor
9. Study center terminated by Sponsor
10. Other

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at an Early Termination (ET) Visit. A final assessment will be defined as completion of the evaluations scheduled for all patients at Visit 8. All patients discontinuing the study prematurely should enter the 1-week safety follow-up period (Visit 8: ET).

Patients who discontinue from the study and do not return to the study center for final assessments must be requested in writing to return to the study center for a final assessment (Visit 8). A copy of the letter, together with the source documentation, will be kept in the Investigator‘s files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study center staff will be contacted by the Sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

9.3.4 PATIENT REPLACEMENT PROCEDURES

Patients in this study who prematurely discontinue treatment will not be replaced.

9.4 TREATMENTS

Patients meeting the eligibility criteria at the end of Visit 2 (Baseline) will be randomized in open label, sleep hygiene controlled 6-week study fashion to compare the efficacy of 1 of 4 treatment groups: CBT-I, FOA, Combined CBT-I and FOA and Sleep Hygiene (Placebo) different behavioral approaches for the treatment of adult subjects with insomnia.

9.4.1 ASSIGNMENT TO TREATMENT AND SCHEDUILNG

Each participant will be assigned a “Participant Number” (PN). The first seven digits will identify the participant with date of birth followed by the first letter in their first name (given at birth). Digits the first three digits will identify the participant. The first participant assigned a PN will be 001. The second participant assigned a PN will be 002, etc. The 4th digit will identify the participant’s gender (M/F). The

5th digit will identify the participant's treatment type [1 = Focus of Attention (FOA); 2 = Cognitive Behavior Therapy for Insomnia (CBT-I); 3 = Combination of FOA and CBT-I (Combined); and 4 = Placebo (Sleep Hygiene only). Digits 5-6 will identify the primary study staff delivering the treatment. An example might be 01 = Brie Everard.

9.4.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

The Research Coordinator will determine the scheduling:
If you participate, your time commitment will include six one hour appointments with your study staff. These appointments will be on a weekday day, at 11:00am, 12:00 noon or 2:00pm. As a participant, you will be assigned to on weekday for a one hour appointment for six consecutive weeks. Please put an X beside each time that works for you on each day.

Monday@	____ 11:00am;	____ 12:00 noon;	____ 2:00pm
Tuesday@	____ 11:00am;	____ 12:00 noon;	____ 2:00pm
Wednesday@	____ 11:00am;	____ 12:00 noon;	____ 2:00pm
Thursday@	____ 11:00am;	____ 12:00 noon;	____ 2:00p

Treatment providers will be required to declare at least one and preferably two of these times (11am, noon and/or 2pm) as times they will be available to delivery treatment, given two week notice of a participant being assigned. The Research Coordinator will make effort to inform each provider when it is likely they will be assigned a new participant.

The Research Coordinator will inform the treatment provider one week in advance of a probably participant being assigned, also informing the treatment provider of the treatment to be utilized (FOA, CBT-I, Combined and Sleep Hygiene).

The Research Coordinator will keep an Excel spread sheet in order to systematically assign subjects (participants) to treatment. Participants will be randomly assigned to treatment and then assigned to the next treatment provider in a systematic, non-biased manner. The first four treatment providers will be randomly designated by the Research Coordinator as the first, second, third or fourth treatment provider to be assigned the participant. The first participant in the clinical trial will go to the provider declared first to be assigned. The second participant in the clinical trial will go to the provider declared second to be assigned. Similarly for assignment of a participant to the third and fourth provider, the fifth participant will be assigned to the provider who had been randomly designated as the first to be assigned a participant. The assignment will proceed, sixth participant to the provider who had been assigned the second participant in the study, etc. The Research Coordinator will use Excel spread sheet in order to determine which treatment provider is next to be assigned a participant.

At the end of the In Person Screening and Data Gathering, the Research Coordinator will inform the participant of the time and date of their first treatment session and the name of the treatment provider.

The Research Coordinator will direct the participant to arrive a few minutes early and to check in at the front desk in the first floor reception area. The participant will be told to tell the receptionist their name, the name of their treatment provider, and that they are receiving treatment for insomnia in the Insomnia Clinical Research Trial.

The Research Coordinator will schedule the participant with one of the treatment providers. The treatment will be at either 11:00am, 12 noon or 2:00pm depending on which one hour block of time that treatment provider has reserved for treatment delivery. The Research Coordinator will schedule the initial session in Practice Fusion with 5 weekly repeats. The Research Coordinator will then send an email to the treatment

provider indicating the name of the client, the time and date on which the first session is scheduled, and the treatment the provider is to deliver (FOA, CBT-I, Combined and Sleep Hygiene).

9.4.3 CLINICAL PROCEDURES

The study staff will follow the six session protocol for treatment delivery. Each of the six sessions is scripted so as to provide standardization, and the study staff will generally be reading the script. The first session is identical across all four treatments. For specifics, see file folders entitled CBT-I, FOA, Combo and Sleep Hygiene.

9.4.4 DATA GATHERING DURING TREATMENT

Ongoing self-report data pertaining to the participant's sleep using a Weekly Sleep Log. Weekly Sleep Logs will be completed by the participant and brought to each treatment session. At the beginning of each session, the study staff will review the Weekly Sleep Log for completion. After the treatment session has ended and during the same day, the study staff will forward the Weekly Sleep Log to the Research Coordinator.

The Research Coordinator will enter the following information onto the DATA SHEET:

1. **SL; Sleep Latency (time to fall asleep in minutes)**
2. **NOA: Number of Awakenings**
3. **WASO: Wake After Sleep Onset (in minutes)**
4. **SL + WASO (in minutes)**
5. **TOB: Total Time Out of Bed in minutes**
6. **TST: Total Sleep Time (in minutes)**
7. **TIB: Time In Bed (total, in minutes)**
8. **SE: Sleep Efficiency = TST/TIB (as a decimal)**

9.4.5 END OF TREATMENT

SAFETY FOLLOW UP PERIOD

Coordinated and administered by Research Coordinator. Completed after last treatment session; can be on that day but not before the treatment session; must be no later than one week after that date.

