A Novel Use of a Sleep Intervention to Target the Emotion Regulation Brain Network to Treat Depression and Anxiety

Study Protocol and Statistical Analysis Plan

NCT04424407

December 10, 2020

Study Protocol

TARGETING INSOMNIA RELATED EMOTION BRAIN DYSREGULATOIN (TIRED-BRAIN)

Protocol Number: IRB-56961
National Clinical Trial (NCT) Identified Number: NCT04424407
Principal Investigator:
Andrea N. Goldstein-Piekarski, PhD
Grant Title: A Novel Use of a Sleep Intervention to Target the Emotional Regulation Brain Network and Treat Depression and Anxiety
Grant Number: 1 R61 MH120245-01
Funded by: The National Institute of Mental Health
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Important Note: The aforementioned grant encompasses R61 and R33 phases. The enclosed information refers only to the R61 phase.

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
	Not Applicable; this is the first version of the protocol	

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Andrea Goldstein-Piekarski

Title: Clinical Assistant Professor

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

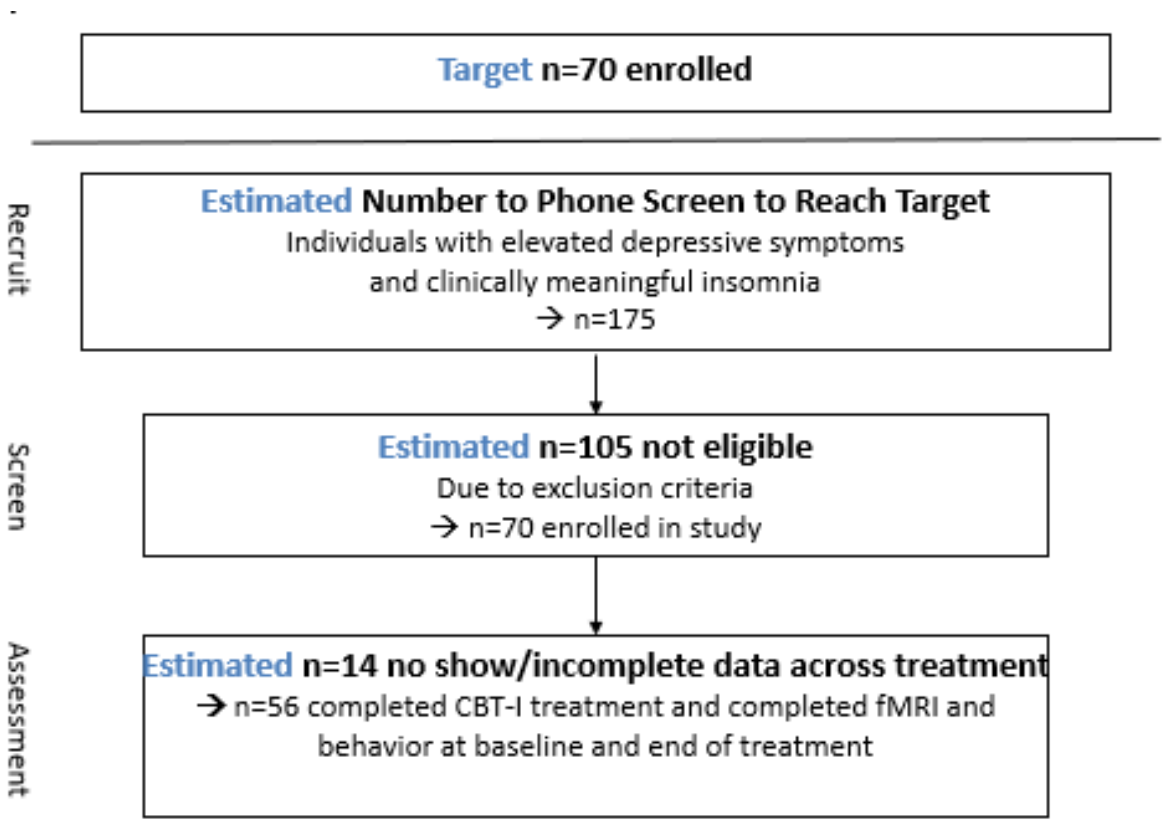
Title: A Novel Use of a Sleep Intervention to Target the Emotional Regulation Brain Network and Treat Depression and Anxiety

Grant Number: 1 R61 MH120245-01

Study Description: **Background:** Several lines of evidence suggest that insomnia contributes to emotionally distressing depressive mood symptoms through disruption of brain networks that regulate emotional functions. Of particular concern, insomnia is associated with an increased risk for suicide, even when accounting for the presence of other depressive symptoms. However, we do not yet know to what degree that the emotion regulation brain network is modified by the restoration of sleep, or whether the degree to which a sleep intervention engages these neural targets mediates reductions in depressive symptoms and suicidality. **Objective:** This proposal investigates the impact of a proven sleep intervention on engagement of the emotion regulation brain network as a putative mechanistic target. **DESIGN/METHODS:** In the **R61 phase**, a mechanistic trial will demonstrate feasibility and establish whether the emotion regulation brain network is modified (the target is engaged) when patients show improvements in insomnia symptoms following a proven psychosocial sleep intervention. Participants will be 70 adults experiencing elevated depressive symptoms and clinically meaningful insomnia. Depressive symptoms and insomnia will be assessed prior to, and weekly while receiving six Cognitive Behavioral Therapy for Insomnia (CBT-I) sessions across a period of eight weeks. CBT-I improves sleep patterns through a combination of sleep restriction, stimulus control, mindfulness training, cognitive therapy targeting dysfunctional beliefs about sleep, and sleep hygiene education. Emotion regulation network neural targets will be assayed prior to and following completion of CBT-I treatment. If the Go milestone criteria are met, the R33 phase (years 3-5) will include a 2-arm randomized controlled trial. We will enroll new participants (n=150) and randomize them in a 1:1 ratio to the CBT-I or to the credible control treatment for insomnia group. Participants will complete a refined measurement protocol based on the R61 phase study. **Specific aims:** R61 aims are to demonstrate (1) feasibility and (2) that CBT-I modifies emotion regulation network function according to pre-specified Go milestone criteria. **IMPACT:** Characterizing these associations may offer the potential to gain a deeper understanding of the neurobiological mechanisms underlying depression in the presence of insomnia. Our results will advance an evidence-based mechanistic approach to treating, and ultimately preventing, the emotionally distressing and potentially life-threatening impact of insomnia.

Objectives:	**1. Demonstrate feasibility and 2. target engagement in a single arm clinical trial (Study 1**). We will enroll 70 adults with elevated depressive symptoms (BDI ≥ 14) who are also experiencing clinically meaningful insomnia (≥15 ISI). Given the high comorbidity rates, anxiety will not be exclusionary. Participants will receive six sessions of CBT-I over eight weeks. CBT-I is an efficacious intervention that improves subjective and objective measures of insomnia. At both baseline and post-treatment, we will assay emotion regulation neural targets (using fMRI), depressive symptoms and suicidality, and each subject will complete an over-night sleep EEG recording. Depression, suicidality, and insomnia symptoms (actigraphy and ISI) will be assayed at baseline and each week throughout treatment to assess week-to-week improvements following an increasing number of CBT-I sessions. **Milestones (Go/NoGo Criteria):** 1. Feasibility: Enroll 70 participants and retain ≥80% at the end of treatment; 2. Target Engagement: For a go decision at least 1 of 3 emotion regulation tasks must exhibit an improved group mean (M) value with a boundary value (Standard Deviation (SD)/2) in the direction of improvement for **both** amygdala reactivity ((M-SD/2) ≤-0.35) **and** amygdala-mPFC connectivity ((M+SD/2) ≥0.35. The targets that meet these criteria will be carried over as primary targets of emotion regulation network function in the R33 phase.
Endpoints:	Primary Endpoint: emotion regulation brain function
Study Population:	70 patients with moderate to severe sleep disturbance and at least mild depressive symptoms as measured by the Beck Depression Inventory (BDI).
Phase or Stage:	1
Description of Sites/Facilities Enrolling Participants:	The study will be conducted at Stanford University School of Medicine.
Description of Study Intervention/Experimental Manipulation:	SLEEP MANIPULATION The sleep manipulation is Cognitive Behavioral Therapy for Insomnia (CBT-I). Treatments will be delivered in six 50-minute treatment sessions within an eight-week period by a PhD psychologist who is experienced in administering the study treatments. The CBT-I therapy will be delivered according to protocols and materials from our large-scale VA implementation of CBT-I. These materials include a published sleep self-help book, a published therapist guide, and the CBT-I therapist manual.
Study Duration:	24 months
Participant Duration:	This study lasts 11-weeks, and includes screening, baseline visit, treatment, and end-of treatment visit. Participants will be scheduled for 6 treatment visits across an eight-week period. All study measures will be collected at baseline and week 11 end of treatment visit.

1.2 SCHEMA


Target n=70 enrolled
Recruit
Estimated Number to Phone Screen to Reach Target
Individuals with elevated depressive symptoms
and clinically meaningful insomnia
→ n=175
Screen
Estimated n=105 not eligible
Due to exclusion criteria
→ n=70 enrolled in study
Assessment
Estimated n=14 no show/incomplete data across treatment
→ n=56 completed CBT-I treatment and completed fMRI and
behavior at baseline and end of treatment

1.3 SCHEDULE OF ACTIVITIES

Participant Schedule:

version 2.0	Pre-Treatment					Treatment						ETX	
12-Nov-20		Visit 1		Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	
	Day -91 to -8	Day -14 ± 7		Day 1		Day 14 ± 7	Day 21 ± 7	Day 28 ± 7	Day 35 ± 7	Day 42 ± 7	Day 49 ± 7	Day 56 ± 7	
	Pre-screening	Sceening		Baseline		treatment	treatment	treatment	treatment	treatment	treatment		
Questionnaire		PM	AM	PM	AM	session #1	session #2	session #3	session #4	session #5	session #6	PM	AM
Phone screen	◆												
Consent Form		◆											
Demographics		◆											
Acute/Unstable Chronic Illness Checklist		◆											
Berlin Questionnaire		◆										◆	
Medication List		◆										◆	
DUKE		◆										◆	
MINI		◆										◆	
Apnea Link		◆											
Adverse Events				◆		◆	◆	◆	◆	◆	◆	◆	
Emotion regulation questionnaire (ERQ)				◆								◆	
Difficulty in Emotion Regulation Questionnaire (DERS)				◆								◆	
Toronto Alexithymia Scale (TAS-20)				◆									
Imaging					◆								◆
RSA				◆	◆							◆	◆
FIRST				◆									
Morningness Eveningness Questionnaire				◆									
Pittsburgh sleep quality index				◆								◆	
Dysfunctional Beliefs About Sleep (Dbas)				◆								◆	
Insomnia Severity Index (ISI)		◆		◆		◆	◆	◆	◆	◆	◆	◆	
Stanford Sleepiness Scale		◆		◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Consensus Sleep Log		◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
PSG				◆								◆	
Actigraph				◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
BDI		◆		◆	◆	◆	◆	◆	◆	◆	◆		◆
PHQ-9				◆								◆	
RRS-short				◆								◆	
S-STS		◆		◆		◆	◆	◆	◆	◆	◆	◆	
BAI					◆	◆	◆	◆	◆	◆	◆		◆
Penn State Worry Questionnaire				◆								◆	
GAD-7				◆								◆	
CHICa irritibility and cognitive sub-scales				◆								◆	
SHAPS					◆							◆	
Profile of Mood States (POMS)			◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Faces Task (TBD)					◆								◆
WHOQOL				◆								◆	
SF-36 (RAND) Version1				◆								◆	
RBANS					◆								◆
Credibility/Expectancy Questionnaire						◆							
Working Alliance Inventory							◆				◆		
Treatment Adherence Survey											◆		
Treatment Satisfaction Survey											◆		

2 INTRODUCTION

2.1 STUDY RATIONALE

Insomnia is a defining characteristic of depressive disorder, risk factor for developing depression, and can exacerbate the severity of other depressive symptoms. Of particular concern, insomnia is associated with an increased risk for suicide, even when accounting for the presence of other depressive symptoms. Sleep problems, including insomnia, also disrupt function of the amygdala and its connectivity with the medial prefrontal cortex (mPFC): regions that regulate emotion and contribute to depression pathophysiology. Thus, these regions are promising targets for the mechanisms by which an empirically supported insomnia intervention may improve depression. We aim to assess whether 1) amygdala and amygdala-mPFC connectivity are response biomarkers of the effects of Cognitive Behavioral Therapy for Insomnia (CBT-I) on depressive symptoms, 2) changes in amygdala and its mPFC connectivity mediate reductions in depressive symptoms, and 3) baseline amygdala and its mPFC connectivity are predictive biomarkers for reductions of depressive symptoms following CBT-I.

OBJECTIVE*:* **1. Demonstrate feasibility and 2. target engagement in a single arm clinical trial (Study 1**). We will enroll 70 adults with elevated depressive symptoms (BDI ≥ 14) who are also experiencing clinically meaningful insomnia (≥15 ISI) and at least mild depressive symptoms as measured by the Beck Depression Inventory (BDI). Participants will receive six sessions of Cognitive Behavioral Therapy for Insomnia (CBT-I) over eight weeks. CBT-I is an efficacious intervention that improves sleep patterns through a combination of sleep restriction, stimulus control, cognitive therapy targeting dysfunctional beliefs about sleep, and sleep hygiene education. At both baseline and post-treatment, we will assay emotion regulation neural targets (using functional magnetic resonance imaging), emotional distress, and each subject will complete an over-night sleep EEG recording. Depression, suicidality, and insomnia symptoms (actigraphy and ISI) will be assayed at baseline and each week throughout treatment to assess week-to-week improvements following an increasing number of CBT-I sessions.

Milestones (Go/No-Go Criteria): Feasibility: Enroll 70 participants and retain ≥80% at the end of treatment; Target Engagement: For a go decision at least 1 of 3 emotion regulation tasks must exhibit an improved group mean (M) value with a boundary value (Standard Deviation (SD)/2) in the direction of improvement for **both** amygdala reactivity ((M-SD/2) ≤-0.35) **and** amygdala-mPFC connectivity ((M+SD/2) ≥0.35. The targets that meet these criteria will be carried over as primary targets of emotion regulation network function in the R33 phase.

NOVELTY & IMPACT: Characterizing these associations may offer the potential to gain a deeper understanding of the neurobiological mechanisms underlying depression in the presence of unhealthy sleep patterns. Our results will advance an evidence-based mechanistic approach to treating, and ultimately preventing, the emotionally distressing and potentially life-threatening impact of sleep disruption.

