Non-Pharmacological Treatments for Insomnia in Chronic Traumatic Brain Injury

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CITI Training current				

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Behavioral Sciences - Child and Adolescent Psychiatry and Child Development				
CITI Training current				Y

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CITI Training current				Y

Participant Population(s) Checklist — Yes/No

- Children (under 18) — N
- Pregnant Women and Fetuses — N
- Neonates (0 - 28 days) — N
- Abortuses — N
- Prisoners — N
- International Participants — N
  Please enter the countries separated by comma
- Impaired Decision Making Capacity — N
- Cancer Subjects — N
- Laboratory Personnel — N
- Healthy Volunteers — N
- Students — N
- Employees — N
- Other (i.e., any population that is not specified above) — Y

Study Location(s) Checklist — Yes/No

- Stanford University
- Clinical & Translational Research Unit (CTRU)
- Stanford Medicine Health Care
  Tri-Valley
- Stanford Medicine Children's Health
- VAPAHCS (Specify PI at VA) — Y
  Ansgar J. Furst, PhD
- Other (Click ADD to specify details)

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General Checklist

1. Multi-site	**Yes/No**
• Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)	N

2. Collaborating Institution(s)	**Yes/No**
• Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.	N

3. Cancer Institute	**Yes/No**
• Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol).	N

4. Clinical Trials	**Yes/No**
• Investigational drugs, biologics, reagents, or chemicals?	N
• Commercially available drugs, reagents, or other chemicals administered to subjects that are being studied?	N
• Investigational Medical Device / Commercial Medical Device used off-label or if being studied?	N
• IDE Exempt Device (Commercial Medical Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Medical Devices)	N
• Will this study be registered on clinicaltrials.gov? (See Stanford decision tree)	Y
• Who will register for ClinicalTrials.gov? NCT# 03261674	N

5. Tissues and Specimens	**Yes/No**
• Human blood, cells, tissues, or body fluids (tissues)?	Y
• Tissues to be stored for future research projects?	Y
• Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see Material Transfer Agreements	N

6. Biosafety (APB)	**Yes/No**

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• Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? If yes, please complete the Gene Transfer Protocol Application Supplemental Questions and upload in Attachments section.	N
• Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N
• Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N

7. Human Embryos or Stem Cells **Yes/No**

• Human Embryos or Gametes?	N
• Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells)	N

8. Veterans Affairs (VA) **Yes/No**

• The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS).	Y
• The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes.	Y
• The research is sponsored (i.e., funded) by VAPAHCS.	Y
• The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in connection with her/his VAPAHCS responsibilities.	Y
• The research is conducted using any property or facility of VAPAHCS.	Y

9. Equipment **Yes/No**

• Use of Patient related equipment? If Yes, equipment must meet the standards established by Biomedical Engineering (BME) (650-725-5000)	Y
• Medical equipment used for human patients/subjects also used on animals?	N
• Radioisotopes/radiation-producing machines, even if standard of care? ; More Info	N

10. Payment **Yes/No**

• Subjects will be paid/reimbursed for participation? See payment considerations.	Y

11. Funding **Yes/No**

• Training Grant?	N
• Program Project Grant?	N

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- Federally Sponsored Project? Y
- Industry Sponsored Clinical Trial? N

Funding

Funding - Grants/Contracts

Funding Administered By : VA
SPO # (if available) :
Grant # (if available) : 1 I01 RX002319-01A2
Funded By (include pending) : Department of Veterans Affairs
Principal Investigator : Ansgar J. Furst, PhD

Grant/Contract Title if different from Protocol Title :
Cognitive behavioral therapy for insomnia in chronic traumatic brain injury

Y For Federal projects, are contents of this protocol consistent with the Federal proposal?
N Is this a Multiple Project Protocol (MPP)?
N Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

Dr. Furst is the Associate Director of Neuroimaging at the War Related Illness and Injury Study Center (WRIISC) at VAPAHCS. He is also a Clinical Associate Professor of Psychiatry and Behavioral Sciences and of Neurology and Neurological Sciences at Stanford University School of Medicine and a research scientist at the VA Palo Alto Polytrauma System of Care (PSC). He is a co-investigator on several TBI projects both at the VA and at Stanford University and has extensive experience in the execution of clinical trials. Dr. Furst is also affiliated with the MIRECC and will oversee the project in its entirety. He will coordinate between key personnel, study team and consultants. Dr. Furst will also be in charge of writing progress reports and manuscripts related to the project.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