FEEDBACK QUESTIONNAIRE:

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Quality of Life Enjoyment and Satisfaction (Q-LES)**
8. **Columbia Suicide Severity Rating Scale (C-SSRS)**

THREE MONTH FOLLOW UP:

WEEKLY SLEEP LOG (WSL)

Data entry completed for one week at each administration [At in person intake, each week during treatment and at 3, 6 and 12 months]

[Each of the following is needed for data entry as an average for the last 7 nights]

1. **SL; Sleep Latency (time to fall asleep in minutes)**
2. **NOA: Number of Awakenings**
3. **WASO: Wake After Sleep Onset (in minutes)**
4. **SL + WASO (in minutes)**

5. **TOB: Total Time Out of Bed in minutes**
6. **WASO: Waking Time After Sleep Onset in minutes**
7. **TST: Total Sleep Time (in minutes)**
8. **TIB: Time In Bed (total, in minutes)**
9. **SE: Sleep Efficiency = TST/TIB (as a percentage)**
10. **Beck Depression Inventory (BDI)**
11. **Beck Anxiety Inventory (BAI)**
12. **Insomnia Severity Index (ISI)**
13. **Self Report Sleep Measures (SRSM)**
14. **Clinical Global Impression (CGI)**
15. **Clinical Global Impression – Severity scale (CGI-S)**
16. **Columbia Suicide Severity Rating Scale (C-SSRS)**

SIX MONTH FOLLOW UP:

This is the same as the THREE MONTH FOLLOW UP except that the following three are added.

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

TWELVE MONTH FOLLOW UP:

This is the same as the SIX MONTH FOLLOW UP adding the Feedback Questionnaire.

1. **Beck Depression Inventory (BDI)**
2. **Beck Anxiety Inventory (BAI)**
3. **Insomnia Severity Index (ISI)**
4. **Self Report Sleep Measures (SRSM)**
5. **Clinical Global Impression (CGI)**
6. **Clinical Global Impression – Severity scale (CGI-S)**
7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

A schematic of the study design is presented in Figure 9.1-1. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit can be found in Section 9.5.3.

9.4.6 SELECTION AND TIMING OF SIX SESSION TREATMENT FOR EACH PATIENT

The study staff will follow the six sleep hygiene treatment session at visits 2, 3, 4, 5, 6 and 7. Each of the six sessions is scripted so as to provide standardization, and the study staff will generally be reading the script. The first session is identical across all four treatments. For specifics, see file folders entitled CBT-I, FOA, Combo and Sleep Hygiene.

9.4.6.1 SCREENING PERIOD

At Screening (Visit 1) after written consent is obtained, patients enter a screening period of up to 14 days. No treatment is administered during the screening period.

9.4.6.2 RANDAMIZATION OPEN LABEL SLEEP HYGIENE CONTROLLED SIX WEEK STUDY TREATMENT PERIOD

Patients who meet all eligibility criteria at Screening (Visit 1) and who continue to meet all the eligibility criteria for participation in the study at the Baseline Visit (Visit 2) will be assigned a "Participant Number" (PN). The first seven digits will identify the participant with date of birth followed by the first letter in their first name (given at birth). Digits the first three digits will identify the participant. The first participant assigned a PN will be 001. The second participant assigned a PN will be 002, etc. The 4th digit will identify the participant's gender (M/F). The 5th digit will identify the participant's treatment type [1 = Focus of Attention (FOA); 2 = Cognitive Behavior Therapy for Insomnia (CBT-I); 3 = Combination of FOA and CBT-I (Combined); and 4 = Placebo (Sleep Hygiene only). Digits 5-6 will identify the primary study staff delivering the treatment. An example might be 01 = Brie Everard.

9.4.6.3 SAFETY FOLLOW-UP PERIOD

Patients who complete 6 weeks of randomized, open label sleep hygiene controlled treatment are eligible to enter the safety follow-up period. Patients who discontinue the study prematurely should also enter the safety follow-up period. No sleep hygiene treatment session is administered during the safety follow-up period.

9.4.7 CONCOMITANT MEDICATIONS

A list of example medications as concomitant medications is provided in Appendix III. Medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or any new medications added will be recorded in the eCRF.

9.4.7.1 PERMITED MEDICATIONS/TREATMENTS

Therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor.

FOR INSOMNIA:

Eszopiclone, zolpidem, zolpidem extended-release, zopiclone or zaleplon for insomnia may be continued provided the medication has been used in a consistent manner for **4 weeks prior to enrollment.** Following enrollment, these medications may also be introduced in patients not previously treated as necessitated by insomnia that emerges or worsens during the study.
In these patients, **the medications will be permitted up to 3 times a week at the following doses (not permitted within 8 hours of efficacy measures):**

1. Zolpidem (maximum of 10 mg/day)
2. Zolpidem extended release (maximum of 12.5 mg/day)
3. Zaleplon (maximum of 20 mg/day)
4. Eszopiclone (maximum of 3 mg/day)
5. Zopiclone (maximum of 7.5 mg/day)
6. Suvorexant (maximum of 10 mg/day)

These medications must be administered before bedtime as recommended in their prescribing information. **The medication must be documented on the concomitant medications page of the eCRF. No such medication is permitted within 8 hours of psychiatric or neurological assessments.**

FOR ANXIETY OR AGITATION:
Episodic use of benzodiazepines up to approximately 2 mg/day lorazepam equivalent dose and for up to 3 consecutive days at a time **may** be given for anxiety-related conditions and agitation (**not permitted within 8 hours of efficacy assessments**).

9.4.7.2 PROHIBITED MEDICATIONS/TREATMENTS

The decision to administer a prohibited medication/treatment is done with the safety of the patient as the primary consideration. When possible, the Sponsor should be notified before the prohibited medication/treatment is administered.

The following medications are prohibited:

1. Antipsychotics
2. Antidepressants
3. Stimulants
4. Anticonvulsants/mood stabilizers
5. Dopamine-releasing drugs or dopamine agonists
6. Psychotropic drugs not otherwise specified (including herbal products and certain nutritional supplements)

Appropriate washout of prohibited medications is to be conducted at the discretion of the Investigator and should begin as soon as practical following consent and screening.

9.4.8 OTHER RESTRCTIONS

9.4.8.1 ALCOHOL

It is recommended that patients abstain from alcohol consumption during the study.