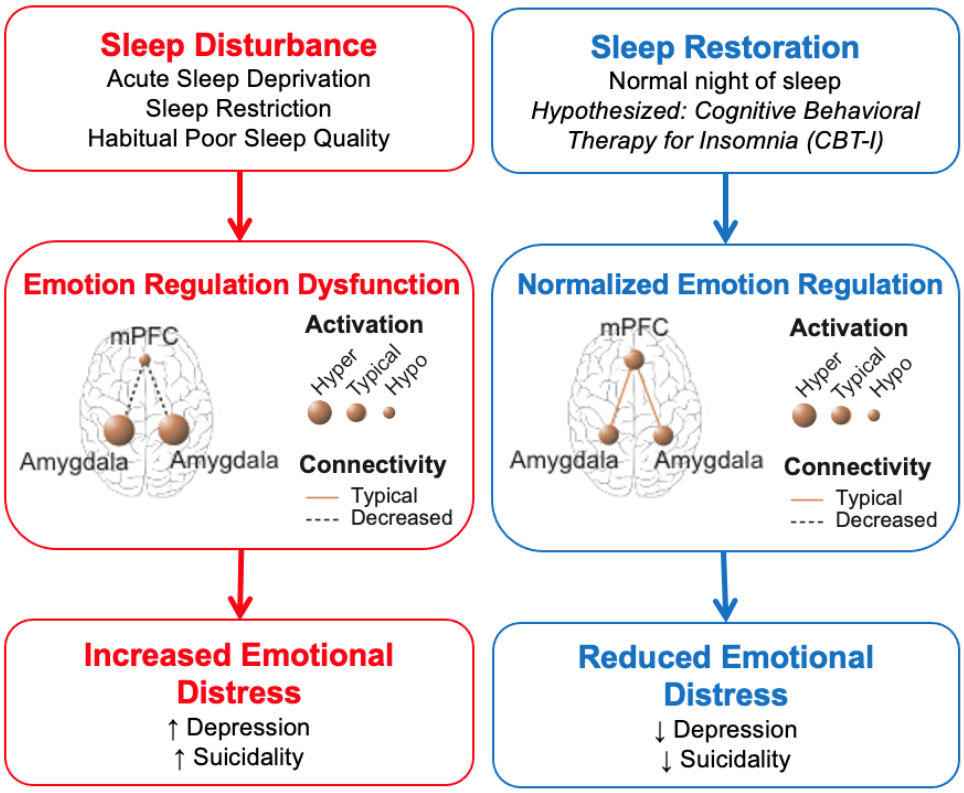
2.2 BACKGROUND

2.2.1 SIGNIFICANCE

Depression and insomnia are prevalent, costly, and commonly comorbid. An estimated 16 million American adults experience major depressive disorder (MDD)[1] each year, which is a leading cause of disability, lost productivity, and death in the United States[2], estimated at over $210.5 billion per year[3-7]. Sleep problems, especially insomnia, are a core feature of depressive disorder and predict the severity of other depressive symptoms, such as low mood, emotion regulation deficits, and suicide risk.[8-15] For example, in a large sample of adults with depression, 83% of individuals endorsed at least one insomnia complaint[16]. Moreover, conservative estimates indicate that those with mood disorders are at least twice as likely to develop sleep difficulties[13,16]. Sleep complaints are often unresolved following depression treatment and residual sleep impairments significantly increase risk for depression relapse[17]. Of particular concern, insomnia is associated with an increased risk for suicide**,** even when accounting for the severity of other depressive symptoms[18-22]**.** Thus, optimizing the precision and potency of sleep interventions, particularly among those with depression, and elucidating the mechanism of such effects, promises sizable mental and public health benefits. Addressing this critical need, this R61/R33 project aims to advance the mechanistic understanding of how insomnia and recovery impacts depressive and suicidal symptoms through the emotion regulation brain network (**Figure 1**). Using a precision medicine approach, we aim to prototype a model to identify which patients demonstrate a reduction in depressive and suicidal symptoms as a result

Figure 1. Conceptual Framework: (Below) Sleep disturbance contributes to depressive symptoms through impairments in emotion regulation brain function, particularly in fronto-limbic regions of the amygdala and mPFC (part of the Negative Affect Network[23,24]). (Right) Conversely, sleep restoration is hypothesized to alleviate depressive symptoms by normalizing fronto-limbic regulation of emotion.

of a targeted sleep intervention.



Insomnia is a modifiable, transdiagnostic target for both preventing and treating depressive symptoms. Insomnia is both a symptom of psychiatric illness, and a strong predictive factor in its development[10-13] and prognosis[17,25]. Mechanistic, pre-clinical studies show that sleep deprivation increases anxiety and depression[11,26-31].

Individual differences in sleep architecture and physiology are also associated with depressive symptoms and suicidal ideation[19,31-36]. MDD is frequently accompanied by decreased sleep continuity and depth[37], which can be improved by a behavioral insomnia treatment[38,39]. Depression is also associated with increased REM pressure[37]. More recent work has described sleep abnormalities associated with depressive symptoms using spectral analysis of the EEG signal, including decreased delta activity during Non-Rapid Eye Movement Sleep (NREM) associated with perceptions of stress, and increased alpha activity during NREM associated with depression symptoms[40]. Additionally, individual differences in REM sleep spectral profiles are associated with next-day emotion regulation network function and behavioral performance on emotion tasks[31,32,34]. Importantly, these spectral markers are highly localized over the frontal cortex such that using full-scalp EEG, as proposed in the current application, is necessary to obtain spatial coverage and resolution necessary to detect region-specific

changes.

While limited in number, these studies support the hypothesis that sleep disruption and abnormal sleep physiology may be a causal risk factor in the development, maintenance, and exacerbation of depressive symptoms as well as other indicators of emotional distress in psychiatric disorders. **Critically, there is evidence from PI Goldstein-Piekarski's (Figure 2) that sleep disruption is a modifiable target that can reduce other depressive symptoms, including suicide risk specifically,** making sleep-targeted behavioral therapies attractive and tractable therapeutic opportunities. Findings from

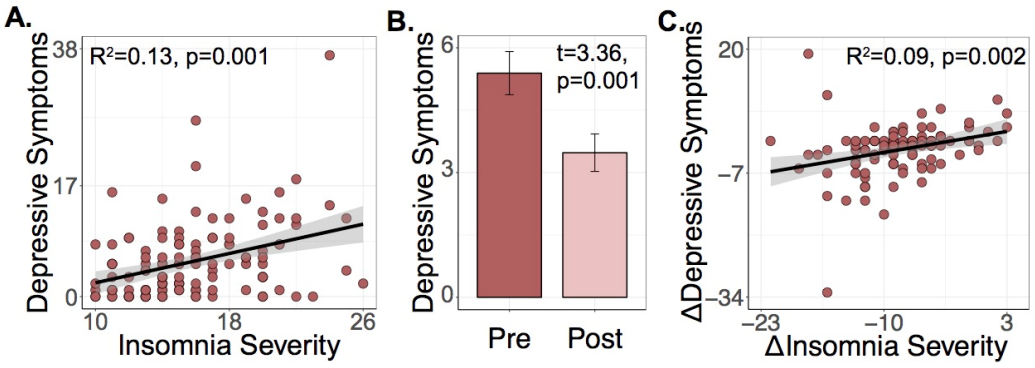


Figure 2*. Preliminary Data: Associations between insomnia (ISI) and depressive symptoms (BDI after excluding the sleep items). Data from 106 older adults seeking treatment for insomnia. This study excluded Axis-I diagnoses.* ***A.*** *Insomnia was associated with depressive symptoms at baseline.* ***B****. Depressive symptoms decreased after receiving CBT-I* ***C.*** *The reduction in insomnia severity was associated with the reduction in depressive symptoms, such that those with the greatest reduction in insomnia experienced the greatest reduction in other depressive symptoms.*

Co-I Manber also suggest that at least with respect to subjective sleep measures, improvements in sleep mediate changes in depression symptoms, but not the reverse[41]. While promising, these studies were designed with sleep improvement as the primary outcome measures, not depression. As a result, the effect sizes from these studies are likely underestimated, and we do not have a true characterization of the efficacy of using sleep treatment to improve depression in those with insomnia. Indeed, when restricting analyses to those with relatively higher depression scores at baseline (BDI ≥ 14; the proposed inclusion criteria for the current study), Co-I Manber and Bernert found a large effect for CBT-I in reducing other depressive symptoms (Cohen's d = 1.45). Similarly, a large effect size was found for reducing suicidal ideation posttreatment (Cohen's d = 1.83). However, we currently lack a complete understanding of neurobiological mechanisms mediating relationships between improved sleep and reduced depressive symptoms, which hinders our ability to identify

which individuals will experience a reduction in depression following a targeted sleep intervention.

Impaired emotion regulation brain function may causally link insomnia and depression. Neuroimaging studies implicate an extended limbic network (Emotion Regulation Network (ERN)), that includes the amygdala and associated medial Prefrontal Cortex (mPFC), that optimizes emotional behaviors, including identifying/attending to salient stimuli and generating/regulating the emotional response to these stimuli[23,42-48]. The amygdala is particularly involved in attending and generating bottom-up emotional responses to emotionally-salient stimuli, while the PFC is involved in top-down regulation of amygdala activation in response to negative emotions[42-47]. Both hyper-reactivity of the amygdala as well as hypo-connectivity of mPFC-amygdala are theorized to contribute to the development and maintenance of maladaptive behaviors commonly observed in MDD[49-53] including poor emotion regulation[54-56]. Supporting this hypothesis, MDD show profiles of dysfunction within the ERN, including hyper-reactivity in the amygdala[57-64] and reduced top-down control, as measured by hypo-connectivity between the amygdala and mPFC during emotion tasks[65-69] and at rest[67,70-72]. Preliminary data shown below also support these associations (see **Figure 3**)

These same regions are impaired by experimentally induced and naturalistic sleep disruption (including insomnia) and may be improved by intervening sleep. Acute sleep deprivation, sleep restriction, and poor habitual sleep (including insomnia) all amplify amygdala reactivity to negative experiences[30,31,73-77]. This signature of excessive amygdala reactivity caused by sleep disruption, has routinely been linked to decreases in functional connectivity with the mPFC[73-77]. These alterations in brain function are also paired with changes in affective behavioral outcomes and subjective reports of significant clinical relevance. For example, inter-individual differences in mPFC-amygdala connectivity following sleep deprivation are significantly correlated with concurrent sleep-loss increases in subjective anxiety[76]. Preliminary data from a sample of unmedicated participants with a range of depressive symptoms, demonstrates robust associations between amygdala hyperactivity and insomnia severity as measured by the insomnia item from the BDI; this converges with evidence that insomnia symptom severity mediates known associations between depression and amygdala hyperactivity (**Figure 3**). Critically, and guiding our hypothesis that CBT-I may reduce depressive symptoms through improving ERN dysfunction, a full night of sleep normalizes amygdala reactivity and re-establishes mPFC-amygdala connectivity the following day[32]. Taken together with the aforementioned background this evidence strongly suggests that **sleep disruption, including insomnia, causes a dysfunctional brain state as well as emotional distress that strongly resembles that of MDD, and that may be reversible with a targeted sleep intervention.**

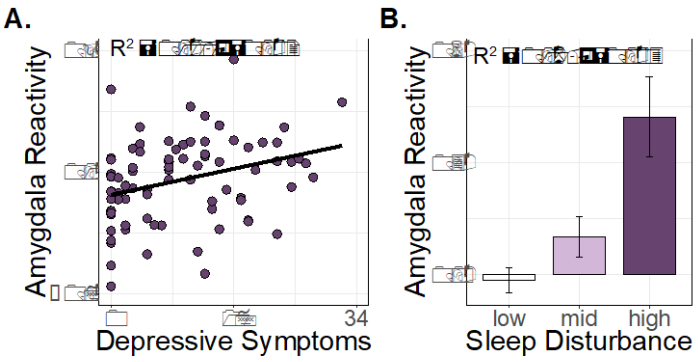
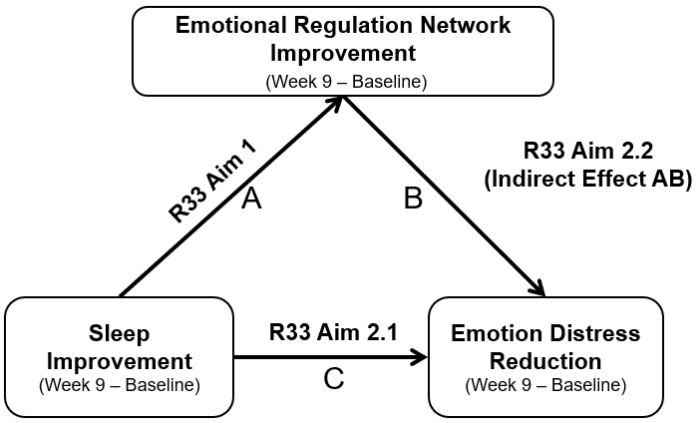


Figure 3. *Preliminary Data: Emotion regulation network function (amygdala reactivity to subliminal threat) is associated with both* ***A.*** *Depressive symptoms (BDI) and* ***B.*** *Sleep disturbance (Insomnia item of the BDI) in a sample of 87 unmedicated individuals ranging from no depression through clinical depression.*

Figure 4. Conceptual frame work and Specific Aims 1 and 2 for the R33 phase



In this R61/R33 project, we aim to test the hypothesis that alleviating insomnia reduces other depressive symptoms by normalizing ERN function (**Figure 4**). In the R61 phase, we will conduct a mechanistic trial to determine whether an insomnia intervention with proven efficacy engages ERN functioning (R61 **Aim 1**). Then, if the Go criteria are met, in the R33 phase we will test ERN engagement against an active control condition **(**R33 **Aim 1)**. We will also test the hypothesis that changes in ERN function mediate improvements in depressive symptoms (R33 **Aim 2**).

Discrete patterns of emotion regulation brain function and sleep physiology may identify patients whose other depressive symptoms are a consequence of insomnia. Identifying these patterns will aide in the delivery of sleep interventions to the appropriate patient population. PI Goldstein-Piekarski and Co-I Williams, as well as others, have identified distinct profiles of engagement of the ERN[78,79] that predict response to antidepressant and behavioral treatments for depression. Similarly, PI Goldstein-Piekarski and others have identified biomarkers related to sleep physiology that predict next-day ERN engagement as well as emotional

consequences following acute sleep deprivation[31,80], which may inform treatment response. These findings support the hypothesis that discrete profiles of ERN function, as well as sleep architecture and physiology prior to treatment, may prospectively identify individuals that would show a reduction in depressive symptoms, including suicide risk, by treating insomnia (**R33 Aim 3)**.

2.2.2 INNOVATION

This study represents innovation at three levels: (1) Conceptual novelty: To date, three largely nonoverlapping lines of research have characterized the association between (i) insomnia and depression, (ii)depression and ERN function, (iii) sleep and ERN function. Together, these lines of research suggest that maladaptive ERN function may be an intermediate step between insomnia and depression, and that sleep is a modifiable target through which emotional distress can be reduced. **However, this study represents the first study to explicitly evaluate ERN engagement as a mediator and predictor of depressive symptom improvement following an insomnia intervention**. As such, these aims will clarify mechanisms through which insomnia can lead to other depressive symptoms and help develop personalized, mechanism-focused preventative strategies and treatments. The current approach represents a necessary first step in identifying individuals in which depression is a direct consequence of insomnia. (2) Methodological & Technical: **Our study implements a multimodal, neuroimaging approach that fuses sleep EEG with full-scalp coverage, fMRI, and ERN function assessments during emotion reactivity and regulation**. While each technique alone has proven useful in the context of depression research, combining these techniques promises to elucidate ERN engagement and sleep physiology mechanisms that mediate changes in depressive symptoms following a sleep intervention in a manner not previously possible. Moreover, by capitalizing on these multimodal domains, we can more clearly identify individuals whose depression is caused by insomnia and thus who are mostly likely to benefit from such an intervention. (3) Public & Mental health: While depression is one of the most prevalent and costly psychiatric conditions across the lifespan, there are currently no means to tailor treatment to a specific, underlying dysfunction. **A major outcome of this study will therefore be a novel and clinically-useful mechanistic model that predicts treatment response to better treat depressed individuals with co-morbid insomnia.**

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

From past experience, potential risk to participants is expected to be minimal. During data collection, the potential risks to participants will be as follows:

Brain Imaging Assessments: The principal piece of equipment used in this protocol is a 3 Tesla GE magnetic resonance imaging (MRI) scanner. The risks associated with MRI are minimal. A small number of people may feel claustrophobic inside the machine. The study will be immediately stopped via button press if this occurs. Study personnel and technicians will be on site during all acquisitions to address any such discomfort. To minimize fatigue, sufficient breaks are provided to participants during the scanning procedure, and the experimenter regularly inquires as to whether there is anything that s/he can do to facilitate the participant's comfort. Routine contraindications to MRI include presence of any metal implants (pacemaker, aneurysm clips, neurostimulators, cochlear, eyes, tattoos with ink contraindicated for MRI scanning). All participants will be appropriately screened for the presence of any such implants and/or health conditions that prohibit their MRI scanning for research purposes, using Stanford's CNI MRI screening forms. Participants who can participate in the MRI session will be screened with a metal detector before entering the magnet room for their safety. During

the scan there is a slight risk participants might experience changes in temperature in specific body parts or peripheral nerve stimulation despite adequate measures taken to prevent these from occurring. Study personnel and MRI technologists will be on site during all acquisitions and will be trained to monitor and address any such discomfort in a timely manner. Upon participation in MRI studies, research subjects are exposed to the risk of a brain abnormality being observed. We will follow an established procedure to inform and protect our research participants in case of an incidental MRI finding.

Ambulatory Polysomnographic Recording: The polysomnographic evaluation is strictly non-invasive. The equipment is well-maintained and appropriate grounding procedures are used to protect participants. Small sensors (electrodes) are positioned on the participant's scalp, face and body. Minor skin irritation may result from the application of these electrodes. Other than the time duration, there are no known adverse effects on participants resulting from either the assessment procedures. Some participants may have face or bodily hair that may cause minor discomfort during removal similar to a bandage. Disposable razors will be available for participants who wish to remove hair prior electrode placement.