All staff will have completed all VA- and Stanford-required training in Human Subjects, Good Clinical Practice, Privacy, and HIPAA, and any required training for specific procedures. All staff will be trained in

this protocol by the Protocol Director. Some staff have also worked with similar protocols, and all staff members are very familiar with procedures for this study. Any new staff who join the project will take all required training before beginning work on the project, and will be carefully trained on all necessary aspects of the protocol by the Protocol Director or a senior research associate who supervises staff for this project. Data privacy and proper specimen collection procedures will be stressed before subject contact is allowed.

c) Facilities.

Provide the location(s) where the research will be conducted, including physical address if not conducted on site at Stanford University, Stanford Hospital on Pasteur Dr., Lucile Packard Children's Hospital on Welch Rd. or VAPAHCS. Describe the facilities and resources available to conduct the research at these sites.

The project will take place at the War Related Illness and Injury Study Center (WRIISC) and the VA Mental Illness Research, Education, and Clinical Center (MIRECC), located at VA Palo Alto Health Care System, Palo Alto Division and the Stanford Sleep Disorders Center. Private interview rooms and a large conference room are available for this project, as well as office space for staff.
Urine and blood samples will be taken and processed by trained staff in the VA Palo Alto Veterans Affairs Medical Center.

d) Sufficient time.

Explain the time that you and your research team will allocate to perform the research activities, including data analysis.

We will have sufficient time to conduct and complete the research. Each of the investigators has sufficient time available to conduct their part of the research.
Each participant will spend approximately 32 weeks in the project.
We expect to begin recruitment in November, 2018.
We expect project will be completed by the end of 2023.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

We plan to recruit research subjects from the War Related Illness and Injury Study Center (WRIISC) and the VA Palo Alto Polytrauma System of Care (PSC) and from local clinicians. The WRIISC and PSC specialize in the care of Traumatic Brain Injury patients and therefore have ample access to this patient population for recruitment.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

The Protocol Director or a senior research associate will provide psychological resources to participants, if necessary. Appropriate referrals will be made when necessary in the judgment of the physician and/or psychologist. As the study takes place at the VA Palo Alto medical center, medical assistance is readily available if needed.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

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1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

The purpose of this study is to evaluate the relative efficacy and effectiveness of Cognitive Behavioral Therapy for Insomnia compared to an active control condition (Arousal-Based Therapy for Insomnia, previously referred to as Desensitization Therapy for Insomnia)in patients with mild Traumatic Brain Injury.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

Sleep-wake disturbances are present across the spectrum of TBI severity and can arise early after injury, during treatment in hospital, or during inpatient rehabilitation, and often persist for years after the injury. These problems are particularly prevalent in cases of mild TBI (mTBI), which represents the majority of cases of TBI treated in Veterans. Sleep-wake disturbances can exacerbate other outcomes of TBI, particularly cognitive deficits, pain, fatigue, and mood disturbances (Orff, Ayalon, & Drummond, 2009; Ouellet, Beaulieu-Bonneau, & Morin, 2015). In a recent meta-analysis (Mathias & Alvaro, 2012) roughly 50% of TBI patientswere found to have sleep disturbances.

VA clinicians have been trained in non-pharmacologic insomnia treatments. TBI with insomnia (TBI-I) patients are frequently prescribed sleeping medications with their associated side-effects. To address the general problem of insomnia in Veterans, over 650 VA clinicians have been trained between 2012 and 2014 by the VISN 21 MIRECC to provide Cognitive Behavior Therapy for Insomnia (CBT-I), an evidence-based non-pharmacological insomnia treatment. Although CBT-I has been suggested to be a compelling treatment alternative in TBI-I there is not enough conclusive data available to-date to warrant this claim.