9.4.9 MONITORING TREATMENT COMPLIANCE

Six Week treatment session compliance during any period will be closely monitored by capturing the date and time of each visit. If a scheduled visit does not occur, the Sponsor must be notified and the reason captured in the eCRF.

9.4.10 TREATMENT AFTER DISCONTINUATION

Patients whose sleep symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the randomization six week study period will be allowed to discontinue the study and start appropriate treatment at the Investigator‘s discretion. This new treatment will not be provided by the Sponsor. Patients who initiate a new treatment must be discontinued from the study.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 DIAGNOSTIC AND EFFICACCY ASSESSMENTS

9.5.1.1 DIAGNOSTIC ASSESSMENTS

Complete diagnostic interview per DSM-5. To be eligible, the person must meet the DSM-5 diagnostic criteria for 780.52 Insomnia Disorder. This includes a cumulative minimum average sum of 30 minutes or more of time spent, adding number of minutes of inability to initiate or return to sleep plus number of minutes of early morning awakening with inability to return to sleep.
If the person does not meet diagnostic criteria, thank them for their interest and inform the person that they are not eligible. Provide the specific reason for ineligibility. For example, the person may not meet one or more required aspect of the diagnostic criteria for Insomnia Disorder per DSM-5.
If the person meets eligibility criteria and DSM-5 diagnostic criteria for insomnia disorder, provide the person with a copy of the Informed Consent form. Have the person follow along as you read the form aloud in their presence.
At the end of this process, if the person is still interested in participating, go through the **Informed Consent Form for Participants in Insomnia Study** with the participant.

9.5.1.2 EFFICACY ASSESMENTS

The efficacy assessments (CGI -S) will be administered by a psychiatrist, doctoral level clinical psychologist, or other study staff who has extensive professional training and experience in the diagnosis of mental illness and who meets the training requirements and qualifications standards set by the Sponsor.

9.5.1.3 THE CLINICAL GLOBAL IMPRESSIONS-SEVERITY

The CGI-S (Guy, 1976) is a clinician-rated scale used to rate the severity of the patient‘s current state of mental illness compared with a patient population with MDD. The patient will be rated on a scale from 1 to 7 with 1 indicating a —normal**, "not at all ill"** and 7 indicating —among the most extremely ill patients.“ The CGI-S will be administered by the Investigator or a sub-investigator with extensive professional training and experience in assessing mental illness and qualifications standards set by the Sponsor and rater training vendor.

9.5.2 SAFETY ASSESMENTS

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented.

9.5.2.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).
For the purpose of the study center‘s data collection responsibilities, any untoward event that was reported from the time the patient signed the ICF until 30 days after the final protocol-defined study visit or the last known dose of IP (if the final visit does not occur) is to be considered an AE.

EXAMPLES OF AEs ARE AS FOLLOWS:

1. Changes in the general condition of the patient
2. Subjective symptoms offered by or elicited from the patient
3. Objective signs observed by the Investigator or other study center personnel
4. All diseases that occur after signing informed consent, including any change in severity or frequency of pre-existing disease
5. All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

9.5.2.2 CAUSALITY ASSESSMENT

The causality assessment must be recorded on the appropriate AE reporting page of the patient‘s eCRF.
Causal relationship must be assessed by answering the following question:
Is there a reasonable possibility the **sleep study treatment** caused the event?

Yes: There is evidence to suggest a causal relationship between the sleep study treatment and AE, i.e.:

1. There is a reasonable temporal relationship between the IP and the event, and/or
2. The event is unlikely to be attributed to underlying/concurrent disease or other factors, and/or
3. Positive de-challenge and/or re-challenge exist

No: There is no evidence to suggest a causal relationship between the sleep study treatment and AE, i.e.:

1. There is no reasonable temporal relationship between the IP and the event, or
2. The patient did not take the IP, or
3. The event is likely to be attributed to underlying/concurrent disease or other factors, or
4. The event is commonly occurring in the (study) population independent of IP exposure

9.5.2.3 SEVERITY ASSESMENT

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient‘s eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4).
Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.5.2.4 SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose:

1. Results in death
2. Is life threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity, or
5. Is a congenital anomaly/birth defect

Important medical events that may not result in death, belief threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of IP dependency or drug abuse.
Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.
Preplanned hospitalizations (e.g, elective procedures for pre-existing conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.5 REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a non leading question such as, —How do you feel since your last visit?“ Study center personnel will record all pertinent information in the patient‘s eCRF. All AEs must be recorded on the appropriate AE reporting page of the patient‘s eCRF whether or not they are considered causally related to the sleep study treatment..
For every AE, the Investigator must:

1. Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and casual relationship
2. Document all actions taken with regard to the IP
3. Detail any other treatment measures taken for the AE
4. Document the outcome of the AE

In addition, patients are to be reminded, as described in the ICF and in accordance with Section 9.5.2.1, to notify study center personnel of any AEs occurring during the 30-day poststudy period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least one of the following conditions is met: 1) the event meets the criteria for an SAE (see Sections 9.5.2.4 and 9.5.2.5), and/or 3) the event is judged by the Investigator to be potentially causally related to sleep study treatment.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to the sleep study treatment. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

9.5.2.6 COLUMBIA SUICIDE SEVERITY RATING SCALE

The C-SSRS is an instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS will be completed at all study visits. At Screening (Visit 1), the C-SSRS will be completed for the patient‘s lifetime history of suicidal ideation and behavior (Appendix X). At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit (Appendix XI). The C-SSRS will be evaluated and signed at each visit by a qualified staff member (i.e, the Investigator or designee that has extensive professional training and experience in assessing mental illness), before the patient leaves the study center.

9.5.3 SCHEDUAL OF ASSESSMENT

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0. The descriptions of the procedures to be performed at each visit are provided in the following sections. Upon providing written informed consent, patients enter a screening period of up to 14 days. Following the screening period, patients enter the randomized, open label , sleep hygiene controlled six- week study to compare the efficacy of four (CBT-I, FOA, Combined CBT-I and FOA and Sleep Hygiene) different behavioral approaches for the treatment of adult subjects with insomnia.