Self-Report and Cognitive Assessments: The risks associated with the web-based self-report and cognitive assessments are minimal. They have not caused distress in the 5,000 healthy participants or the 1,100 patients who have completed these assessments in prior studies

Cognitive Behavioral Therapy for Insomnia Intervention: The CBT-I intervention has been well tolerated in the past. The study therapist will be experienced and sensitive to clinical issues. While treatments are intended to contribute to the development of nonpharmacological alternatives to current treatments for insomnia with comorbid emotional distress, the treatment protocol is not intended as a withdrawal procedure from sleeping medications. Those volunteers who are taking sleeping or other psychotropic medications at the time of recruitment will be admitted to the study only if they withdraw from the medication under the supervision of their physician. They may then be evaluated for inclusion in the study when they have been successfully withdrawn from the medication for a minimum of three weeks. Thus, no side-effects of medication withdrawal in these patients is planned as part of the treatment protocol.

COVID-19 Mitigation: There is a risk of contracting COVID-19 as a result of interacting with new individuals and places. The research team has put together mitigation protocols to help minimize the risk of contracting COVID-19. All researchers and participants will be required to wear face coverings, use hand sanitizer upon entering buildings, observe room density requirements set forth by Stanford, and maintain social distancing (> 6 feet separation) throughout the session when possible. There will be times during the scanning session and sleep recording hook-up where it will not be possible to maintain social distance. During these times researchers will wear additional protective equipment including a face shield to minimize potential exposure. Researchers will disinfect all surfaces and equipment the participant comes into contact with. Researchers will be required to complete a Health Check prior to entering the lab. Participants will complete a COVID-19 screening call prior to arrival on campus. Only researchers and participants who do not present symptoms of COVID-19 will be allowed to participate in research.

All interviews, questionnaires, and laboratory procedures have been carefully selected with regard to their reliability and validity, their relevance to the hypotheses of the study, and evidence from prior research (in our own laboratories and as reported in the literature) that these methods can be used without adverse effects on the participants.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants are expected to benefit from this proposal since CBT-I has been shown to be efficacious for treating insomnia. Further, recent studies including preliminary data from our own lab, have found that these benefits

may go beyond treating insomnia, but also alleviating other emotional distress including anxiety and depressive symptoms. Additionally, results of the proposed study may help to identify which individuals would benefit from a sleep intervention as well as develop new interventions for other individuals with similar conditions and guide future research endeavors. Other potential benefits include 1) participants will have their psychiatric symptoms evaluated by a trained Clinical Psychologist; 2) participants' quality of life may be improved. Overall, the risk/benefit ratio is favorable since the procedures used in the research study are similar to those used in clinical practice.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This innovative project contributes to the understanding how sleep disruption and emotion regulation brain functions contribute depressive symptoms. The outcomes will help further a neural system-based understanding of emotional distress-related dysfunction that arises from loss of sleep, and may be remedied with a sleep intervention. Understanding these neural and sleep mechanisms will advance the evidence base for classification and treatment personalization for this population. Thus, the benefit to society could be substantial.

Although all research has risks, the risks to patients of the proposed research are well understood and will be explained to participants. There is little risk from the assessment procedures.

The long-term potential benefit of this research is to provide a neural and sleep based model to support classification and clinical management of depressive symptoms that arise from sleep disruption. Reflecting these goals, the potential benefits of the research are substantial. The risks associated with participation in these studies are minimal compared to the potential benefits of improvement for clinical practice.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVES

3.1.1 GO/NO-GO MILESTONES

1. Feasibility of recruitment and retention: enroll 70 participants and retain ≥80% at 11 weeks. In our study of older adults (mean age=68.51, SD=5.78) described above, 87% of our sample was retained at the end of treatment visit at 11 weeks. In a prior study that included adults with comorbid depression and insomnia (mean age=47.4, SD=12.6), 93% of the individuals completed treatment[81].

2. Emotion Regulation Network Target Engagement: This will be determined using the precision interval approach. The goal is to demonstrate sufficient variation for further investigation[82,83]. We hypothesize that CBT-I will improve ERN function by reducing amygdala reactivity and increasing amygdala-mPFC connectivity. Thus, for the amygdala, improvement is likely reflected in an absolute negative mean change value with a lower fixed-width interval boundary (M-SD/2), where M is the mean and SD is the standard deviation, which is also substantially in the negative direction. Similarly, the amygdala-mPFC improvement is reflected by an absolute increase mean change with an upper fixed-width interval boundary (M+SD/2). For a GO decision, we will require at least 1 of 3 emotion regulation neuroimaging tasks must exhibit improvement by having both a group mean change of amygdala activation with symmetric 1 SD intervals whose lower bound is less than an absolute precision criterion of (M-SD/2) ≤ -0.35, and a positive group mean change of the amygdala-mPFC connectivity whose upper bound is greater than an absolute precision criteria of (M+SD/2) ≥ 0.35. The criterion ±0.35 was selected as a value

clearly indicating more than "noise," as it places a substantial portion of the subjects in the improvement range, and thus is of potential clinical importance to warrant further study[82].

3.1.2 PRIMARY ANALYSES

We hypothesize that in this single-arm study treatment with CBT-I will lead to improvements in Emotion Regulation Network function. Specifically, we predict that sleep restoration will be associated with greater decreases in amygdala reactivity and increases in mPFC-Amygdala Connectivity. An extended analysis of covariance (ANCOVA) will be used to test the primary hypothesis of change in Emotion Regulation Network function from baseline to end of treatment. We will characterize the association between our primary measures of Emotion Regulation Network function and that of our proximal outcome (sleep disruption as defined by sleep-EEG derived sleep efficiency) using a regression framework with age and sex included as covariates.

3.1.3 SECONDARY ANALYSES

We will examine the treatment effect on outcomes as measured by validated self-report questionnaires and sleep disruption measurements. We will also examine the association of change in Emotion Regulation Network function with change in outcomes from other domains. We will also explore associations between emotion regulation related behaviors and physiology including behavior on the neuroimaging emotion regulation tasks (implicit threat priming, emotional conflict, and emotional response), measures of emotional reappraisal and suppression as assessed with the Emotion Regulation Questionnaire and the other domains, and Respiratory Sinus Arrhythmia (RSA). The statistical approach to analysis of the treatment effect on these outcomes will use ANCOVA, analogous to the analysis of target engagement (above).

Some measures will be collected daily (e.g. actigraphy and sleep logs) and weekly (BAI, BDI, CSSRS, BSS) over the course of treatment. Our general approach is to apply mixed linear models, using the daily/weekly reports to construct an individual specific estimate (functionally the mean and coefficient of variation of daily measurements for each naturalistic measure over a week) for baseline and follow-up, and then testing the effect of time (thus testing the within-person change over time). Random intercepts and slopes (and their covariance) at the person level will be included in our models. Random intercepts will be used to account for the clustering of observations within individuals across time; random slopes for key within-person predictors (e.g. 'time' or pre to post in this case) will be included to allow within-person slopes to be stronger for some individuals and weaker for others. In cases where random slopes are observed, we will test for potential subgroups/moderation (e.g., by age, sex, etc.; although we note that the small sample size somewhat limits our statistical power for such moderation tests).

3.2 EXPLORATORY ANALYSES

[redacted]

3.3 STUDY MEASURES

All study measures will be collected at baseline and at the week 11 end of treatment visit. The primary study measures are listed in **Table 1** and the secondary measures are listed in **Table 2**.

Table 1a. Primary Endpoints

Purpose	Construct	Paradigm/Method	Domain	Measure (or region) of interest
Mechanistic Target, Response, & Predictive Biomarker	Emotion Regulation Network function	Supraliminal emotional reactivity paradigm (Faces)	fMRI	Amygdala reactivity and mPFC-Amygdala Connectivity
		Subliminal emotional reactivity paradigm (Faces)	fMRI	Amygdala reactivity and mPFC-Amygdala Connectivity
		Emotion Regulation Task (images)	fMRI	Amygdala reactivity and mPFC-Amygdala connectivity
Clinical outcome (R61)	Insomnia	Sleep Architecture	PSG	Sleep Efficiency (SE)
Clinical outcome (R33)	Depression	Beck Depression Inventory	Self Report	Total score after excluding the sleep items

Abbreviations: functional Magnetic Resonance Imaging (fMRI); medial Prefrontal Cortex (mPFC); Polysomnography (PSG);

Table 2. Secondary Endpoints

Construct	Paradigm/Method	Domain	Measure (or region) of interest
Emotion regulation	RSA	Physiology	Respiratory Sinus Arrhythmia during a paced breathing task
	Emotion Task HRV	Physiology	HRV recorded simultaneously with fMRI during tasks
	Threat Priming	Behavior	Reaction time and memory for threat/happy primed faces
	Emotional Response	Behavior	Ratings of emotional stimuli during emotion regulation task
	Emotion Regulation	Self Report	Emotion regulation ability assessed by the ERQ, DERS, TAS-20
Sleep Disturbance	Sleep Continuity	Actigraphy	WASO, TST, SE, SOL, # of arousals, as measured by actigraphy
	Sleep Architecture	PSG	WASO, TST, TIB, SOL, # of arousals, duration in REM/NREM, etc.
	Sleep Physiology	PSG	Power density spectral analysis of Delta, Theta, Alpha, Sigma, beta & Gamma bands across electrodes and sleep stages.
	Sleep HRV	Physiology	HRV recorded during sleep initiation and sleep stages
	Sleep Complaints	Self Report	Subjective complaints of insomnia as measured by the ISI
Emotional Distress	Suicidality	Self Report	Suicidal ideation and behaviors as assessed by the S-STS
	Anxiety	Self Report	Anxiety symptoms assessed by the BAI and GAD-7
	Depression	Self Report	Depressive symptoms assessed by the PHQ-9
	Rumination	Self Report	Assessed by the RRS-short and PSWQ
	Anhedonia	Self Report	Assessed by the SHAPS
	Mood States	Self Report	Assessed by the Profile of Mood States (POMS)
	Irritability	Self Report	Assessed by the CHICa
Current Functioning	Quality of Life	Self Report	Assessed by the WHOQOL and SF-36
	Cognitive function	Behavior	Assessed by the RBANS and Emotional Face Recognition task

Abbreviations: Heart Rate Variablity (HRV); Emotion Regulation Questionnaire (ERQ)[84]; Wake After Sleep Onset (WASO); Total Sleep Time (TST); Sleep Efficiency (SE); Sleep Onset Latency (SOL); Rapid-Eye Movement Sleep (REM); Non-REM (NREM); World Health Organization Quality of Life

(WHOQo); Repeatable Battery for the Assessment of Neuropsychological Status(RBANS)[85]

3.3.1 EMOTION REGULATION NETWORK FUNCTION

Primary measures of ERN function will include amygdala reactivity, as well as mPFC-amygdala connectivity as measured by generalized psychophysiological interaction (gPPI)[86]. ERN function will be assessed using three validated neuroimaging tasks of emotional reactivity and regulation described in detail below (**Section 8.1.6**). Prior work from PI Goldstein-Piekarski and others has suggested that sleep disruption may differentially impact the reactivity to emotional faces from that of emotional scenes[30,31,73,87]. Thus, we have selected three tasks that span emotional reactivity and regulation across both face and scene stimuli. We will focus *a priori* on regions of the amygdala and mPFC due to prior findings that they are sensitive to sleep status and are altered in anxiety and depression. We will also examine the degree of target engagement as indexed by changes in the corresponding behavioral responses from these tasks as well as emotion regulation ability as assessed by questionnaires as secondary analyses (summarized in **Table 2**).

3.3.2 INSOMNIA

Eligibility will be determined on the subjective report of insomnia (ISI). Sleep Efficiency (SE) measured on the overnight PSG recordings will verify that the sleep intervention produces improvements in insomnia as a mediator of the target-depressive symptom relationship and as a proximal outcome measure. SE as measured by actigraphy across the duration of the study will serve as a secondary and convergent measure of insomnia. We recognize that subjective measures of sleep disturbance do not always correspond with the objective measures of sleep disturbances determined using PSG sleep architecture. Recent evidence suggests that the differences between subjective and objective sleep disruption may be explained by hyperarousal during sleep as reflected in high frequency EEG spectral power including alpha, beta, and sigma activity, using spectral analysis of the PSG[88]. Thus, we will also examine alpha, beta, and sigma activity during NREM as additional secondary measures of sleep disturbance.

3.3.3 DEPRESSIVE SYMTPOMS

The BDI[89] total score after removing the sleep items will be used as the primary outcome measure of depressive symptoms. Given that suicide is a risk associated with insomnia independent of other depressive symptoms, suicidality (CSSRS and BSS) will be included as a secondary outcome measure. Given the high comorbidity between insomnia, depression, and anxiety, we will also assess anxiety using the Beck Anxiety Inventory (BAI[90]) as a secondary outcome. In addition to the baseline and end of treatment assessments, the BDI, BAI, BSS and CSSRS will be assessed weekly prior to each treatment session. Additional secondary measures related to specific aspects of emotional distress relevant to depression are listed in **Table 2**.

3.3.4 CURRENT FUNCTIONING (SECONDARY MEASURES)

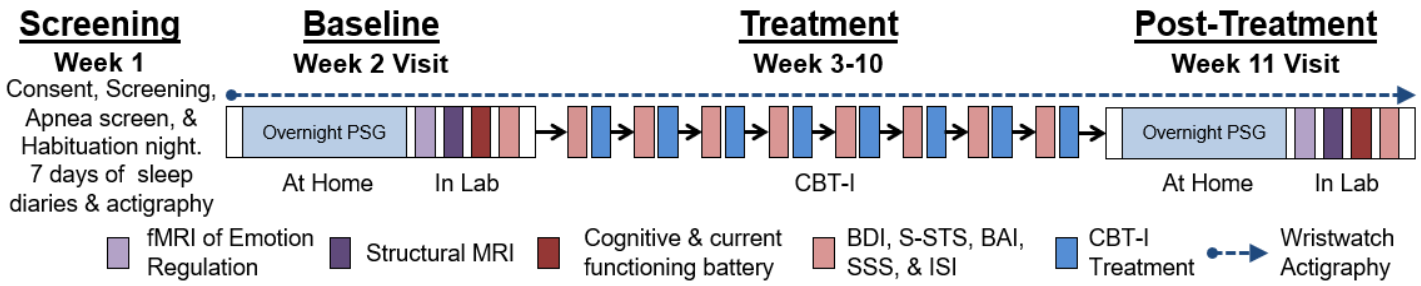
Cognitive function and current functioning measures are listed in **Table 2.** These measures are included because sleep disruption and depression have documented negative impact on cognition, current functioning, and quality of life[92-95].

4 STUDY DESIGN

4.1 OVERALL DESIGN

The R61 phase is a single-arm clinical trial with 70 eligible participants. The R61 phase aims to assess feasibility of recruitment and retention, as well as to establish a proven sleep intervention's ability to engage neural circuits involved in the regulation of emotion.

Figure 5. Study 1 Design and flow of testing



4.1.1 RANDOMIZATION

N/A

4.1.2 SLEEP MANIPULATION

CBT-I improves sleep through a combination of behavioral interventions (stimulus control (SC), sleep restriction (SR)), cognitive therapy (CT) as well as additional components such as mindfulness training and sleep hygiene education. SC is an intervention that re-establishes the connection between the bed/bedroom with sleep to help develop a more consistent sleep/wake pattern[96-99]. SR leads to higher quality sleep by limiting time spent in bed[99] to the actual amount of sleep, thereby creating mild sleep deprivation and increasing the homeostatic sleep drive[101-105]. Like CT for other disorders, CT for insomnia targets maladaptive thoughts and cognitions that may interfere with sleep[106,107].

4.1.3 STUDY SITES

The study will be conducted at the Stanford University. All study personnel have Stanford affiliation and have access to the resources.

Recruitment and screening: Recruitment activities will occur at the Psychiatry Building at Stanford University Medical Center or digitally off-campus using Stanford VPN. Additionally, recruitment materials will be posted around the VA, Stanford campus, social media and other online sites, and public spaces that allow postings. Participants will be screened in private interview rooms available in the Stanford Psychiatry building located at 401 Quarry Rd.