The primary objective of this randomized clinical trial is to assess the efficacy of CBT-I versus an active control condition, Arousal-Based Therapy for Insomnia (ABT-I), in TBI-I patients. A secondary aim is to explore potential baseline moderators of response to CBT-I. Several baseline characteristics like insomnia severity, "time spend in bed", cognitive arousal or pain may moderate the treatment outcome. Knowledge of such moderators would help with personalizing future therapies and hence improve outcomes.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

This is a study of insomnia in humans who suffered traumatic brain injury.

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the research participant will undergo. Sections in the protocol attached in section 16 can be referenced, BUT do not

copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care. For research involving collaborators, please specify the respective roles of Stanford and each collaborator on the protocol.

SCREENING
Web Screen: Web advertisements will point interested participants to our study website, which will include a brief web survey to help determine basic eligibility. More info in section 8i.

Phone Screen:
Respondents will be given a brief description of study procedures and our research goals. If interested, they will be asked for their consent for a formal telephone screening interview. Upon receipt of consent, participants will be interviewed by telephone regarding their current symptoms and medical histories to determine if we should proceed to in-person evaluation. With their consent, a review of their VA medical charts will also be conducted to help confirm eligibility.

Screening Session:
This evaluation session will last approximately 2-3 hours to perform relevant psychological tests, and gather medical, psychiatric, and medication histories. This visit will take place in person or via Telehealth.

Screening for Obstructive Sleep Apnea and Periodic Limb Movement Disorder:
The Berlin Questionnaire will be used to screen for sleep apnea symptoms, and the Duke Structured Interview will be used to screen for both symptoms of both Obstructive Sleep Apnea and Periodic Limb Movement Disorder. Participants who are determined to be at high risk for these disorders will be referred to Pulmonary Medicine for further evaluation.

Summary Research Team Meeting and Sleep Disorders Diagnosis:
Before a subject will be entered into the treatment, the summary research team will review all aspects of the case to determine ultimate eligibility. All evidence collected during the screening will be used to develop formal sleep disorders diagnoses.

BASELINE
Two Weeks of Baseline Sleep Logs:
At the end of the first screening session, participants will be shown how to complete daily sleep logs for the duration of the study to provide subjective sleep data. We will use a modified Consensus Sleep Diary-E for our sleep log. Sleep logs will be returned to us during in person visits, or via MyHealtheVet.

Baseline Evaluation:
In this session subjects will complete psychological evaluations. Cognitive testing will be administered on paper and using the CANTAB Connect Research software via iPad. A blood sample will be collected at this visit.

Optional Polysomnography (PSG):
Participants who agree will be set up with a Compumedics Siesta

ambulatory overnight PSG recording at the end of their baseline evaluation. Participants will then return home to sleep, and return the next morning to provide urine and blood samples. VA approved taxi and hotel service may be offered for those traveling long distances or who don't have a ride to and from the VA for the PSG.

Blood and Urine samples:
Urine samples will be collected at baseline, eight-week and six-month visits for all participants. Urine samples will be screened by the PAVAHCS laboratory for several exclusionary medications and drugs, and results will be uploaded to the participant's secure medical file.

A total of two blood samples will be drawn over the course of the study - once at baseline and once after treatment has been completed. A trained, experienced nurse or phlebotomist will draw the blood. These blood samples will be processed by the VA laboratory to test for inflammatory markers, and the results will be uploaded to the participant's secure medical file. If they consent to storage of blood samples, the samples will later be used to examine genetic material.

If we are unable to complete labwork, overnight PSG or in-person cognitive tests due to VA restrictions or participant refusal as a result of COVID-19 concerns, we will not exclude these participants from the study.

TREATMENT
Our hypotheses will be tested in a randomized parallel groups design. Randomization will be based on type of treatment assignment: either to Cognitive Behavior Therapy for Insomnia (CBT-I) or Arousal-Based Therapy for Insomnia (ABT-I)(previously referred to as Desensitization Therapy for Insomnia) for the 6-week treatment phase.

CBT-I (SR & CT):
The CBT-I adopted in this trial will be based on our large-scale VA implementation of CBT-I and includes a published sleep self-help book, a published therapist guide, and the CBT-I therapist manual appended. It comprises both SR and CT as outlined below. The CBT-I therapy protocol consists of six sessions (an initial assessment and five treatment sessions). Treatment begins with a comprehensive sleep assessment and case conceptualization, which are used to guide selection and sequencing of CBT-I components. Treatment components include stimulus control, sleep restriction therapy, relaxation, and cognitive therapy. The final session focuses on maintenance of gains and relapse prevention.