9.5.3.1 Visit 1 (Screening)

At Screening (Visit 1), study procedures will be reviewed with the patient, and documentation of informed consent will be obtained (Section 5.3). After informed consent is obtained, patients will be assigned a unique “Participant Number” (PN) (Section 5.0). A review of inclusion/exclusion criteria and other screening assessments will be conducted to determine the patient‘s eligibility for enrollment (Sections 9.3.1 and 9.3.2).

At Screening (Visit 1), the following procedures will also be performed:

1. Obtain and record medical (surgical, neurological), psychiatric history
2. Obtain and record prior medication history, nondrug psychiatric treatment history, and current medication status
3. Review of all inclusion/exclusion criteria
4. Administer ISI (Insomnia Severity Index)
5. Administer BAI (Beck Anxiety Inventory)
6. Administer BDI (Beck Depression Inventory)
7. Administer SRSM (Self Report Sleep Measures)
8. Administer WSL (Weekly Sleep Log

9. Administer CGI-S (Clinical Global Impression –Severity Scale)
10. Administer CGI (Clinical Global Impression)
11. Administer Q-LES (Quality of Life Enjoyment and Satisfaction)
12. Administer C-SSRS (Columbia-*Suicide* Severity Rating *Scale*)
13. Review concomitant medications

Schedule Visit 2 up to 14 days after Visit 1

9.5.3.2 Visit 2 (or Baseline Visit)

The Baseline Visit 2 will be conducted up to 14 days after Screening (Visit 1) to determine whether the patient is eligible to continue into the randomization, open label, sleep hygiene controlled 6 week study treatment period.

At the visit 2, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale*)*
6. Review and record AEs
7. Eligible patients will be assigned an "Participant Number" (PN).

Administer Randomization (must occur after all efficacy and safety assessments)
Schedule Visit 3

9.5.3.3 Visit 3

At Visit 3, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale*)*
6. Review concomitant medications

Schedule Visit 4

9.5.3.4 Visit 4

At Visit 4, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)
6. Review concomitant medications

Schedule Visit 5

9.5.3.5 Visit 5

At Visit 5, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)
6. Review concomitant medications

Schedule Visit 6

9.5.3.6 Visit 6

At Visit 6, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)
6. Review concomitant medications

Schedule Visit 7

9.5.3.7 Visit 7

At Visit 7, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer SRSM (Self Report Sleep Measures)
3. Administer CGI-S (Clinical Global Impression –Severity Scale)
4. Administer CGI (Clinical Global Impression)
5. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)
6. Review concomitant medications

Schedule Visit 8 (Follow up Period)

9.5.3.8 Visit 8 (1 Week Follow up Period)

At Visit 8, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer ISI (Insomnia Severity Index)
3. Administer BAI (Beck Anxiety Inventory)
4. Administer BDI (Beck Depression Inventory)
5. Administer SRSM (Self Report Sleep Measures)
6. Administer WSL (Weekly Sleep Log
7. Administer CGI-S (Clinical Global Impression –Severity Scale)
8. Administer CGI (Clinical Global Impression)
9. Administer Q-LES (Quality of Life Enjoyment and Satisfaction)
10. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)

Schedule Visit 9 (3 Months Follow up Period)

9.5.3.9 Visit 9 (3 Months Follow up Period)

At Visit 9, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria

2. Administer ISI (Insomnia Severity Index)
3. Administer BAI (Beck Anxiety Inventory)
4. Administer BDI (Beck Depression Inventory)
5. Administer SRSM (Self Report Sleep Measures)
6. Administer WSL (Weekly Sleep Log
7. Administer CGI-S (Clinical Global Impression –Severity Scale)
8. Administer CGI (Clinical Global Impression)
9. Administer C-SSRS (Columbia-Suicide Severity Rating Scale)

Schedule Visit 10 (6 Months Follow up Period)

9.5.3.10 Visit 10 (6 Months Follow up Period)

At Visit 10, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer ISI (Insomnia Severity Index)
3. Administer BAI (Beck Anxiety Inventory)
4. Administer BDI (Beck Depression Inventory)
5. Administer SRSM (Self Report Sleep Measures)
6. Administer WSL (Weekly Sleep Log
7. Administer CGI-S (Clinical Global Impression –Severity Scale)
8. Administer CGI (Clinical Global Impression)
9. Administer C-SSRS (Columbia-Suicide Severity Rating Scale*)*

Schedule Visit 11 (12 Months Follow up Period)

9.5.3.11 Visit 11 (12 Months Follow up Period)

At Visit 11, the following procedures will be performed:

1. Review of all inclusion/exclusion criteria
2. Administer ISI (Insomnia Severity Index)
3. Administer BAI (Beck Anxiety Inventory)
4. Administer BDI (Beck Depression Inventory)
5. Administer SRSM (Self Report Sleep Measures)
6. Administer WSL (Weekly Sleep Log
7. Administer CGI-S (Clinical Global Impression –Severity Scale)
8. Administer CGI (Clinical Global Impression)
9. Administer C-SSRS (Columbia-Suicide Severity Rating Scale*)*

Any clinical findings obtained during the Follow-up Visit will be followed until the condition returns to pre-study status, has resolved or stabilized, or can be explained as being unrelated to sleep study treatment. A follow-up visit, if one should be necessary, will take place within 7 days of sleep study treatment termination.

9.5.3.12 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the Investigator. Additional examinations may be performed as necessary to ensure the safety and well-being of the patients during the study.

9.6 DATA QUALITY ASSURANCE

9.6.1 DATA MONITORING

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study center staff to review the procedures to be followed during the study. Manual data capture (MDC) functionality training is provided via computer-based training to train investigators and authorized designees on recording the data in the eCRFs using the MDC system. After the first patient is enrolled, the Sponsor representative, a Regional Site Manager or designee, will periodically monitor the progress of the study by conducting on-site visits. This Regional Site Manager or designee will review query status remotely, possibly warranting more frequent communication and/or study center visits with the Investigator and the study center staff. The Investigator will make available to the Regional Site Manager or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study center staff will be responsible for data entry of patient data into the eCRFs via the MDC system, resolving data queries generated via the MDC system and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the MDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 DATA RECORDING AND DOCUMENTATION

Data collection will involve the use of the MDC (Manual data capture) system, to which only authorized personnel will have access. Patient‘s data are to be entered into the MDC system by the Investigator or designee using their assigned MDC user account. After data entry into the MDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edit checks, data monitoring, and reviews, queries may be electronically issued to the study center and should be answered electronically via the MDC system. Each query will carry identifying information (assigned username, date, and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient‘s data via a data query will be approved by the Investigator prior to final database lock.
After all data have been reviewed and all issues have been resolved, the database will be locked. All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g, copies of eCRFs, laboratory reports, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, the FDA, or other health authorities.