Phone/RedCap screens: Phone screens will be conducted at the Stanford Psychiatry Building or digitally off-campus using Stanford VPN and the secure jabber phone lines. The data will be stored on a secure RedCap database administered by Stanford. Alternatively, the participant may complete the phone screen questions via Stanford RedCap.

Consent: This will be undertaken in the Stanford Psychiatry Building. Private and confidential rooms are available for the consent process.

Clinical interviews and behavioral testing: This will be undertaken at the Center for Cognitive and Neurobiological Imaging (CNI) and in the Stanford Psychiatry Building. Both locations have private interview rooms available for this purpose. The behavioral testing will be undertaken both using physical testing batteries and a computerized battery.

Imaging: Scans for functional imaging will be undertaken at the Center for Cognitive and Neurobiological Imaging (CNI) for the fMRI component of the study. The 3.0 Tesla MRI machine as well as relevant computers and electronics is well established.

Treatments: The sleep manipulation interventions and control treatment will be administered in private rooms at the Stanford Psychiatry Building.

Data Analysis: Data analysis will be conducted at the Stanford Psychiatry Building on computers with Stanford LAN access. All data will be stored on Stanford servers and in locked file cabinets in the Stanford Psychiatry Building.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 JUSTIFICATION OF A SINGLE-ARM MECHANISTIC TRIAL

This phase of the study is a single-arm mechanistic trial. For this phase, the aims are to determine feasibility and target engagement. The measures of emotion regulation network function that meet the Go criteria will be carried over as primary targets of emotion regulation network function in the R33 phase.

4.3 JUSTIFICATION FOR INTERVENTION

The CBT-I intervention will be delivered according to protocols and materials from our large-scale VA implementation of CBT-I[108] . The intervention materials include a published sleep self-help book, a published therapist guide, and the CBT-I therapist manual[108,109].

Participants must complete 5 sessions of treatment to have evaluable data for analyses related to the primary objectives to ensure there is sufficient improvement in sleep.

4.3.1 GENERAL INTERVENTION CONSIDERATIONS

To minimize the documented effects of expectancy/demand factors[111,112], participants will be given the counter-demand intervention information that improvement is not anticipated until after the intervention ends. During the sleep manipulation phase, the participant and study psychologist meet on a weekly basis. In these sessions,

participants will have the chance to discuss any problems they may encounter in complying with the intervention and to ask questions about the rationale of the intervention. The study psychologist and participant work collaboratively to come up with solutions for dealing with the significant life-style changes that treatment compliance can involve.

4.3.2 CONSIDERATION OF GENERALIZABILITY

To test the hypothesis that sleep restoration reduces depressive symptoms, it is important that the therapists remain focused on insomnia and avoid providing general psychotherapy. We will instruct the therapist to limit their interventions to the target symptoms. To that end, the therapist will not provide general psychotherapy for depression and/or anxiety. In particular, the CBT-I manual instructs the therapist to limit cognitive restructuring to sleep-related cognitions and to refrain from explicit generalization to other domains. When participants raise issues that are either outside the scope of the specific treatment or outside the scope of the study, the provider will respectfully redirect focus to sleep symptoms and treatment. The only exception is when the clinical presentation necessitates an immediate intervention, such as when the participant expresses suicidal thoughts; however, therapists will be trained to redirect this to the PI, where procedures will follow this study's DSMP. Any safety planning or referral back to the PI will be tracked for future study. Past research supports feasibility and integrity of treatment delivery using CBT-I. Our experience indicates that participants and treatment providers are able to adhere to and accept similar limits.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, all 6 intervention sessions, and the end of treatment assessment.

The end of the study is defined as completion of the end of treatment assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Males and females of any racial or ethnic group, aged 25-60 to avoid age-related brain pathologies that could interfere with assessments to be made in the study. Children below the age of 18 will not be included in this study based on evidence of altered circadian rhythmicity in adolescence, which could confound sleep-stage effects and because a separate, age-specific study in children is warranted and preferable.
2. Subjective complaint of insomnia associated with daytime impairment or distress (ISI ≥ 15)
3. Insomnia complaint ≥ 3 months in duration

4. Subjective complaint of depressive symptoms as defined by scores ≥ 14 on the BDI
5. Fluent and literate in English
6. Written, informed consent.
7. Low risk for complications from COVID-19

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Presence of other sleep or circadian rhythm disorder as these disorders may have distinct underlying neural causes and thus confound emotion regulation network brain function biomarkers targeted here.
   The presence of these disorders will be assessed by the DUKE structured interview for Sleep Disorders
2. Use of psychotropic medications that would significantly impact sleep, alertness, or mood
3. Use of non-prescription medications or substances that would significantly impact sleep and are unwilling or unable to discontinue for >2 weeks.
4. Excessive alcohol consumption (>14 drinks per week or > 4 drinks per occasion)
5. Presence of suicidal ideations representing imminent risk as determined by the empirically-supported, standardized suicide risk assessment (described fully below in Tables 1 & 2 and in the Data and Safety Monitoring Plan document).
6. General medical condition, disease or neurological disorder that interferes with the assessments
7. Substance abuse or dependence
8. Mild traumatic brain injury (history of physical brain injury or blow to the head resulting in loss of consciousness >5 minutes)
9. Severe impediment to vision, hearing and/or hand movement, likely to interfere with the ability to complete the assessments, or are unable and/or unlikely to follow the study protocols
10. Pregnant or breast feeding
11. Current or lifetime history of bipolar disorder or psychosis
12. Current or expected cognitive behavior therapy for another condition
13. Received cognitive behavioral therapy for insomnia within the past year
14. Acute or unstable chronic illness: including but not limited to: uncontrolled thyroid disease, kidney, prostate or bladder conditions causing excessively frequent urination (> 3 times per night); medically unstable congestive heart failure, angina, other severe cardiac illness as defined by treatment regimen changes in the prior 3 months; stroke with serious sequelae; cancer if < 1 year since end of treatment; asthma, emphysema, or other severe respiratory diseases uncontrolled with medications; and neurological disorders such as Alzheimer's disease, Parkinson's disease and unstable epilepsy as defined by treatment regimen changes in the prior 3 months; unstable adult onset diabetes as defined by treatment regimen changes in the prior 3 months.
15. Current exposure to trauma, or exposure to trauma within the past 3 months
16. Working a rotating shift or an unconventional daytime shift (ending after 1900 h)
17. Underlying health condition that is at risk for complications from COVID-19

5.3 LIFESTYLE CONSIDERATIONS

During this study participants will be asked to:

- Wear study equipment while sleeping on 3 separate nights.
- Complete sleep diary entries daily.
- For CBT-I, participants will have their time in bed restricted initially and will be assigned earlier bedtimes and rise times. If daytime sleepiness increases during the time in bed restriction phase, participants will be discouraged from driving vehicles. Daytime napping will also be restricted to 30-45 minutes 7-9 hours after wake time.
- Adhere to basic sleep hygiene recommendations, including eliminating caffeine after lunchtime, limiting consumption of alcohol, nicotine, and heavy foods close to bedtime, and scheduling rigorous exercise earlier in the day. If nocturnal urination is a cause of sleep disruption, consumption of liquids will be limited two hours before bedtime.
- Refrain from starting new medications or dietary supplements for sleep.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study or phone screen but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include not meeting criteria for insomnia or taking sleeping pills. Rescreened participants will be assigned the same participant number as for the initial screening. Screen failures could also occur when an individual is no longer interested in participating in study procedures.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

5.5.1 RECRUITMENT STRATEGIES

Recruitment and retention strategies have been developed from the study team's extensive experience recruiting participants with cognitive impairment, sleep disturbance, and neuropsychiatric symptoms in past projects. Based off of this experience we will continue to target potential participants using referrals, community outreach, and online postings.

Referrals. We will recruit participants through referrals from both other research studies and clinics within the Stanford Hospital and the Palo Alto VA. We will also recruit participants through referrals from collaborating Community Health Centers (CHCs), including community clinics, in the Alameda, San Francisco, San Mateo, and Santa Clara counties. These CHCs and community clinics have multiple locations throughout the different counties and provide affordable healthcare, including mental health resources and therapy options, to low income and underrepresented populations.

Community Outreach. The community outreach recruitment activities will consist of posting flyers, sending postcards in the mail, tabling in clinics, and giving presentations. Flyers will be posted on bulletin boards in coffee shops, in grocery stores, around Stanford University's campus, and in any other public spaces that allow postings. In addition, postcards will periodically be sent through a company that does targeted mailings around the Bay Area. In-person community outreach will be done through presentations and tabling. Presentations about CBT-I and Insomnia will be done at local community

group meeting (i.e. Rotary, Lions Club, Kiwanis) to raise awareness for the problem of sleep disruption and to spread word about the research study. In addition, study staff will set up a table with flyers and brochures about the research study in local clinics to talk with individuals about the study and give information on how to participate

Online Postings. We will utilize online recruitment methods including social media, Craigslist, and online community newspapers. We will create an electronic flyer that can be posted on various websites and easily shared from one person to another. We will also utilize lab accounts on social media sites like Facebook and Twitter to post information about the study.

Collaborative Approach for Asian American and Pacific Islanders Research and Education (CARE) Registry: The CARE Registry will provide researchers contact information of volunteers that may be eligible for their study. The researchers must contact potential participants within one month of receiving their contact information.

Consideration of Study Staff Safety. When recruiting in the community, study staff will always go in groups. They will never go into a private area with a potential participant, such as a car, house, or other enclosed areas. If a potential participant is posing a potential danger or is making study staff uncomfortable, they are permitted to end the conversation and destroy participant's contact information.

5.5.2 RETENTION AND ENGAGEMENT STRATEGIES

As an integral part of our recruitment and retention plan, we will implement a series of strategies that have proven effective in our previous clinical trials to achieve participant engagement, retention and data completeness. These include the following:

1. careful staff selection and standardized training in trial-specific protocols, rapport building, motivational interviewing, and problem solving as appropriate to their study roles;
2. legally adequate, effective informed consent;
3. prudent participant incentives and flexible scheduling;
4. promotion of study identity;
5. ongoing monitoring of recruitment and retention;
6. up-to-date participant contact information and two emergency contacts;
7. diligent efforts to re-engage inactive participants; and
8. alternative means of obtaining measurements.

To maximize retention and ensure that participants fully understand the demands and nature of the study before they enroll, recruitment staff will, as part of a detailed informed consent process, carefully review study requirements with the participants, explain the concept of the study and stress the importance of follow-up assessment. We additionally maintain a sophisticated participant database in REDCap, with robust reporting functions that will prompt assessment staff which participants are due to be scheduled for a visit and permit continuous monitoring of visit completion status. Research personnel will be persistent in attempting to recontact and engage noncompliant participants in subsequent follow-ups. Protocols of Co-Is with similarly, but more stringent inclusion criteria, yet excellent retention profile (low attrition through treatment completion and follow-up), and no AE (e.g. NCT01958541, NCT01770587) will be modeled and adapted to support retention and recruitment

within the current study. In addition to this and a detailed tracking database, we will also track website data analytics, source of new contacts, and ratio of screen:eligibility and eligibility:enrollment metrics to further evaluate the efficiency of recruitment strategies and further refinements to enhance feasibility of study target goals and enrollment milestones.

The methods to track enrollment described above will also aid in participant engagement and retention. Additional measures will nonetheless be taken to further increase retention. During screening, study staff will collect multiple forms of contact information (i.e. cell phone, email, mailing address, home phone) from each participant. This information will be stored in the encrypted database to be utilized for appointment reminders. Study staff will remind participants and confirm their appointment times through the participants' preferred method of contact. Study staff will also send reminder text messages (with the participants' permission) from a lab cell phone.

We will offer financial hs
for time taken to complete assessment visits and completing the study. Participants will be thanked for their time, following the study, and asked for feedback regarding feasibility and their experience completing the study.
Based on the above, and feasibility data from similar protocols by our group, we expect ≥80% retention rate through treatment and end of treatment assessments for Studies 1 and 2, and a ≥70% retention rate for the 6 month follow-up for Study 2. These numbers are consistent with Co-I Bernert's previously collected RCT on a behavioral insomnia intervention for suicide risk (NCT01958541) in a sample of N=77 high risk participants. In this study, which had more stringent inclusion criteria and a higher-risk sample, for which retention tends to be poor, feasibility data revealed discontinuation prior to treatment in only 9% of cases; retention was otherwise 100% through post-treatment phases. Attrition at follow-up was 3.8%, with no AE reported throughout the trial and excellent treatment adherence observed (>85% completed 75% of treatment sessions; >74% completed 100% of treatment sessions). The methods in NCT01958541 used to support retention and adherence will be adapted to the current project and aligned with in-use strategies to support the above strategy.

5.5.3 INCLUSION OF WOMEN AND MINORITIES

No one will be excluded from participation in the research on the basis of gender, race, or ethnicity. Individuals of both sexes and all racial and ethnic origins will be eligible for participation in the study.

Based on the records from our previous studies completed in the Bay Area as well as the race/ethnicity distribution in Santa Clara County, we estimate the following breakdown by age, gender, race and ethnicity:

All minority participants who qualify for inclusion in the proposed research based on diagnostic considerations will be included. For our sample, we plan to recruit an equal number of men and women (50%). Our recruiting procedures in the past have allowed us to obtain a representative sampling of participants in the Palo Alto/Stanford area according to minority status (See **Table 3**). Based on data from area census reports and on the distribution of subjects who have participated in our previous studies, we estimate enrollment of approximately 25.6% Hispanic and 74.4% non-Hispanic individuals. We estimate further that the distribution across the NIH-specified racial categories will be approximately: 1.2% American Indian/Alaska Native, 37.5% Asian, 0.5% Native Hawaiian or Other

Pacific Islander, 2.8% Black or African American, 25.6% Hispanic, and 31.6% white. We will continually monitor our recruitment numbers related to diversity. If our numbers are not meeting the anticipated percentages by minority group, we will increase our targeted efforts to reach each group through targeted postcard distribution, and engagement in local community centers. We have an outreach program for our other clinical programs and expect that the recruited sample for the proposed study will exceed past participation of minority participants. The ultimate goal of these efforts is to increase our presence in minority communities and thereby to increase minority representation among our participants.

We will track accrual by sex, race and ethnicity each week throughout the study enrollment period. We will conduct valid analyses of the intervention effect as modified by sex and race/ethnicity, without requiring high statistical power for each subgroup given their exploratory nature.

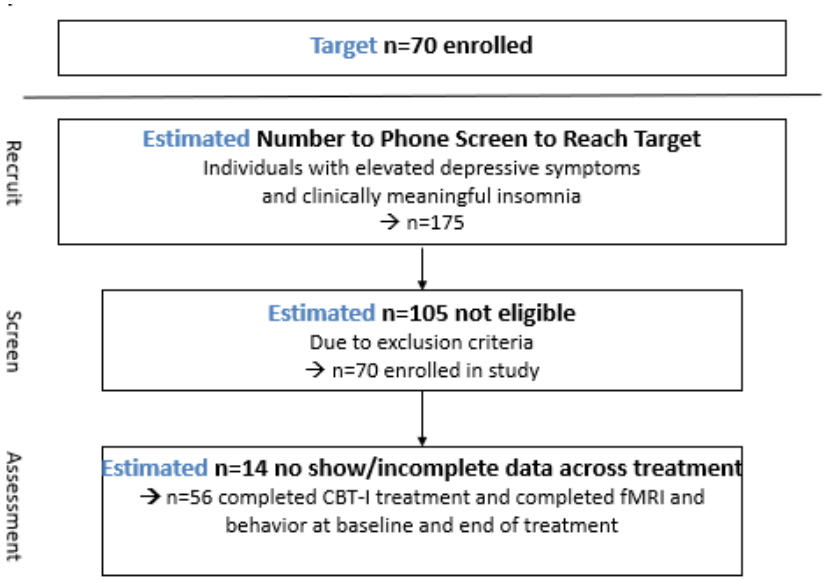
Table 3. Anticipated Enrollment Break-down

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaskan Native	1	0	0	0	1
Asian	13	14	0	0	27
Native Hawaiian or other Pacific Islander	0	1	0	0	1
Black or African American	1	1	0	0	2
White	11	10	9	9	39
More than one Race	0	0	0	0	0
Total	26	26	9	9	70

5.5.4 ANTICIPATED RECRUITMENT, ENROLLMENT, AND RETENTION

We anticipate needing to recruit a total of 175 participants to achieve our target enrolment of 70 eligible participants after the phone and in person screening session (See Figure 5). With all these measures, we expect greater than an 80% retention rate or better for the end of treatment follow-up (See Figure 5).