9.6 STATISTICAL METHODS AND DETERMINATION OF SMAPLE SIZE

9.7.1 SAMPLE SIZE

It is estimated that 320 prospects will need to be screened in order to have 40 per group for a total of 160 participants.

9.7.2 ANALYSIS POPULATIONS

1. **Safety Population:** will include all randomized subjects who meet eligibility criteria and meet with their treatment provider for session 1.

2. **Intent-to-Treat Population:** will include all subjects who meet with their treatment provider for session 1 and for whom the treatment provider determines the subject meets diagnostic criteria for 780.52 Insomnia Disorder.
3. **Pre-Protocol (PP) Population:** will include all subjects who complete the 6 sessions of treatment as well as the 3 month, 6 month and 12 month follow up assessment. It is estimated that 80% of those who complete session 1 will complete session 6. It is estimated that 80% of those who complete session 6 will complete the 3 month, 6 month and 12 month follow up assessments. This will result in 25 participants who will have completed the entire study.

9.7.3 SAFAETY PARAMETERS

Safety parameters comprise the C-SSRS.
The number and percentage of patients with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the patient's lifetime, during the treatment period, and during the safety follow-up period will also be presented by treatment group for the Safety Population. Supportive listings will be provided and will include the "Participant Number" (PN), lifetime history, and post baseline values. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in patients who have suicidal ideation or suicidal behavior will also be provided.

9.7.4 COMPUTER METHODS

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

9.8 DATA AND SAFETY MONITORING BOARD

The study will be conducted under the supervision of an independent DSMB to be chartered to review safety data at predetermined points during the study. The DSMB may also decide to meet and review safety data at other time points should it be deemed necessary. The DSMB is responsible for the ongoing review of safety data in the clinical study and for making recommendations concerning the continuation, modification, and termination of the study (FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006). All analyses that are required to support the DSMB will be performed by an independent unblinded statistician not otherwise involved in the study. Details of the DSMB membership, meeting schedule, and data review and analysis will be documented in the DSMB Charter.
Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB, and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 CHANGES IN THE COUNDUCT OF THE STUDY OR PLANNED ANALYSIS

Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB, and the signature page, signed by the Investigator, has been received by the Sponsor. If the

protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.10 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, duration of treatment, failure to perform the required assessments at specified time points, scheduling of visits not in accordance with specifications, or patient safety. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the Sponsor.
Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.
An important protocol deviation is a form of protocol deviation that has a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Important protocol deviations must be reported to the Sponsor within 24 hours, if possible. The IRB must be notified within the time period dictated by the IRB associated with this study.

10.0 STUDY SPONSORSHIP

This study is sponsored by Puget Sound Psychiatry Center (PSPC) Bothell, WA.

10.1 STUDY TERMINATION

The Sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 REPORTING AND PUBLICATION

All data generated in this study are the property of the Sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and the Sponsor and will follow the Sponsor' Standard Operating Procedure on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must provide the following to the Sponsor before the start of the study:

1. A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA

2. A fully executed contract.

3. The curricula vitae for the Investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician‘s license.

4. A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1.

5. A copy of the IRB-approved ICF

6. A copy of the HIPAA authorization form, or other local privacy applicable forms

7. A list of the IRB members or the US Department of Health and Human Services general assurance number

8. A copy of the laboratory certifications and reference ranges

9. The Investigator‘s Statement page in this protocol, signed and dated by the Investigator

10. Financial disclosure agreement, completed and signed by the Investigator and all sub-investigators listed on Form FDA 1572. The Investigator and all sub-investigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.

11.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the supplies (ActiWatch, Computers and Scales) are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or sub-investigators. The supplies must be stored in a secured place and must be locked. The Investigator must maintain adequate records documenting the receipt of all study supplies. The Sponsor will supply forms on which to record the date of the supplies was received and all unused supplies must be returned to the Sponsor.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by the Sponsor through the MDC (Manual data capture) system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by signing the completed eCRF casebook submitted to the Sponsor. The Investigator must maintain and retain accurate documentation that supports the information entered into the MDC system for source document verification and possible regulatory inspection.

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, regulatory documents, calibration logs, or reports and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-

rays, and ECGs) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period. The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and "Participant Number" (PN). Patient's names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the "Participant Number" (PN) and the full name, address, and telephone number.

12.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol (PSPC-17-01, Dated:) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Investigator's Name

13.0 APPENDICES

APPENDIX I ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained for each patient participating in a clinical research study. This consent must include the following items:

1. A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient‘s participation
2. A description of any reasonably foreseeable risks or discomforts to the patient
3. A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence).
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
5. A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA, the Sponsor, the IRB, or an authorized contract research organization may inspect the records
6. For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
7. An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient‘s rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required.)
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled
9. A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
10. The expected circumstances for which the patient‘s participation may be terminated by the Investigator without regard to the patient‘s consent
11. Any additional costs to the patient that may result from participation in the research

12. The consequences of a patient‘s decision to withdraw from the research and procedures for an orderly termination of the patient‘s participation
13. A statement that significant new findings developed during the course of the research that may relate to the patient‘s willingness to continue participation will be provided to the patient
14. The approximate number of patients involved in the study
15. A statement of permission, providing consent for the patient to participate (eg, —I agree to participate . . .“)
16. A place for the patient‘s signature and date of signing of the ICF

A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient.

APPENDIX II CONTACT INFORMATION

Contact information for the Sponsor personnel is maintained in the Study Reference Manual.

APPENDIX III CONCOMITANT MEDICATIONS

Medications which are considered necessary for the patient's welfare may be given at the discretion of the Investigator. If the permissibility of a specific medication/treatment is in question, please contact the Medical Director.

Concomitant Medications
Date of Visit:__/__/___ Patient Initials:_____ Subject Number:_____

Note: if yes is not checked, patient is not taking listed medication/nutrient

Nutrient	Consumed 2 weeks prior to randomization?	Date Consumed
CYP3A4 Modulators (e.g. grapefruit juice, St John's Wort)	□ Yes □ No	

Common Concomitant Medications (these are examples, not a complete list)

Drug	Currently Taking?	Dosage (if yes)	Indication
Barbiturates (ex. Phenobarbital)	□ Yes □ No		
Carbamazepine (ex. Tegretol)	□ Yes □ No		
Erythromycin (ex. Erythrocin, EES)	□ Yes □ No		
Valproic acid (ex. Depakote, Valparin)	□ Yes □ No		
Oxcarbazepine (ex. Trileptal)	□ Yes □ No		

Other Concomitant Medications (these are examples of CYP3A4 inhibitors/inducers)

Drug	Currently Taking?	Dosage (if yes)	Indication
Amiodarone (ex. Cordarone, Pacerone)	□ Yes □ No		
Amprenavir (ex. Agenerase)	□ Yes □ No		
Aprepitant (ex. Cordarone)	□ Yes □ No		
Atazanavir (ex. Reyataz)	□ Yes □ No		
Buspirone	□ Yes □ No		
Chloramphenicol (ex. Chloromycetin, Chlorsig)	□ Yes □ No		
Cimetidine (ex. Tagamet)	□ Yes □ No		
Ciprofloxacin (ex. Ciloxan, cipro)	□ Yes □ No		

Clarithromycin (ex Crixan, Biaxin)	□ Yes □ No		
Clozapine	□ Yes □ No		
Cyclosporine (Neoral, Sandimmune)	□ Yes □ No		
Delavirdine (ex Rescriptor)	□ Yes □ No		
Diethyl-Dithiocarbamate	□ Yes □ No		
Diltiazem (ex Cardizem, Dilacorxr)	□ Yes □ No		
Desmopressin (DDAVP)	□ Yes □ No		
Dexamethasone (ex decadron)	□ Yes □ No		
Efavirenz (ex. Sustiva)	□ Yes □ No		
Fluconazole (ex. Diflucan)	□ Yes □ No		
Fluvoxamine (ex Luvox)	□ Yes □ No		
Fosamprenavir (ex Lexiva)	□ Yes □ No		
Gestodene	□ Yes □ No		
Glucocorticoids (ex Cortisol) chronic use	□ Yes □ No		
Imatinib (ex Gleevec)	□ Yes □ No		
Indinavir (ex. Crixivan)	□ Yes □ No		
Itraconazole	□ Yes □ No		
Ketoconazole (ex Feoris, Nizoral)	□ Yes □ No		
Lithium	□ Yes □ No		
Mibefradil (ex Posicor)	□ Yes □ No		
Modafinil (ex Provigil, Alertec, Modavigil)	□ Yes □ No		
Nefazodone (Serzone, Nefadar)	□ Yes □ No		
Nelfinavir (ex Viracept)	□ Yes □ No		
Norfloxacin (ex Noroxin)	□ Yes □ No		
Nevirapine (ex Viramune)	□ Yes □ No		
Oxytocin	□ Yes □ No		
Phenytoin (ex. Dilantin)	□ Yes □ No		
Pioglitazone (ex Actos, Glustin)	□ Yes □ No		
Pregabalin	□ Yes □ No		
Ritonavir (ex Norvir)	□ Yes □ No		
Rifabutin (ex Mycobutin)	□ Yes □ No		
Rifampin (ex Rifadin)	□ Yes □ No		
Saquinavir (ex Invirase)	□ Yes □ No		
St John's Wort	□ Yes □ No		
Telithromycin (ex Ketek)	□ Yes □ No		
Troleandomycin (ex Triocetin)	□ Yes □ No		
Troglitazone (ex Rezulin, Resulin or Romozin)	□ Yes □ No		
Verapamil (ex Isoptin, Verelan, Calan, Bosoptin)	□ Yes □ No		
Voriconazole (ex Vfend)	□ Yes □ No		

APPENDIX IV **Beck Depression Inventory (BDI)**

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick the one statement in each group which best describes the way you have been feelings the PAST WEEK, INCLUDING TODAY. Circle the number beside the statement you picked. Be sure to read all the statements in each group before making your choice.

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

Sadness
0. I do not feel sad.
1. I feel sad much of the time.
2. I am sad all of the time.
3. I am so sad or unhappy that I can't stand it.

Pessimism
0. I am not discouraged about my future.
1. I feel more discouraged about my future than I used to be.
2. I do not expect things to work out for me.
3. I feel my future is hopeless and will only get worse.

Past Failure
0. I do not feel like a failure.
1. I have failed more than I should have.
2. As I look back I see a lot of failures.
3. I feel I am a total failure as a person.

Loss of Pleasure
0. I get as much pleasure as I ever did from the things I enjoy.
1. I don't enjoy things as much as I used to.
2. I get very little pleasure from the things I used to enjoy.
3. I can't get any pleasure from the things I used to enjoy.

Guilty Feelings
0. I don't feel particularly guilty.
1. I feel guilty over many things I have done or should have done.
2. I feel guilty most of the time.
3. I feel guilty all of the time.

Punishment Feelings
0. I don't feel like I am being punished.
1. I feel I may be punished.
2. I expect to be punished.
3. I feel I am being punished.

Self-Dislike
0. I feel the same about myself as ever.
1. I have lost confidence in myself.
2. I am disappointed in myself.
3. I dislike myself.

Self-Criticalness
0. I don't criticize or blame myself more than usual.
1. I am more critical of myself than I used to be.
2. I criticize myself for all of my faults.
3. I blame myself for everything bad that happens.

Suicidal Thoughts or Wishes
0. I don't have any thoughts of killing myself.
1. I have thoughts of killing myself, but I would not carry them out.
2. I would like to kill myself.
3. I would kill myself if I had the chance.

Crying
0. I don't cry anymore than I used to.
1. I cry more than I used to.
2. I cry over every little thing.
3. I feel like crying, but I can't.

Agitation
0. I am no more restless or wound up than usual.
1. I feel more restless or wound up than usual.
2. I am so restless or agitated that it's hard to stay still.
3. I am so restless or agitated that I have to keep moving or doing something.

Loss of Interest
0. I have not lost interest in other people or activities.
1. I am less interested in other people or things than before.
2. I have lost most of my interest in other people or things.
3. It's hard to get interested in anything.