Figure 5. Consort Diagram



6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

6.1.1.1 COGNITIVE BEHAVIORAL THERAPY

BACKGROUND AND RATIONALE FOR CBT-I

CBT for insomnia is based largely on Spielman's conceptual model for primary insomnia. This model identifies predisposing factors, precipitating events, and perpetuating mechanisms that contribute to the development of chronic insomnia. Some individuals may be particularly predisposed or vulnerable to sleep difficulties by virtue of having a highly sensitive, or malfunctioning biological sleep system or a hyperactive arousal system that interferes with sleep. Circumstances such as stressful life events often precipitate sleep difficulties. This is more likely to occur in individuals with a predisposition for insomnia. In most cases the sleep difficulties are transient and resolve when the original distress subsides. In some cases, the patient becomes overly focused on the sleep problem. This focus tends to perpetuate sleep difficulties as it can produce heightened anxiety about sleep and lead to the development of maladaptive strategies and practices that, although intended to improve sleep, actually worsen it. Such maladaptive strategies include avoidance behaviors during waking hours (e.g., cancelling planned activities due to fatigue or fear such activities will interfere with next night's sleep), varying bed time and/or wake time, spending excessive time in bed, and developing rigid sleep-related rituals.

These behaviors are manifestations of increased sleep effort. Simply stated, the patient is trying too hard to sleep. In response to poor sleep patients also develop sleep-interfering cognitions, such as overestimating and worrying about the negative consequences of poor sleep, approaching bedtime with fear of failure, etc. Thus, patients' cognitive responses to their sleep problems and many of the practices that they adopt for coping with it end up prolonging or exacerbating the very problem they are trying to solve. The cognitive-behavioral approach to insomnia aims to modify behaviors that sustain or add to patients' sleep problems and correct cognitions that lead to heightened anxiety about sleep and to maladaptive sleep-related behaviors.

6.1.2 ADMINISTRATION AND/OR DOSING

CBT-I will consist of 6 sessions administered ideally once a week over a period of six to eight weeks. A full-dose will be defined as completing all 6 sessions. Sessions will occur either face-to-face or via Stanford Zoom with a PhD/PsyD psychologist, or graduate student under the supervision of a licensed PhD/PsyD psychologist, who is experienced in administering the study treatments and has completed the CBT-I training. Study sessions will occur in treatment rooms at Stanford or via Stanford Zoom. The full description of treatment details can be found in Section 6.1.1, Study Intervention or Experimental Manipulation Description and Appendix C.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

All treatment sessions will be audio and/or video recorded, and the recordings will be securely uploaded to an encrypted server. Treatment fidelity will be monitored in a randomly selected subset of 10% of the sessions. Treatment fidelity will be rated using a treater fidelity questionnaire (Appendix D).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 RANDOMIZATION PROCEDURES

N/A

6.3.2 BLINDING PROCEDURES

N/A

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Since compliance with CBT treatment elements has been found to be variable, it will be measured for potential influence on outcomes[112]. Weekly review of daily sleep logs and their correspondence with actiwatch data will be used as an additional proxy of treatment compliance during the course of treatment. At the end of treatment participants will complete a treatment adherence questionnaire explicitly designed for CBT-I[114]. We have used this method to check for compliance in earlier research[115].

6.5 CONCOMITANT THERAPY

For this protocol, participants may not use psychotropic medications that may significantly impact sleep, alertness, or mood until after visit 9 (end of treatment). The use of medications specifically used for sleep are not allowed during until after visit 9 (end of treatment). Medication usage will be assessed at each study visit and documented in the relevant Case Report Form (CRF).

Participants may not receive cognitive behavioral therapy for other conditions (e.g. depression) until after visit 9 (end of treatment).

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a participant discontinues from CBT-I but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue

- The participant will complete the emotional distress and sleep questionnaires that are administered at each treatment session at the time of discontinuation. Thereafter, the participant will be included in all future scheduled assessments (including emotional distress and sleep questionnaires), even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, including repeated failure to complete sleep diaries, adhere to treatment protocol requirements (ex. prescribed sleep schedule), or engage productively in treatment sessions.
- Lost-to-follow up; unable to contact participant (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Increase in bothersome nightmares for a week under treatment. We have not seen consistent reporting of nightmares with the proposed treatments, however that is always possible, hence again we would want to make sure that that occurred for at least a week before a patient was discontinued.

Patients will be allowed to continue in the protocol after an SAE independent of treatment, e.g. hospitalization following a fall. All treatments are considered active and patients will be allowed to continue their treatment as a courtesy. Similarly, patients will be allowed to continue if it is discovered following treatment initiation that they meet an exclusion criterion (either newly developed or not previously recognized) if the study physician and psychologist deem there are no additional risks to the participant in continuing treatment. However, data from such participants will not be included in statistical analyses since such SAEs and other exclusions may affect sleep. Patients will not be restarted if their sleep deteriorates meeting the above criteria and they are discontinued from the protocol.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF). Participants who sign the informed consent form, but have not yet received the study intervention, and subsequently withdraw, or are discontinued from the study will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she receives treatment and fails to return for 3 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the laboratory for a required study visit:

- Study personnel will attempt to contact the participant, the ideal will be to reschedule the missed visit within one week for treatment sessions, and within two weeks for the end of treatment visit, counsel

the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls or emails and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1 PHYSICAL EXAMINATION

N/A

8.1.2 CLINICAL INTERVIEWS

DUKE[116]. The Duke Structured Interview for Sleep Disorders is a structured interview which screens for sleep disorders in accordance with criteria of both the DSM-IV and the international classification of sleep disorders (ICSD-2). The DUKE is composed of 4 modules that assess sleep disorder symptoms associated with complaints of insomnia, sleep disorders associated with complaints of hypersomnia, circadian rhythm sleep disorders, and sleep disorders associated with parasomnias.

MINI[117]. The Mini International Neuropsychiatric Interview is a brief structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders. It assesses the 17 most common mental health disorders selected based on current prevalence rates. The MINI uses branching tree logic.

8.1.3 QUESTIONNAIRES

Columbia Suicide Severity Rating Scale[117] . The Columbia Suicide Severity Rating Scale (CSSRS) is an assessment tool the evaluates suicidal ideation and behavior.

Beck Scale for Suicidal Ideation. The Beck Scale for Suicidal Ideation is a 21 questions evaluation of suicidal thinking that helps identify individuals at risk. It also helps measure a broad spectrum of attitudes and behaviors.

Insomnia Severity Index (ISI)[118]. The Insomnia Severity Index (ISI) is a 7-item self-report measure of insomnia type, severity, and impact on functioning. The items consist of: severity of sleep onset, sleep maintenance, early morning awakenings, sleep dissatisfaction, interference with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Items are scored from 0 to 4 (0 = no problem, 4 = very severe problem). Score ranges of insomnia are: 0-7 absent, 8-14 sub-threshold, 15-21 moderate, and 22-28 severe. The ISI has good validity and reliability.

Pittsburg Sleep Quality Index[119]. The Pittsburg Sleep Quality Index (PSQI) is a 19-item self-report questionnaire that measures sleep quality from seven categories: subjective sleep quality, sleep latency,

sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Items are scored from 0 - 3, and a global sum of 5 or greater indicates poor sleep quality. The PSQI has high validity and reliability (Cronbach's alpha = 0.83).

Dysfunctional Beliefs About Sleep (DBAS)[120]. The DBAS-16 is self-report questionnaire consisting of 16 questions. The DBAS-16 uses a personal rating response format of 0-10 to assess 4 factors consisting of perceived consequences of insomnia, worry/helplessness about insomnia, sleep expectations, and medication.

Morningness Eveningness Questionnaire[121]. The MEQ consists of 19 questions that assess degree of alertness and activity associated with differences in morningness and eveningness. The MEQ mainly uses questions with a 4-choice format that correspond to a definite morning type, moderate evening type, and definite evening type.

Beck Depression Inventory (BDI)[89] . The BDI-II is a 21-item self-report scale that assesses the severity of depression symptoms. The depression items consist of: sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex. Items are scored from 0 to 3, and higher scores indicate greater levels of severity. The ranges for depression are: 0-13 minimal, 14-19 mild, 20-28 moderate, and 29-63 severe. The BDI-II has high validity and reliability.

Beck Anxiety Inventory (BAI)[90]. The BAI is a 21-item self-report scale that assesses the severity of anxiety symptoms. Items are scored from 0 to 3 (0 = not at all, 3 = severe). Higher scores indicate greater levels of severity, and the ranges for anxiety levels are: 0-9 normal to minimal, 10-18 mild to moderate, 19-29 moderate to severe, and 30-63 severe. The BAI consists of two factors: somatic and cognitive.

World Health Organization Quality of Life Assessment (WHOQOL)[122]**.** The WHOQOL-BRIEF is a 26-item brief version of the WHOQOL, that measures quality of life based on six domains: physical health, psychological state, level of independence, social relations, environment, and spirituality/religion/personal beliefs. Four general items about subjective overall QOL and health are also included. Only domain and general item scores are calculated in the WHOQOL-BREF. Items are scored on scales of 1 to 5, and higher scores indicate higher quality of life.

Patient Health Questionnaire (PHQ-9)[123]. PHQ-9 is a self-administered instrument for screening, diagnosing, monitoring, and measuring the severity of depression. It rates the frequency of symptoms as "0" (not at all) to "3" (nearly every day) and has been validated for use in primary care. The PHQ-9 total score ranges from 0 to 27 and is categorized as follows: None or minimal depression 0-4, Mild depression 5-9, Moderate depression 10-14, Moderately severe depression 15-19, and Severe depression 20-27. Cronbach's alpha coefficients range from 0.86 to 0.89 and test-retest correlations range from 0.84-0.95 within 48 hours and from 0.81-0.96 at 7-day reassessment. PHQ-9 scores were found to be highly correlated with Beck Depression Inventory scores in the general population (r=0.73).

Generalized Anxiety Disorder Scale (GAD-7)[124]. GAD-7 is a valid and reliable 7-question scale to screen for 4 anxiety disorders: Post Traumatic Stress Disorder, Panic Disorder, Generalized Anxiety Disorder, and Social Phobia. A score of ≥10 indicates a high probability of 1 or more of these disorders. Cronbach's alpha is 0.92 and test-retest correlation is 0.83. GAD-7 scores also correlate highly with scores of 2 commonly- used anxiety scales: the Beck Anxiety Inventory (r=0.72) and the anxiety subscale of the Symptom Checklist-90 (r=0.74).

Emotion Regulation Questionnaire (ERQ)[125]. ERQ is a 10-item self-report survey assessing individual differences in the habitual use of two emotional regulation strategies: cognitive reappraisal (6 items)

and expressive suppression (4 items). Cognitive reappraisal is a strategy that involves interpreting an emotion-eliciting situation in a way that changes its emotional impact, whereas expressive suppression is a form of response modulation that involves restraining emotion expressive behavior. The ERQ shows high levels of internal consistency in measuring both strategies in a large, diverse sample (Reappraisal factor α=.79 and Suppression α= .73). Test-retest reliability across 3 months was .69 for both scales.

Penn State Worry Questionnaire (PSWQ)[126]. The PSWQ is a 16-item questionnaire that aims to measure the trait of worry, using Likert rating from 1 (not at all typical of me) to 5 (very typical of me). Research suggests that the instrument has a strong ability to differentiate patients with generalized anxiety disorder (GAD) for other anxiety disorders.

Stanford Sleepiness Scale (SSS). The SSS is a single item subjective measure of sleepiness using a Likert rating from 1 (feeling active and vital) to 7 (almost in reverie).

Consensus Sleep Log[128]. The consensus sleep log contains information from seven days of reporting the following measures: Wake after Sleep onset (WASO), Time in Bed (TIB), Sleep onset Latency (SOL), Total Sleep Time (TST), caffeine and alcohol use, and naps.

Profile of Mood States(POMS)[128]. The POMS is a questionnaire with 24 items and four scales to assess mood. The four scales are depression and anxiety, fatigue, vigor, and irritability. These scales are internally consistent and have good scale fit.

Snaith-Hamilton Pleasure Scale (SHAPS). The Snaith-Hamilton Pleasure Scale (SHAPS) is a self-administered, paper-and-pencil questionnaire with 14 items assessing four domains of pleasure response/hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink.

CHICa (Irritability and Cognitive Subscales)[129]. The CHICa is a 26 item self-report measure of impaired thermoregulation, disrupted appetite, affective problems, and lowered level of cognitive functioning. Each question is a four-point scale from 0 ('definitely no/untrue') to 3 ('definitely yes/true').

Difficulty in Emotion Regulation Scale (DERS). The DERS is a 36 item self-report measure of emotion regulation deficits that is designed to capture clinically relevant problems.

SF-36 (RAND) Version 1[130]. The SF-36 is a 36-item, self-administered survey to assess comprehensive quality-of-life measures. It consists of eight sections: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, and mental health. This survey is widely used and has been proven to be a reliable indicator of quality-of-life measures.

Toronto Alexithymia Scale (TAS-20)[131]. The TAS-20 is a 20-item self-report measure of alexithymia from multiple perspectives: difficulty identifying and distinguishing between feelings and bodily sensations, difficulty describing feelings, reduced daydreaming, and externally-oriented thinking.

Ruminative Response Scale (RRS-Short). The RRS is a 10-item questionnaire that measure ruminative tendencies.

Ford Insomnia Response to Stress Test (FIRST)[132]. The FIRST is a 9 item questionnaire regarding sleep disturbance in response to commonly experienced stressful situations, such as before an important meeting the next day or after an argument.

Credibility/Expectancy Questionnaire[133]. The Credibility/Expectancy Questionnaire is a scale for measuring treatment expectancy and rationale credibility. The questionnaire derives two predicted factors: cognitive based credibility and relatively more affectively based expectancy. The participant will see one section related to thinking and one section related to feeling. It has high internal consistency within each factor and good test-retest reliability.

Working Alliance Inventory[135]. The Working Alliance Inventory is a measure of therapeutic alliance assessing three aspects: agreement on the tasks of therapy, agreement on the goals of therapy, and

development of an affective bond. A high score on the survey is associated with improved outcomes for clients. The reliability compared to the Helping Alliance Questionnaire was good (α> 0.80).

Treatment Adherence Survey. The Treatment Adherence Survey is a self-report survey assessing the participant's adherence to the insomnia treatment.

Treatment Satisfaction Survey. The Treatment Satisfaction Survey is a self-report survey assessing the satisfaction and effect of the insomnia treatment.

8.1.4 PERFORMANCE BASED ASSESSMENTS

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[135]. RBANS is a brief, individually administered battery that measures cognitive decline in older patients and a neuropsychological screening in younger patients.

8.1.5 SLEEP ASSESSMENTS

On nights prior to study entrance, habitual sleep time and quantity will be measured with sleep logs and wrist actigraphy. Apnea link will be used on the night of the screening visit to assess for obstructive sleep apnea. Full nights of polysomnography will be acquired using full-scalp electrode coverage to test hypotheses related to sleep physiology.

8.1.5.1 APNEA LINK

Participants will undergo a screening for Obstructive Sleep Apnea (OSA) as part of the study screening session. The participants will take the device home and wear it while they sleep in their own bed. The device measures movement, respiration, and oxygen desaturation while the participant is asleep in order to report an Apnea Hypopnea Index (AHI), used to diagnose OSA. If a participant is found to have an moderate sleep apnea (AHI >= 15), they will be excluded from the study. Participants will return the next morning to return the Apnea Link.

8.1.5.2 POLYSOMNOGRAPHY (PSG)

Acquisition. PSG will be used to measure sleep on the nights before the baseline, baseline, end of intervention, and follow-up experimental visits as has done by PI Goldstein-Piekarski in previous studies[30,31,136]. PSG will be acquired using a 32-channel, EEG system (Compumedics, Siesta), validated for sleep recording. Electroencephalography (EEG) will be recorded at 26 standard locations conforming to the extended International 10-20 System (FP1, FP2, F7, F3, FZ, F4, F8, FC3, FC4, T7, C3, CZ, C4, T8, TP7, CP3, CPZ, CP4, TP8, P7, P3, PZ, P4, P8, O1, O2) using an EEG cap (Compumedics, QuickCap). Electrooculography (EOG) will be recorded at the right and left outer canthi (right superior; left inferior). Electromyography (EMG) will be recorded via three electrodes (one mental, two submental). Reference electrodes will be recorded at both the left and right mastoid (A1, A2). Data will be sampled first at 800Hz by the amplifier, digitized at 400Hz. All data will be stored unfiltered (recovered frequency range of 0.1-100Hz), except for a 60 Hz notch filter to remove mainline noise.

Sleep Scoring. Sleep-staging will be performed in accordance with standardized techniques using C3, C4, O1, O2, right and left EOG and EMG channels. EEG and EOG will be referenced to the contralateral mastoid and filtered to 0.3-35Hz. EMG will use a bipolar montage filtered to 10-70Hz and 0.1-12Hz, respectively. Sleep will be visually scored in 30-second epochs using the C3-A2

derivation according to standard criteria[137]. Polygraph data collected by the Siesta is transferred to a PC computer system equipped with Compumedics' Profusion PSG4 software. The software quantifies the manual scoring and produces concise reports that include measures of all sleep stages, sleep latency, total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency (SE). Manual scoring will be conducted on recordings that do not have the subject's name, diagnosis, or study phase attached. 10% of the records will be randomly distributed to a second technologist who will score them blindly (will require 90% concordance across scorers).

Sleep Architecture Variables of Interest.

Sleep Onset Latency (SOL) is the time (minutes) from "lights out" or start of total recording time, to actually falling asleep as indicated by EEG changes.

Number of Arousals is determined by number of times of awakening by EEG changes.

Wake After Sleep Onset (WASO) are periods of wakefulness occurring after sleep onset, before final awakening (sleep offset).

Total Sleep Time (TST) is the total time (minutes) spent asleep, from the start of sleep onset to sleep offset, subtracting any periods of wakefulness. TST includes stages N1, N2, N3, and REM sleep. Sleep Efficiency (SE) is calculated as TST divided by total time spent in bed, multiplied by 100. Duration in sleep stages of non-rapid eye movement (NREM) sleep includes stages N1, N2, and N3, and is measured in minutes. The duration of sleep outside of those stages that is associated with specific EEG stages is REM sleep.

Spectral Analysis. In addition to sleep staging, on the experimental nights topographical EEG power spectral density analysis associated with sleep stages will be calculated in the Delta (0.5-Hz), Theta (4-7Hz), Alpha (7-11Hz), Sigma (12-15Hz), Beta-1 (15-20Hz), Beta-2 (20-35Hz) and Gamma (35-45Hz) bands, according to published methodsmethods[139-147].

Respiratory Sinus Arrhythmia. RSA during a paced breathing task will be collected and analyzed as described in prior Co-I Gross publications on the evening before, and morning after each sleep recording (baseline, end of treatment, and at follow-up). Two channels of respiration measured with inductive plethysmography bands will temporarily replace other non-essential electrodes in the montage above.

8.1.6 NEUROIMAGING

All imaging will be conducted on a single scanner at the Stanford Center for Cognitive and Neurobiological Imaging (CNI).

8.1.6.1 PRIMARY FUNCTIONAL TASKS (APPROXIMATELY 34 MINUTES ON TASK)

Emotional reactivity paradigm (faces; ~10 minutes on task)[148-150]. This task reliably activates the amygdala and is well suited to clinical patient studies[62,151-155]. The task is described fully in Korgaonkar et al.[156]. In brief, stimuli were drawn from a standardized series of facial expressions of threat-related emotions (fear, anger), loss-related emotions (sadness) and reward-related emotions (happiness), along with neutral[157]. In both the supraliminal and subliminal conditions, a total of 240 stimuli are grouped in blocks of 8 faces for the same emotion, with each emotion block repeated 5 times and presented in a pseudorandom order. In the supraliminal condition, each face is presented for 500ms, with an interstimulus interval of 750ms. In the subliminal condition, faces are presented in a validated backward masking design to prevent conscious awareness[148].

Implicit Emotion regulation paradigm (faces; ~13 minutes on task). This task was designed to probe mPFC-modulated regulation and is described in full in Etkin et al.[158]. Participants are asked

to identify an expression of fear or happy, while ignoring an overlying word labeling the expression ("fear" or "happy"). The word either matches the facial expression (congruent) or conflicts with it (incongruent). Face stimuli are presented for 1s followed by a variable duration fixation (3-5s) for optimal signal estimation[158]. This emotional conflict induces reliable engagement of the vmPFC[158,160,161]. Poor threat regulation in this paradigm is observed in both anxiety disorders and MDD[160,161].

Emotion reactivity and regulation paradigm (scenes; ~11 minutes on task). This task is based on the psychological principles of weakening and appraising negative emotional states and has been utilized recently in several prior publications and is described fully in Fonzo et al. and Minkel et al.[162,163]. In short, participants are asked to "look" or "decrease" their emotional response to 30 Negative and 15 neutral valance images taken from the IAPS[163] Trials begin with a 2 second cue prompting them on whether they should "look" or "decrease" emotions to the subsequent emotional image. Either a negative or neutral image will then be presented for 7 seconds, followed by 4 second period where they are asked to rate their level of emotional negativity on a scale from 1 (Not at all negative) to 5 (Very much negative). A 1-3s variable duration fixation screen preceded the onset of the next trial. Images are presented in a pseudorandom order such that no more than two of the same instruction or 4 negative stimuli could be presented consecutively. Of the negative images, 15 were paired with the instruction "look" and 15 were paired with the instruction to "Decrease." All 15 neutral images are presented with the instruction "look." Prior to entering the scanner participants are given instructions on strategies for both the look and decrease conditions and are several practice images that are not included in the fMRI task[162,163].

8.1.6.2 SECONDARY FUNCTIONAL TASKS (APPROXIMATELY 35 MINUTES)

Resting State (eyes open; 10-30 min). A series of stand-alone eyes-open resting state scans of 10-30 min in duration separated into 2-6 five-minute runs will be acquired and analyzed using established methods from the HCP protocol[165]. Wakefulness will be monitored via eye tracking.

Go-NoGo Task (5 min). This task measures impulsivity (for 'Go' responses) versus inhibition (for 'NoGo' responses). Based on the color of the word 'press', the participant is instructed to either press or refrain from pressing the button. A green 'press' signifies the 'Go' response meaning the participant is instructed to press the button. A red 'press' signifies the 'NoGo' response meaning the participant is not supposed to press the button. Performance is based on reaction time and number of errors.

8.1.6.3 MRI ACQUISITION

Functional. fMRI images will be acquired during the above emotion paradigms using an echo planar imaging (EPI) MR sequence with these parameters: TR=2000ms, TE=27.5ms, matrix=64x64, FOV=24cm, flip angle=90. A 3D SPGR sequence is collected for normalization of functional images to standard space, as well as a field map for EPI unwarping.

Structural. T1-weighted images will be acquired using an HCP-equivalent inversion recovery fast SPGR sequence with an inversion time of 450ms, a TR of 6.3ms, a TE of 2.8ms, and a flip angle of 12°. T2-weighted images will be acquired with an HCP-equivalent 3D fast spin-echo sequence with a TE of 76ms and a TR of 2.5s. For the latter two sequences, the field of view will be 24cm with a 320x320 matrix size and a slice thickness of 0.8mm (isotropic voxel size $0.8mm^3$).

Diffusion-weighted: DTI was collected using single-shot, dual-spin-echo, echo-planar imaging sequence (84 unique directions; *b* = 1,250 s/ mm2; TR = 8,700 ms; TE = 8,700 ms; resolution = 2.0 mm isotropic; 70 slices; scan duration = 13 min 29 s). Nine non-diffusion-weighted (*b* = 0 s/mm2)

volumes were additionally collected for anatomical localization and regis- tration purposes.

8.1.6.4 PRE-PROCESSING AND DATA EXTRACTION.

Standard pre-processing methods in SPM8 used in PI Goldstein-Piekarski and Co-I Williams prior publications will be implemented in Matlab (Mathworks, Inc., Natick, MA). These include realignment, slice timing correction, spatial normalization to the MNI template[165] and smoothing at 8mm FWHM. First-level models: For each participant, trial-related activity will be assessed by convolving a vector of trial/block onsets with a canonical hemodynamic response function in the context of a GLM[166] in each paradigm. Six movement-related covariates from realignment (three rigid-body translations/three rotations) will be used as regressors of no interest in the design matrix for modeling movement for the tasks. Connectivity between the mPFC-Amygdala will be assessed using PPI analyses[86] with the amygdala as the seed. Region of interest (ROI) analyses will be performed using established methods[168], to identify BOLD-dependent signal change in the regions of interest for each network. Beta values for each participant and ROI will be extracted for regression analyses.

8.1.7 GENETICS

N/A

8.2 SAFETY ASSESSMENTS

8.2.1 PHYSICAL EXAMINATION

N/A

8.2.1 QUESTIONNAIRES

Acute/Unstable Chronic Illness Is a self-administered checklist designed to reveal uncontrolled or unstable illnesses during screening. The checklist evaluates for uncontrolled diabetes, thyroid disease, kidney, prostate, or bladder conditions, congestive heart failure, angina, sever cardiac illness, stroke, cancer, asthma, emphysema, respiratory disease, chronic pain conditions such as fibromyalgia, and neurological disorders such as Parkinson's disease, and unstable epilepsy.

The Columbia Suicide Severity Rating Scale is an assessment tool the evaluates suicidal ideation and behavior. Individuals are considered high risk if they endorse a 4 and will be evaluated by study PI, Co-I clinicians, and DSMB for inclusion in this study. If individuals are considered low or moderate risk, they will be monitored over the following weeks. If individuals are considered to be of high and imminent risk, the researcher will help the participant seek immediate clinical care, either through his/her doctor or, if the doctor is not available, through local emergency services.

BDI-II Suicide item during treatment is a 21-item self-administered survey which assesses depression symptoms in the past two weeks. Item 9 of the BDI assesses suicidal thoughts and wishes. If the participant answers anything other than "0-I don't have thoughts of killing myself," study staff will ask follow-up questions and notify the clinician.

Beck Scale for Suicidal Ideation. The Beck Scale for Suicidal Ideation is an evaluation of suicidal thinking that helps identify individuals at risk. It also helps measure a broad spectrum of attitudes and

behaviors. If the participant answers anything other than "0-I don't have thoughts of killing myself," study staff will ask follow-up questions and notify the clinician.

8.2.2 IMAGING

See section Reporting Events to Participants

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An **Adverse Event (AE)** is any untoward medical occurrence, including any abnormal sign, symptom, or disease *temporally* associated with study participation, whether or not considered related to participation in the research.

- An AE is deemed to be associated with the use of the study device if there is "a reasonable possibility that the experience may have been caused by the device."
- Chronic problems which are unchanged from baseline are not considered AEs. However, worsening of an ongoing condition would be considered an AE.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A **Serious Adverse Event (SAE**) is an adverse event that

- results in death
- is life-threatening, or places the participant at immediate risk of death from the event as it occurred
- requires or prolongs hospitalization
- leads to persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of events reported on the "Adverse Events" log will be determined by the site physician as:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Of note, the term "severe" does not necessarily equate to "serious".
- **Life threatening or disabling** – life-threatening or incapacitating.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Definitely unrelated** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in sleep disorders, gerontology, and dementia will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Trained study personnel will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the end of treatment visit (visit 9). At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be reported annually or more often to the DSMB, Stanford IRB, and NIMH staff.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the DSMB and NIMH Program Official as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

The PI and research team will report SAEs to the local IRB per Stanford University's HRPP Policy Guidance "Events and Information that Require Prompt Reporting to the IRB" GUI-P13 1/3 (see Appendix A).

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Incidental MRI findings. In our participant information and consent forms we will explicitly state that the scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. Before participation we will make sure participants have been informed of, understood and consented to the following:

1. All research MRI and fMRI scanning protocols are carried out for scientific purposes and are not optimized to make clinical diagnoses, thus they do not qualify as clinical diagnostic scans.
2. The investigators and personnel on this project are not trained to perform medical diagnosis on MRI scans. The investigators are not responsible for failure to find existing abnormalities in the MRI scans acquired with research protocols.
3. Point 2 notwithstanding, there is a small possibility that during the processing of participants' scans for research purposes, features of the brain that can be considered out of the normal range might be observed. In case such a potential abnormality is observed (i.e. incidental finding), we will follow the established management protocol for incidental findings, as outlined in collaboration with our Stanford imaging facility at CNI. This protocol is as follow:
    i. In the event of a potential incidental finding, research scans are referred to an appropriately qualified individual (neuroradiologist) designated by the CNI Board, for further review. The reviewer will determine if the potential abnormality merits further investigation and will inform the Principal Investigator of the action to be taken.
    ii. The CNI operations team promptly provides a DVD with the scans in question or in another way makes the images available to the reviewer to be read "as is". The reviewer is a doctor specializing in MRI will be asked to look at the images to see if any medical follow-up is needed.
    iii. If follow-up is recommended, the investigator will be informed by CNI. The investigator will then contact the participant with the appropriate information. Because the images are taken using research settings they will not be made available for clinical purposes.
4. When participating in the experiment, the participant agrees with being informed about potential medical problems according to the above-described procedure. The participant is also informed that if such potential problem is reported to the participant, it is the participant's responsibility to seek appropriate help from a qualified professional via their general physician.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

1. **Unanticipated problems (UPs) involving risks to participants or others**
   Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which in the opinion of the Monitoring Entity or the PD meet all of the following criteria:
   a) Unexpected
   in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the subject population being studied;
   AND
   b) **Related to participation in the research** or there is a reasonable possibility or likelihood that the incident, experience, or outcome may have been caused by the procedures involved in the research;
   AND
   c) Harmful
   the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
2. **New Information** that indicates a change to the risks or potential benefits of the research in terms of severity or frequency or impacts the participant's willingness to participate (e.g., DSMB/DSMC Report, other safety information or publication, suspension or premature termination by the sponsor or investigator).
3. **Noncompliance:** An action or activity in human subject research at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of Stanford University, SHC, LPCH, VAPAHCS (e.g., VHA Handbook 1200.5), Palo Alto Veterans Institute for Research (PAVIR) or relevant state or federal laws.
   When the event is:

- Possibly serious
  - Noncompliance that affects the rights or welfare of human subject research participants.
- Possibly continuous
  - A pattern of noncompliance that continues to occur after a report of noncompliance and a corrective action plan has been reviewed and approved by the IRB, after an investigator has been warned to correct errors or noncompliance, or a circumstance in which an investigator fails to cooperate with investigating or correcting non-compliance.

4. **Complaint** unresolved by the research team.
5. **Incarceration** when in the opinion of the PD it is in the best interest of the participant to remain in the study.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

1. Hypothesis 1: enroll 70 participants and retain ≥85% at 11 weeks.

2. Hypothesis 2: At least 60% of participants show an increase in emotional regulation as indicated by any one of the three: i) an increase in mPFC activation, ii) an increase in mPFC-amygdala connectivity, or iii) a decrease in amygdala activation relative to baseline, supporting that the targets can be modified in a majority of participants.

9.2 SAMPLE SIZE DETERMINATION

The primary goals of Study 1 are to verify preliminary evidence of target engagement and to refine the measures selected to use in Study 2. To aid in defining meaningful effect sizes for early stage research, Sheiner and Julious and Patterson proposed the use of precision intervals of pre-specified width to guide sample size determination—an approach that Co-I Ma et al. have used in a prior NIH-funded pilot study. Julious[83] offered a further adjustment to provide Assurance (in a role similar to Power) that a chosen standardized width contains the mean parameter. To obtain a precision interval with standardized half-width 0.50 (similar to a “medium” effect size) with Assurance of 95%, 44 participants are required. For the R61 phase we have planned more conservative sample size of 70 and will retain ≥ 80% (56 participants). This allows for occasional fMRI data collection failures (e.g., no shows and magnet leavers) and will provide more reliable estimates of neural target engagement, defined as the effect of CBT-I on changes in amygdala reactivity and amygdala-mPFC connectivity from baseline to 11 weeks. This will provide reliable estimates of target engagement (i.e., the treatment effect on amygdala activation and amygdala-mPFC connectivity).