Indecisiveness
0. I make decisions about as well as ever.
1. I find it is more difficult to make decisions than usual.
2. I have much greater difficulty in making decisions than I used to.
3. I have trouble making any decisions.

Worthlessness
0. I do not feel I am worthless.
1. I don't consider myself as worthwhile and useful as I used to.
2. I feel more worthless as compared to other people.
3. I feel utterly worthless.

Loss of Energy
0. I have as much energy as ever.
1. I have less energy than I used to have.
2. I don't have enough energy to do very much.
3. I don't have enough energy to do anything.

Changes in Sleeping Pattern
0. I have not experienced any change in my sleeping pattern.
1. I sleep somewhat less than usual –or– I sleep a lot more than usual.
2. I sleep a lot less than usual –or– I sleep a lot more than usual.
3. I sleep most of the day –or– I wake up 1-2 hours early and can't get back to sleep.

Irritability
0. I am no more irritable than usual.
1. I am more irritable than usual.
2. I am much more irritable than usual.
3. I am irritable all the time.

Changes in Appetite
0. I have not experienced any change in my appetite.
1. My appetite is somewhat less than usual –or– My appetite is somewhat greater than usual.
2. My appetite is much less than usual –or– My appetite is much great than usual.
3. I have no appetite at all –or– I crave food all the time.

Concentration Difficulty
0. I can concentrate as well as ever.
1. I can't concentrate as well as usual.
2. It's hard to keep my mind on anything for very long.
3. I find I can't concentrate on anything.

Tiredness of Fatigue
0. I am no more tired or fatigued than usual.
1. I get more tired or fatigued more easily than usual.
2. I am too tired or fatigued to do a lot of the things I used to do.
3. I am too tired or fatigued to do most of the things I used to do.

Loss of Interest in Sex

0. I have not noticed any recent change in my interest in sex.
1. I am less interested in sex than I used to be.
2. I am much less interested in sex now.
3. I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean that you circled zero on each question. You can evaluate your depression according to the Table below.

Total Score	Levels of Depression
1–10	These ups and downs are considered normal
11–16	Mild mood disturbance
17–20	Borderline clinical depression
21–30	Moderate depression
31–40	Severe depression
Over 40	Extreme depression

APPENDIX V Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not At All	Mildly, but it didn't bother me much.	Moderately – it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of the worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/ lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring – Sum each column. Then sum the column totals to achieve a grand score. Write that score here - _____.

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little anxiety could indicate that you are detached from yourself, others, or your environment.

A grand sum between **22 – 35** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time but you want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a physician or counselor if the feelings persist.

APPENDIX VI Goal Motivation Scale

The following three statements are followed by a visual scale in which
0 = “Strongly Disagree” and 9 = “Strongly Agree.” Place a mark on the scale that you feel best represents how much you disagree or agree with the statement.

1. I put a lot of effort toward achieving my goals in life.

2. I am committed to achieving my goals in life.

3. I am willing to work toward achieving my goals in life.

APPENDIX VII Goal Motivation Scale - Insomnia

The following three statements are followed by a visual scale in which
0 = “Strongly Disagree” and 9 = “Strongly Agree.” Place a mark on the scale that you feel best represents how much you disagree or agree with the statement.

1. I put a lot of effort toward resolving my insomnia.

2. I am committed to resolving my insomnia.

3. I am willing to work toward resolving my insomnia.

APPENDIX VIII INSOMNIA SEBVERITY INDEX

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

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APPENDIX IX **SELF REPORT SLEEP MEASURES**

Participant's Name: _____
Date: _____

We want your assessment of specific aspects of your experience with sleep and insomnia during the past week. Be as accurate as you can.

I. Please circle the number/words that best describe how satisfied or dissatisfied you have been about your ability to get to sleep at bedtime during the past week.

-3	-2	1-	0	+1	+2	+3
Very Dissatisfied	Somewhat Dissatisfied	Slightly Dissatisfied	Neither Satisfied Nor Dissatisfied	Slightly Satisfied	Somewhat Satisfied	Very Satisfied

II. Circle the number/words that best describe how satisfied or dissatisfied you are about your frequency of awakenings after having initiated sleep during the past week.

-3	-2	1-	0	+1	+2	+3
Very Dissatisfied	Somewhat Dissatisfied	Slightly Dissatisfied	Neither Satisfied Nor Dissatisfied	Slightly Satisfied	Somewhat Satisfied	Very Satisfied

III. Circle the number/words that best describe how satisfied or dissatisfied you are about your ability to return to sleep after awakenings during the night over past week.

-3	-2	1-	0	+1	+2	+3
Very Dissatisfied	Somewhat Dissatisfied	Slightly Dissatisfied	Neither Satisfied Nor Dissatisfied	Slightly Satisfied	Somewhat Satisfied	Very Satisfied

IV. Please circle the number and words that best describe how satisfied or dissatisfied you are about your average quantity of sleep during this past week.

-3	-2	1-	0	+1	+2	+3
Very Dissatisfied	Somewhat Dissatisfied	Slightly Dissatisfied	Neither Satisfied Nor Dissatisfied	Slightly Satisfied	Somewhat Satisfied	Very Satisfied

V. Which number/words best describe how satisfied or dissatisfied you are about your overall quality of sleep during the past week?

-3	-2	1-	0	+1	+2	+3
Very Dissatisfied	Somewhat Dissatisfied	Slightly Dissatisfied	Neither Satisfied Nor Dissatisfied	Slightly Satisfied	Somewhat Satisfied	Very Satisfied

VI. On a scale of 1 to 10, where 0 is no distress or neutral and 10 is the highest level of distress you can imagine, how distressing has your sleep difficulty been during this past week?

_____ on zero to ten (0-10) scale.

VII. "Social impairment" refers to how much your sleep difficulty negatively impacts your social functioning. How much does it impede or negatively impact your social functioning? If zero equals "Not at all" or no social impairment and 10 is the highest level of social impairment you can imagine, what is your best estimate of the level of social impairment due to your sleep difficulty during the last month?