In addition to testing the Go criteria, the results of the analyses conducted in the R61 phase will be used to refine the list of measures included in the R33 phase. We will use regression models to evaluate which of the study measures improve over the course of treatment in a way that is positively associated with improvement

in sleep. Those measures that yield a clinically meaningful effect as defined by R2=0.10 (medium effect size) in the R61 phase will be maintained in the R33 phase for confirmatory analyses. Using a conservative estimate, in order to detect effects in which changes in sleep explain at least 10% of the variance (i.e. R2 ≥ 0.10) with at least 80% power, we will need 56 participants. This is feasible based on our planned retention strategy, limiting drop out to ≤20%. We will examine changes in depressive symptoms and suicidality trajectories as a function of treatment dose (defined as cumulative sessions of CBT-I) to determine whether target engagement may be occurring earlier in treatment in order to better optimize dose. Age, sex, and symptom severity will be included as covariates.

[redacted]

9.3 POPULATIONS FOR ANALYSES

We will conduct both an intent-to-treat (ITT) analysis using the last observation carried forward and analysis based on completers only, to assess bias caused by dropouts. Emotional distress assessments during the weekly treatment sessions will aid in understanding reasons for dropout.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This project will employ robust statistical methods for each aim to rigorously test our model. We will maintain meticulous version control in the analysis utilizing git and will make our analysis and design code available via github to aid in transparency and methodological reproducibility.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Statistical Analyses: We hypothesize that in this single-arm study treatment with CBT-I will lead to improvements in Emotion Regulation Network function. Specifically, we predict that sleep restoration will be associated with greater increases in mPFC reactivity and mPFC-Amygdala Connectivity, and with decreases in Amygdala reactivity. An extended analysis of covariance (ANCOVA) will be used to test the primary hypothesis of change in Emotion Regulation Network function from baseline to end of treatment. We will characterize the association between our primary measures of Emotion Regulation Network function and that of our proximal outcome (sleep disruption as defined by sleep-EEG derived sleep efficiency) using a regression framework with age and sex included as covariates.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Statistical Analyses Related to Treatment Effects: We will examine the treatment effect on outcomes as measured by validated self-report questionnaires and sleep disruption measurements as well as the association of change in Emotion Regulation Network function with change in outcomes. We will also analyze within-

subject trajectories of BDI and CSSRS scores, as well as sleep variables derived from actigraphy and daily sleep logs as a function of treatment dose, defined as cumulative number of CBT-I sessions.

Statistical Analyses Secondary Measures Related to Emotional Distress: Emotional distress secondary outcomes will be assessed using validated measures including Columbia Suicide Severity Rating Scale (CSSRS), World Health Organization quality of Life Assessment (WHOQoL-BRIEF), Patient Health Questionnaire (PHQ-9), and the Generalized Anxiety Disorder Scale (GAD-7). Secondary sleep disruption outcomes will include subjective experience of sleep disruption as indicated by the Insomnia Severity Index (ISI) and daily sleep logs, as well as sleep continuity and architecture variables derived from overnight sleep-EEG recording and actigraphy. Spectral analysis variables derived from the overnight sleep-EEG recording. We will also explore associations between emotion regulation related behaviors and physiology including behavior on the neuroimaging emotion regulation tasks (implicit threat priming, emotional conflict, and emotional response), measures of emotional reappraisal and suppression as assessed with the Emotion Regulation Questionnaire and the other domains, and Respiratory Sinus Arrhythmia (RSA). The statistical approach to analysis of the treatment effect on these outcomes will use ANCOVA, analogous to the analysis of target engagement (above).

Some measures will be collected daily (e.g. actigraphy and sleep logs) and weekly (BAI, BDI, CSSRS) over the course of treatment. Our general approach is to apply mixed linear models, using the daily/weekly reports to construct an individual specific estimate (functionally the mean and coefficient of variation of daily measurements for each naturalistic measure over a week) for baseline and follow-up, and then testing the effect of time (thus testing the within-person change over time). Random intercepts and slopes (and their covariance) at the person level will be included in our models. Random intercepts will be used to account for the clustering of observations within individuals across time; random slopes for key within-person predictors (e.g. 'time' or pre to post in this case) will be included to allow within-person slopes to be stronger for some individuals and weaker for others. In cases where random slopes are observed, we will test for potential subgroups/moderation (e.g., by age, sex, etc.; although we note that the small sample size somewhat limits our statistical power for such moderation tests).

Statistical Analyses Secondary Measures Related to Cohesive Factors of Dysfunction: Sparse unsupervised clustering and PCA analyses will be used to identify cohesive factors of dysfunction in a) targets of Emotion Regulation Network function, b) sleep disturbances, c) patterns of emotional distress, and d) behavioral measure of Emotion Regulation Network function at baseline. General linear models will be used to quantify the relationships within and between these factors.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics including demographics, objective and subjective sleep disturbances, cognitive impairment, depression, and anxiety.

9.4.6 PLANNED INTERIM ANALYSES

There is no planned interim analysis for this project. The DSMB or NIMH will determine if a planned interim analysis should be conducted. If the DSMB requests a detailed safety review of SAEs or severe AEs by group, then based on that review, the DSMB or NIMH Officer will determine what steps will be taken.

9.4.7 SUB-GROUP ANALYSES

We will examine sex differences and associations with age in *a priori* subgroup analyses, but without requiring conventional statistical power.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Data will be stored in the long format with the end points in separate columns and participants repeated across rows specified by the time points.

9.4.9 EXPLORATORY ANALYSES

[redacted]

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANT

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

- Consent Procedures and Documentation

Procedures for obtaining informed consent. During the consenting process, each prospective participant will meet in a private interview room at the study site with the PI or trained study staff. The information contained in the Informed Consent Form (ICF) is initially described orally to the prospective participant. Care is taken to inform prospective participants repeatedly that participation is entirely voluntary and that they may withdraw at any time and for any reason. Any questions will be answered. The prospective participant is then asked to read the consent form carefully. The prospective participant is asked to summarize the consent form, including the discomforts, risks, and confidentiality sections.

Enough time will be allowed for the potential participant and to make an informed decision, including time to discuss the study with the researchers and ask any questions they may have. We estimate the consenting process will take between 30 minutes and one hour. The potential participant may take the consent home to discuss with others, and return later to sign it if they desire and return at a later time to complete the study visit.

Procedures for documenting informed consent. Only after the prospective participant demonstrates by stating in their own words that they understand the purposes, risks, and potential benefits of the study and they are willing to volunteer, will the participant be asked to sign and date their respective consent forms.

A copy of the ICFs will be given to each participant. This fact will be documented in the participant's record. All original signed consent forms will be stored in the Study Consent Binder in a locked file when not in use.

Provisions for vulnerable populations. We do not anticipate any participants to fall under provisions for vulnerable populations.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be discontinued at any time by the IRB, the NIMH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

Standard procedures for data collection will be employed to minimize the risk to participant confidentiality. An anonymous ID key will replace all details that identify participants before any use or transmission of data. Any details identifying participants will be held in confidence and stored within the secure database. The information obtained in the study will be treated in the strictest confidence and none of the participants in this study will be individually identifiable in any resulting publications or reports. All data files will be kept in password-protected computer files. All research activities will be conducted in as private setting as possible, and all confidential information gathered during the course of interviews and data collection will be entered into password-protected computers. Follow-up interactions will take place by private phone calls and emails to previously identified email addresses private to that participant.

All scanning will take place in the MRI suite in the Center for Cognitive and Neurobiological Imaging (CNI) at Stanford, to which access is restricted except to study personnel. All data will be de-identified after acquisition. PHI will be maintained in the secure REDCap database and password-protected computers in the lab of Dr. Goldstein-Piekarski. Paper copies of PHI and questionnaire data will be kept in locked cabinets in Dr. Goldstein-Piekarski's lab. All computers, external hard disks, USB thumbs, tablet computer, smart phone etc. will be encrypted and password protected. Once acquired, data will be de-identified and given a generic indicator (e.g. IREST001). MRI scans, from which facial information may be reconstructed (and thus an identifier) will be de-identified using conventional face stripping algorithms for MRI data. Audio/video recordings will be edited to obscure facial features and will be marked with a generic identifier. Access to de-identified data will be available to the study personnel and access will be controlled by the study lead investigator and protocol director (Dr. Goldstein-Piekarski). All research staff will undergo training from the lead investigator, including in the means through which confidentiality is maintained.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored in the lab of Dr. Goldstein-Piekarski for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific

study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.]

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored on encrypted computers and in locked files within PI Goldstein-Piekarski's lab at Stanford. After the study is completed, the de-identified, archived data will be transmitted to and stored at the NIMH data archive, for use by other researchers including those outside of the study. Permission to transmit data to the NIMH data archive will be included in the informed consent.

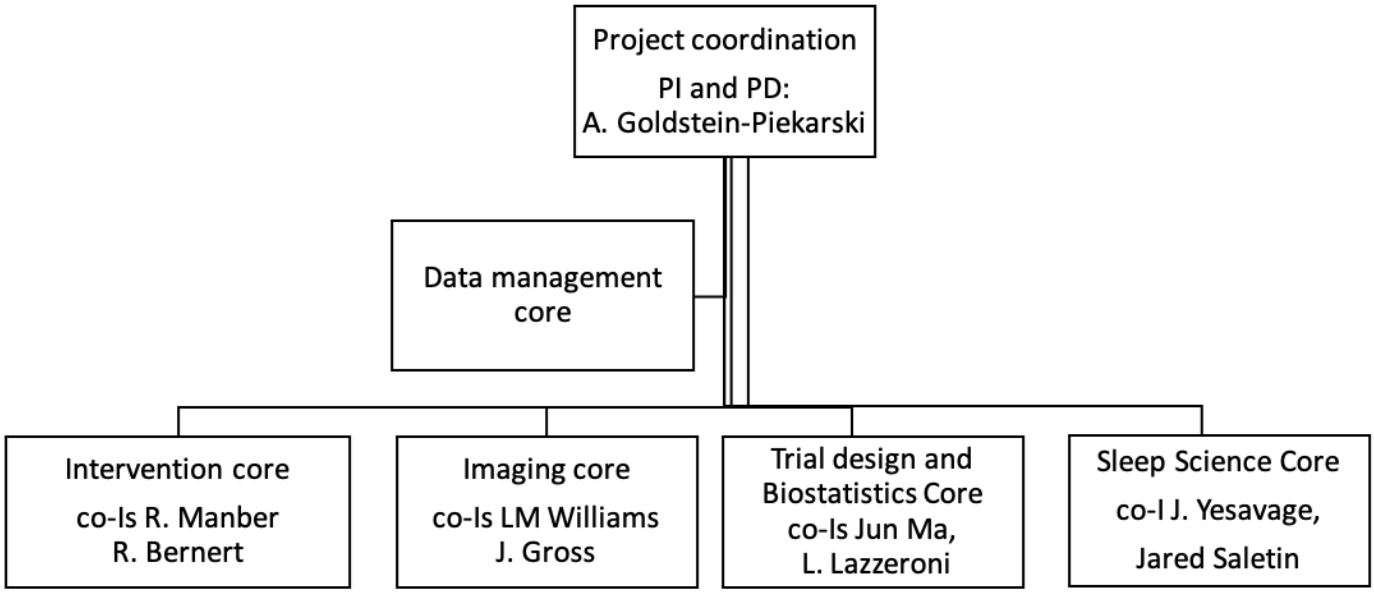
With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples may be stored in one of the National Institutes of Health (NIH) databases with the same goal as the sharing of data with the NIMH data archive. The NIH repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Data Safety Monitoring Board
Andrea Goldstein-Piekarski, PhD *Stanford University School of Medicine* *401 Quarry Rd.* Palo Alto, CA 94304 [redacted] *agoldpie@stanford.edu*	*Daniel Taylor, Ph.D.* *University of Arizona* [redacted]
	Meredith Wallace, Ph.D. *University of Pittsburgh School of Medicine* [redacted]
	Yelena Blank, Ph.D. *Private Practice* [redacted]

10.1.5.1 STUDY TEAM ORGANIZATIONAL STRUCTURE



The team is structured around a collaborative model. PI Goldstein-Piekarski will be the overall study PI and coordinate the data management and operations of the study.

10.1.5.2 INVESTIGATORS AND RESEARCH STAFF

10.1.5.3 PI LEADERSHIP

Andrea Goldstein-Piekarski, PhD will lead the team of investigators and staff and will direct the oversight and coordination of fiscal management, research administration, publications and data sharing, and integration of all resources needed for the project. In particular, she will (1) review and address issues that require judgment over the scientific direction and conduct of the protocol; (2) oversee decisions on any changes in research direction and therefore, have the authority to reallocate funds and resources to best meet the emerging needs of the project; (3) provide communication with in the organizational hierarchy to maintain alignment with operational priorities, and assist with addressing both scientific and implementation questions and barriers; and (4) ensure compliance with participant privacy and confidentiality regulations at all times. Decisions will be made through discussion and consensus building with all the co-investigators. Throughout the process, the PI and co-investigators will remain respectful of the perspectives that each individual brings to the project and will collaborate diligently to ensure scientific rigor and transparency and optimize operational efficiency.

10.1.5.4 RESEARCH STAFF AND POSTDOCTORAL FELLOWS

intervention implementation, (2) recruitment, retention and data collection, and (3) data management and analysis. The Intervention Implementation staff includes a clinical psychologist who will provide treatment to the participants and monitor suicide risk. The clinical psychologist will interface with the Intervention Core including Drs Manber and Bernert. Dr. Bernert and Dr. Yesavage will serve as medical-monitors for the study. The Recruitment, Retention and Data Collection staff are clinical research coordinators who will develop and implement the participant recruitment and retention protocol as well as the data collection procedures, forms and databases in the R61 phase. They will work with the Trial design and biostatistics core to refine the protocols and measures for use in the R33 phase. The two postdoctoral fellows with expertise in neuroimaging and sleep research will also contribute to data collection and ensure ongoing quality of the incoming data. The Data Management and Analysis staff will develop and maintain the data management system and protocols and perform data analyses under the guidance of PI Goldstein-Piekarski and the Trial design and Biostatistics Core.

10.1.6 SAFETY OVERSIGHT

DATA SAFETY MONITORING PLAN

This safety monitoring protocol (**Table 4**) has been successfully employed in two former randomized controlled trials for suicide prevention funded to the Co-I [DOD: W81XWH-10-2-0178, NIH: K23MH093490], and is consistent with previous and in use procedures by the research team. All procedures will be closely supervised by this study's PIs and on-site safety officers, Drs. Bernert and Yesavage. Suicide risk assessment will be conducted using empirically-established risk categorizations (minimal, mild, moderate, severe, imminent; **Table 5**) to routinize clinical decision-making and emergency referral procedures for suicidal behaviors.

TABLE 4: DATA AND SAFETY MONITORING PLAN (DSMP)
Training of Personnel in Suicide Risk Assessment:
1. All study personnel will complete extensive clinical training in suicide risk assessment practices, led by the PI, Safety monitors, and Co-I's. This team will meet regularly to discuss suicide risk assessment, DSMP procedures, adequacy and assessment of training. Though all personnel will receive training, the CSSRS will only be administered only by Master's level staff, clinical doctoral students, or trained clinicians (PIs/Co-Is, Study Clinicians).

Primary Assessment Measure

2. A score ≥ 4 on the CSSRS will prompt standardized suicide risk assessment and administration of The Suicide Checklist and Suicide Assessment Decision Tree (See Below).
    a. If risk is elevated but not imminent, established behavioral methods will be used to effectively manage risk on an outpatient basis. The PI/Safety Monitors will closely monitor decision-making and assessment, and all action taken will be clearly documented.
    b. If risk is imminent, participants will be referred for immediate hospitalization and emergency mental health services. The PI/Co-Is will closely monitor decision-making and assessment, and action taken will be documented.

At Study Initiation:

3. This study will follow warm transfer procedures previously used for triage to the National Suicide Prevention Crisis Line for referral and triage. Established in 2011, this was approved by Stanford University is has been previously used in DSMP protocols conducted by the research team.
4. Participants will be required to provide contact information as part of informed consent procedures, including personal contact information (e.g., physical address, cell) and permission to call an identified next of kin or emergency contact in the case of an emergency. In the rare situation that: a participant is judged to be at imminent risk for suicide, is located offsite, and is unwilling/unable to seek out referred mental health services, next of kin notification will be utilized to coordinate emergency referral.
5. Participants will be provided with emergency referral contact information and 24-hr resources (e.g., 1-800-273-TALK, online chat and text; Crisis Text Line) for outpatient safety monitoring. Participants who endorse symptoms indicative of serious or imminent risk will be warm transferred to appropriate services.
6. Best practices in suicide risk assessment and management procedures will be reviewed at the outset of the study with all participants, as a central component to the informed consent process. Notification of next of kin procedures, and permission to contact this individual in event of a no-show/elevation in risk/circumstances outlined in consent form, will be reviewed prior to enrollment, in addition to confidential/non-confidential referral resources available to the participant in the event of an elevation in symptoms. Emergency resources provision will be regularly provided at the outset of participation.
7. Participants will be explicitly encouraged to contact the PI/Co-Is/Study Clinician if symptoms elevate between screening and intervention sessions via a 24/7 study pager.
8. Participants will be referred to a supervising clinician if a participant experiences distress at any point following enrollment. This will prompt standardized suicide risk assessment according to established frameworks.