_____ on zero to ten (0-10) scale.

If the participant is employed,
VIII. "Occupational impairment" refers to how much your sleep difficulty negatively impacts your occupational functioning, your ability to perform your job. How much does it impede or negatively impact your occupational functioning? If zero equals "Not at all" or no occupational impairment and 10 is the highest level of occupational impairment you can imagine, what is your best estimate of the level of occupational impairment due to your sleep difficulty during the last month?

_____ on zero to ten (0-10) scale.

If the participant is a full time or part time student,
IX. **"Academic impairment" refers to how much your sleep difficulty negatively impacts your academic functioning. How much does it impede your academic functioning? If zero equals "Not at all" or no academic impairment and 10 is the highest level of academic impairment you can imagine, what is your best estimate of the level of academic impairment due to your sleep difficulty during the last month?**

_____ on zero to ten (0-10) scale.

APPENDIX X Clinical Global Impression – Global Improvement (CGI –I) Scale

Patient Name: Date:

Clinician Name:

Rate total improvement whether or not, in your clinical judgment, it is due entirely to drug treatment.

Compared to his/her condition at baseline, how much has he/she changed?

- □ 0 = Not assessed
- □ 1 = Very much improved
- □ 2 = Much improved
- □ 3 = Minimally improved
- □ 4 = No change
- □ 5 = Minimally worse
- □ 6 = Much worse
- □ 7 = Very much worse

APPENDIX XI CLINICAL GLOBAL IMPRESSIONS-SEVERITY
SEVERITY OF ILLNESS

Considering your total clinical experience with this population, how mentally ill is the patient at this time? (Check one)

1 Normal, not at all ill

2 Borderline ill

3 Mildly ill

4 Moderately ill

5 Markedly ill

6 Severely ill

7 Among the most extremely ill patients

APPENDIX XII Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

Name:_____ Date:_____

Taking everything into consideration, during the past week how satisfied have you been with your……

	Very Poor	Poor	Fair	Good	Very Good
…..physical health?	1	2	3	4	5
…..mood?	1	2	3	4	5
…..work?	1	2	3	4	5
…..household activities?	1	2	3	4	5
…..social relationships?	1	2	3	4	5
…..family relationships?	1	2	3	4	5
…..leisure time activities?	1	2	3	4	5
…..ability to function in daily life?	1	2	3	4	5
…..sexual drive, interest and/or performance?*	1	2	3	4	5
…..economic status?	1	2	3	4	5
…..living/housing situation?*	1	2	3	4	5
…..ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5
…..your vision in terms of ability to do work or hobbies?*	1	2	3	4	5
…..overall sense of well being?	1	2	3	4	5
…..medication? (If not taking any, check here _____ and leave item blank.)	1	2	3	4	5
…..How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5

*If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

Scoring the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)

The scoring of the Q-LES-Q-SF involves summing only the first 14 items to yield a raw total score. The last two items are not included in the total score but are stand-alone items. The raw total score ranges from 14 to 70. The raw total score is transformed into a percentage maximum possible score using the following formula:

$$\frac{\text{(raw total score – minimum score)}}{\text{(maximum possible raw score – minimum score)}}$$

The minimum raw score on the Q-LES-Q-SF is 14, and the maximum score is 70. Thus the formula for % maximum can also be written as (raw score –14)/56. The table below converts total raw scores into % maximum scores.

Raw Score	% Maximum	Raw Score	% Maximum	Raw Score	% Maximum	Raw Score	% Maximum
14	0	28	25	42	50	56	75
15	2	29	27	43	52	57	77
16	4	30	29	44	54	58	79
17	5	31	30	45	55	59	80
18	7	32	32	46	57	60	82
19	9	33	34	47	59	61	84
20	11	34	36	48	61	62	86
21	13	35	38	49	63	63	88
22	14	36	39	50	64	64	89
23	16	37	41	51	66	65	91
24	18	38	43	52	68	66	93
25	20	39	45	53	70	67	95
26	21	40	46	54	71	68	96
27	23	41	48	55	73	69	98
						70	100

Citation: Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacology Bulletin 1993;29:321-326.

APPENDIX XIII COLUMBIA-SUICIDE SEVERITY RATING SCALE BASELINE/SCREENING

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

(0) Does not apply

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APPENDIX XIV COLUMBIA SUICIDE SEVERITY RATING SCALE - SINCE LAST VISIT

COLUM BI A-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit
Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia -Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to —Suicidal Behavior“ section. If the answer to question 2 is —yes“ , ask questions 3, 4, and 5. If the answer to question 1 and/or 2 is —yes“ , complete —Intensity of Ideation“ section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. **Have you wished you were dead or wished you could go to sleep and not wake up?** If yes, describe:	**Yes No** 3
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one‘s life/commit suicide (e.g., —I‘ve thought about killing myself“) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.	**Yes No** 3

Have you actually had any thoughts of killing yourself?

If yes, describe:

---

3. Active Suicidal Ideation with Any Methods(Not Plan) without Intent to Act

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place, or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, —I thought about taking an overdose but I never made a specific plan as to when, where, or how I would actually do it…and I would never go through with it."

Have you been thinking about how you might do this?

If yes, describe:

Yes No

---

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to —I have the thoughts but I definitely will not do anything about them."

Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes No

---

5. Active Suicidal Ideation with Specific Plan and Intent

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes No

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____

Type # (1-5) Description of Ideation

Most Severe

Frequency

How many times have you had these thoughts?

(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration

When you have the thoughts, how long do they last?

(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability

Could/can you stop thinking about killing yourself or wanting to die if you want to?

(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents

Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words, you couldn't go on living with this pain or how you were feeling) or wasit to get attention, revenge ,or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others living
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you werefeeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is **any** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. **There does not have to be any injury or harm**, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. **Have you made a suicide attempt?** **Have you done anything to harm yourself?** **Have you done anything dangerous where you could have died?** **What did you do?** **Did you_____ as a way to end your life?** **Did you want to die (even a little) when you_____?** **Were you trying to end your life when you _____?** **Or did you think it was possible you could have died from_____?** **Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** Total # of Attempts _____ **Yes No**
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed, and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. **Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?** If yes, describe:	**Yes No** Total # of Interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. **Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?** If yes, describe:	**Yes No** Total # of Aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). **Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away, or writing a suicide note)?** If yes, describe:	**Yes No**
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No**

Completed Suicide:	Yes No 3
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____

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