Active/intervention phases of the study

9. No shows will be vigorously pursued.
10. Safety Checks will be conducted at all study visits and documented for future review.
11. Safety planning will be conducted if risk is judged to be elevated, prompted by standardized risk assessment findings. Safety planning will be tailored to the individual and his or her level of risk. A safety plan will be outlined via construction and use of a Coping Card. Use of Coping Cards/Collaborative Assessment and Management of Suicidal Symptoms/Safety Planning Procedures are evidence-based for the management of suicidal symptoms in outpatient settings (Joiner et al., 1999; Brown & Stanley, 2008; Jobes 2006). These list internal and external coping strategies to be implemented, should the participant experience suicidal urges at any point in the study; they also list: local community emergency mental health contact numbers, 24-hour crisis hotlines, contact information for study personnel and on-call clinicians, contact information for an identified confidant that the individual may call, should he or she experience increased distress). Lethal means restriction may be a focus of a safety plan, if and when indicated. All safety and risk assessment interactions will be closely supervised by a licensed clinician, and thoroughly documented.
12. 24-hr on-call clinical coverage teams will be assembled and in place throughout active treatment phases, consistent with previous IRB-approved clinical trials among high suicide risk participants (NCT01958541).Participants will be explicitly encouraged to contact the PI/Co-Is/Study Clinician if symptoms elevate between screening and intervention sessions. .
13. Participants will be referred to a supervising clinician if a participant experiences distress at any point following enrollment. This will prompt standardized suicide risk assessment according to established frameworks.

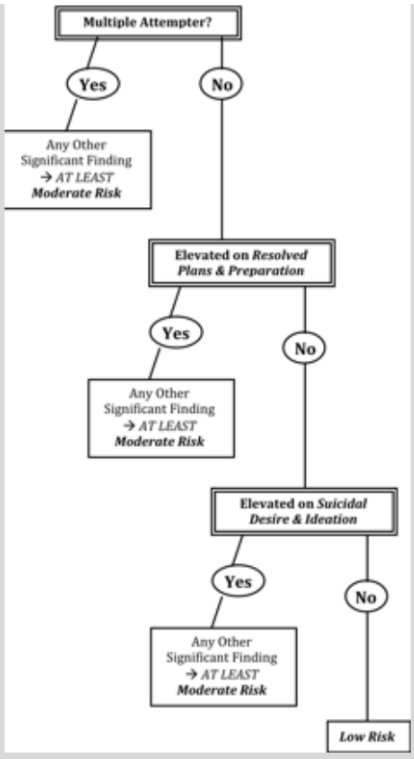
Active/intervention phases of the study

14. No shows will be vigorously pursued.
15. Safety Checks will be conducted at all study visits and documented for future review.
16. Safety planning will be conducted if risk is judged to be elevated, prompted by standardized risk assessment findings. Safety planning will be tailored to the individual and his or her level of risk. A safety plan will be outlined via construction and use of a Coping Card. Use of Coping Cards/Collaborative Assessment and Management of Suicidal Symptoms/Safety Planning Procedures are evidence-based for the management of suicidal symptoms in outpatient settings (Joiner et al., 1999; Brown & Stanley, 2008; Jobes 2006). These list internal and external coping strategies to be implemented, should the participant experience suicidal urges at any point in the study; they also list: local community emergency mental health contact numbers, 24-hour crisis

hotlines, contact information for study personnel and on-call clinicians, contact information for an identified confidant that the individual may call, should he or she experience increased distress). Lethal means restriction may be a focus of a safety plan, if and when indicated. All safety and risk assessment interactions will be closely supervised by a licensed clinician, and thoroughly documented.

17. On-call clinical coverage teams will be assembled and in place throughout active treatment phases.

TABLE 2: OVERVIEW OF SUICIDE RISK CATEGORIZATIONS

References	EVIDENCE-BASED ASSESSMENT FRAMEWORK
1. Joiner TE, Walker RL, Rudd, MD, Jobes DA (1999). Scientizing and Routinizing the Assessment of Suicidality in Outpatient Practice. *Professional Psychology: Research & Practice, 30(5),* 447-453. 2. Rudd DM, Joiner TE, Rajab HM. *Treating Suicidal Behavior: An Effective, Time-Limited Approach*. New York: Guilford Press, Inc; 2001 3. Jobes DA. *Managing Suicidal Risk: A Collaborative Approach*. New York: Guilford Press, Inc; 2006	**I. Previous Suicidal Behavior.** Previous suicidal behavior represents the single m factor in risk assessment, distinguishing 3 clinically distinct groups: a. Suicide ideators b. Single attempter c. Multiple attempters **II. The Nature of Current Suicidal Symptoms: 2 Factors** a. **Resolved Plans and Preparation.** Symptoms (8): A sense of courage to m attempt, A sense of competence to make an attempt, Availability of means f Opportunity for attempt, Specificity of plan for attempt, Preparations for atte of suicidal ideation, Intensity of suicidal ideation b. **Suicidal Desire and Ideation.** Symptoms (9): Reasons for living, Wish to d of ideation, Wish not to live, Passive attempt, Desire for attempt, Expectanc Lack of deterrents, Talk of death **III. Precipitant Stressors.** Interpersonal losses (e.g., separations from loved ones) discord, Legal troubles, Physical or emotional abuse **IV. General Symptomatic Presentation, Including the Presence of Hopelessnes** diagnostic comorbidity in MDD, Alcohol use, Hopelessness **V. Other Predispositions to Suicidal Behavior. P**erson-centered and backgroun risk factors) examples: history of prior attempt (especially multiple attempts); pas psychiatric history; chaotic family history, recent separation or divorce; history of sexual abuse; family history of suicide and mental illness. Demographic variable ethnicity (Caucasian or American Indian), age (elderly), gender (male), marital s or divorced). Behavioral factors: impulsivity or low impulse control
	RISK CATEGORIZATIONS
	**Nonexistent or Minimal Suicide Risk.** **1.** No identifiable suicidal symptoms, no past of suicide attempts or intentional self-ha identifiable suicide risk factors present **Mild Suicide Risk** **1.** A multiple attempter with: no other risk factors **2.** A nonmultiple attempter with: a. Suicidal "Desire and Ideation" of limited intensity and duration, b. No or only mild symptoms of the "resolved plans and preparation" factor c. No, or few other risk factors present **Moderate Suicide Risk** 1. A multiple attempter with: any other notable finding 2. A nonmultiple attempter with moderate-severe symptoms of "resolved plans" facto 3. A nonmultiple attempter with: a. No or mild symptoms of the "resolved plans and preparation" factor b. Moderate-to-severe symptoms of the suicidal desire and ideation factor c. At least 2 other risk factors present **Severe Suicide Risk** 1. A multiple attempter with: any two or more other notable findings 2. A nonmultiple attempter with: a. Moderate/severe symptoms of "resolved plans and preparation" factor an b. At least 1 other risk factor present **Extreme or Imminent Suicide Risk** 1. A multiple attempter with: severe symptoms of the "resolved plans and preparatio 2. A nonmultiple attempter with: a. Severe symptoms of "the resolved plans and preparation factor" and b. At least 2 or more other risk factors present

This study will utilize a comprehensive, in-built infrastructure and set of standard operating procedures that support safe conduct of the current trial. Based on evidence-based best practices in standardized risk assessment and management, subjects at imminent risk will be referred for immediate hospitalization. Proposed procedures have been used in previous IRB-approved proposals by the research team, and DSMP protocols employed by Drs. Goldstein-Piekarski, Bernert, Williams, Manber, and Yesavage. If indicated by suicide risk assessment, safety monitoring will be used according to the protocol below, and treatment will be provided as an enhancement to treatment as usual (TAU). Procedures are consistent with past behavioral insomnia clinical trials among high risk participants.

DATA SAFETY MONITORING BOARD

As a further protection against risk, a DSMB will be formally constituted to: independently review, oversee, and monitor risk procedures for the proposed studies. DSMB construction will be closely guided by the PI's supervision, and consultation with Investigators and Consultants. This DSMB will report to Stanford University IRB regarding study recruitment and adverse event (AE) reporting on at least annual basis. The DSMB will consist of individuals with the following expertise, nonaffiliated with the study: (1) An expert in sleep and mood disorders, (2) A biostatistician with expertise in clinical trials, and (3) A patient advocate. During the proposed intervention, participants will be instructed to report any intervention-emergent AEs or symptoms to study Personnel. These will be closely monitored and assessed on at-least weekly basis. DSMB and Stanford IRB will be immediately advised if a participant reports a serious emerging condition or AE—independent of cause or relation to the intervention. In the rare case that an AE warrants evaluation by the ombuds/patient advocate, DSMB consensus will have power to determine appropriateness of study continuation. Such decisions will be binding.

Data Safety Monitoring Board Members:
1. Daniel Taylor, Ph.D. Dr Taylor is a professor of Professor in the Department of Psychology at the University of Arizona. He is a certified behavior sleep medicine specialist and a dimplomat of the American Board of Sleep Medicine.
2. Meredith Wallace, Ph.D. Dr. Wallace is an Associate Professor in the Department of Psychiatry at the University of Pittsburgh School of Medicine.
3. Yelena Blank, Ph.D. Dr. Blank is a licensed clinical psychologist with a private practice in Mountain View, CA.

Clinical Oversight and Credentials of Those Supervising DSMP Trainings:
1. Rebecca Bernert, Ph.D. [Co-I, Co-Safety Monitor]. Dr. Bernert is an Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University, and Director of the Suicide Prevention Research Laboratory. She has had >15 years of clinical experience evaluating and treating suicidal patients using empirically-supported assessment procedures and within clinical trials, including at Stanford, VA Palo Alto Health Care System (inpatient, outpatient units), and the Stanford Mood Disorders Center and Stanford Sleep Medicine Center. She has administered emergency psychiatric evaluations for involuntary and voluntary inpatient psychiatric hospitalizations among those severely and persistently mental ill; and has worked as a suicide risk assessment crisis monitor to silently rate suicide risk assessment practices among crisis workers at the National Suicide Prevention Lifeline (NSPL), and intervened if necessary (as part of a SAMHSA-funded multi-national research collaborative to evaluate and improve suicide risk assessment practices among crisis workers at NSPL: PI Kalafat). She is a licensed psychologist, and has published on and contributed to VA/DOD clinical practice guidelines in the assessment and management of suicide risk, and ethical practices in suicide prevention. She has previously conducted NIH- and DOD-funded, IRB approved research in clinical trials involving high suicide risk participants. She created a DSMP model for suicide prevention clinical trials at

Stanford that will be utilized in the current study, and previously approved by the NIH Human Subjects Committee for sleep research among those at high risk for suicide. This protocol has since been used across multiple investigators, grants, and institutions for NIH-funded research protocols. DSMP protocols include operationalized procedures for the selection and training of study clinicians, on-call
procedures for risk assessment/supervision of safety; personnel training certifications; coordination of an emergency safety monitoring protocol for referral, reporting, triage, and documentation; and adherence to University and Departmental policies for risk assessment and referral. She is licensed in the state of California (PSY27980) and medically credentialed by Stanford, and as a Stanford provider, is up-to-date on all HIPAA, IRB, and CITI trainings. She will work closely with the PI and collaborate with Dr. Yesavage to oversee safety procedures, and agrees to meet regularly with on behalf of safety considerations related to enrollment and trial conduct.

2. Jerome Yesavage, M.D. [Co-I, Co-Safety Monitor]. Dr. Yesavage holds a joint appointment as a Professor of Psychiatry at Stanford University and is the Associate Chief of Staff for Mental Health and Chief of Psychiatry at the VAPAHCS. He has been PI and Co-I for multiple RCT psychotherapy and pharmacotherapy treatment trials, including those utilizing CBT-I and rTMS for depression. He also serves as the Director of the Stanford/VA Alzheimer's Center, and is licensed as a psychiatrist in the state of California. As Co-I and Co-Safety Monitor, Dr. Yesavage will work closely with Dr. Bernert and the PI to oversee clinical safety issues on the proposed project. He will have planned, frequent meetings and communication with Dr. Bernert and the PI to together establish and review: (1) construction and assembly of a DSMB; (2) training and evaluation of training in suicide risk assessment and certification procedures upfront of study launch and participant recruitment and enrollment; and study-related trainings in DSMP and DSMB reporting (Note: this applies to ALL study personnel, even if they are not in direct contact with participants in treatment); (3) IRB and Human Subjects/HRPO approvals; (4) each participant's screening, enrollment, stage of treatment, clinical status, and DSMP procedures; and (5) documentation of action taken if DSMP procedures are enacted. All procedures will be in accordance with DSMP procedures used in past clinical suicide prevention trials conducted by Co-Safety Monitor, Dr. Bernert. All protocols were previously federally-funded grants that were IRB approved and regularly renewed to support safe conduct of screening, recruitment, enrollment, and data monitoring procedures for behavioral insomnia treatment trials for depression and suicidal behaviors.

3. Rachel Manber, Ph.D. [Co-I]. Dr. Manber is a professor of Psychiatry and behavioral Sciences and the director of the Sleep Health and Insomnia Program (SHIP) at Stanford University. She will serve as Co-I for this study and has 25 years of experience providing CBTi to adults, teens and children. She also has extensive experience in the conduct of federally funded randomized control treatment outcome studies assessing the efficacy of CBTi in various insomnia populations, including those with depression and anxiety. She has worked directly with the PI, and will be involved with training of study personnel in these treatment modalities. She will also will supervise the Intervention core and clinical psychologist in aspects related to treatment.

4. Leanne Williams, Ph.D. [Co-I]. Dr. Williams is Professor of Psychiatry in the Department of Psychiatry and Behavioral Sciences at Stanford University, with joint appointment at the VA Palo Alto HCS, where she serves as Director of PTSD Education and Dissemination at MIRECC. She will serve as Co-I for this study, and has conducted multiple trials supporting feasibility and safety of the current trial. She directs the Personalized and Translational Neuroscience Laboratory (PanLab) Stanford, and has developed a clinical translational neuroscience taxonomy for anxiety and depression [NCT02220309]. In the past 15 years, she has established standardized protocols for brain imaging in biomarker intervention trials that will uniquely support the successful and safe conduct of this study. Dr. Williams has a history of leading and overseeing protocols, including large-scale clinical trials for mood disorders, including among high risk individuals and veterans, which are well-matched to the current study. She has worked directly with the PI, and has
experience working with all members of the research team to support safe conduct of the current study.

Plans for monitoring the accuracy and integrity of the data: The data will be managed by the PI and all data will be stored on a secure server. The Study Coordinator will assist Dr. Goldstein-Piekarski by monitoring the accuracy and integrity of the data. This will be done by verifying that follow-ups are conducted within the target window, verifying that assessments are complete, and the data are entered promptly. The Study Coordinator will audit the research data entered against the source documents. S/he will coordinate IRB and R&D approvals and renewals, study documentation and preparations for audits under the direction of Dr. Goldstein-Piekarski.

1.. Clinical Monitoring

N/A

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Trained study staff will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.8, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCAP, a 21 CFR Part 11-compliant data capture system provided by the Stanford University School of Medicine. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.1 STUDY RECORDS RETENTION

Per the Stanford IRB and HIPPA, research records must be maintained for at least 6 years after study closure. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

Protocol deviations will be captured using a Protocol Deviation Log.

- Any serious protocol deviation (that meets the definition of an SAE or compromises the safety, welfare or rights of participants or others) will be reported to the ISM, NIMH Program Official, and IRB as soon as possible, not more than 10 days after the PI first learns of the deviation.
- The report will describe what steps have been taken and what steps are planned as a result of the event.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIMH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIO

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale

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