Sleep Restriction Therapy (SR). The initial Time in Bed (TIB) prescription is calculated on the average total sleep time (TST) reported by subjects in their baseline sleep logs. Subsequently, the TIB prescription is determined using the formula: TIB = average TST. An additional treatment criterion is that prescribed initial time in bed should never be below 5 hours, even if the average total sleep time (TST) is very low (e.g., 3 hours). After one week, depending on subject's daily sleep logs and discussion with participant about tolerability, the therapist suggests a new TIB prescription. The

initial TIB, retiring times and wake times are set with subject input to ensure tolerability. Daytime sleep will not be manipulated in SR treatment. Napping is neither prescribed nor proscribed. However, if subjects find themselves very sleepy (not just tired, but actually sleepy) they are advised to take a brief (15 to 30 minutes) nap to ensure their safety. These safety naps can be taken at any time because safety is always the most important consideration. Subjects are given additional rationale for the treatment constraints and suggestions for dealing with any difficulties they have in complying with their prescribed sleep schedules. Information on relevant elements of the science of sleep is included in explaining how the treatment works.

Cognitive Therapy (CT). The CT treatment module is designed to meet three general goals: 1) identification of dysfunctional sleep cognitions, 2) challenging their validity, and 3) replacing them with more adaptive substitutes. Several specific techniques designed to meet these goals are discussed in materials distributed to subjects. Systematic self-monitoring for identifying dysfunctional sleep cognitions will be a basic component of the treatment. Replacing inaccurate thoughts through cognitive restructuring involves the identification, evaluation, and modification of maladaptive thoughts. In the context of insomnia, the focus is on sleep-related thoughts that increase arousal, and therefore directly interfere with sleep. Basic concepts about CBT for chronic pain are included in training, for example, directly addressing hopelessness in relation to chronic pain that may interfere with sleep. Once sleep-incompatible thoughts are identified, dysfunctional ideas about the causes and consequences of insomnia and unreasonable expectations about normal sleep can be challenged in a nonjudgmental manner using scientifically based information about sleep and replacing them with more adaptive conceptions. Similar to SR, subjects in CT are given information about relevant elements of the science of sleep and healthy sleep practices.

Arousal-Based Therapy for Insomnia (ABT-I):
The subjects assigned to the "Credible Control Therapy for Insomnia" (ABT-I) condition will receive a quasi-desensitization treatment presented as a means of eliminating the "conditioned arousal," which prolongs nocturnal awakenings. Therapists help each ABT-I recipient develop a chronological 8-item hierarchy of common activities he/she does on awakening at night (eg, opening eyes, clock watching). Therapists also help them develop 6 imaginal scenes of themselves engaged in neutral activities (e.g., reading the newspaper). Each session, ABT-I recipients are taught to pair neutral scenes with items on the 8-item hierarchy so, by the end of the sixth session, all hierarchy items have been practiced with therapist assistance. Each session, the exercise is tape recorded and the patient is given this tape locked in a player. The patients are told to practice their exercises at home once each day, no less than 2 hours before bedtime, but to avoid using the tape or exercise during sleep periods.

We will offer participants the option of completing therapy sessions via Telehealth and will aim to complete all treatment sessions via their chosen modality. If a participant needs to switch modalities

due to unforeseen circumstances (e.g. illness) we will accommodate this request.

FOLLOW UP
The complete package of outcome measures (including optional ambulatory PSG) will be repeated at the week 8 and six-month follow-up sessions. We will tell subjects that we expect the benefits of treatment to continue and/or improve with time and we will also encourage subjects to continue practicing the treatment instructions to maintain their progress.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

There is little risk to the proposed procedures.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

N/A

d) State if photo, audio or video recording will occur. Describe what will become of the photos or recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

No video recordings will be used. Audio recordings will be made of the therapy sessions for quality control purposes. After the results of the study are analyzed the tapes will be stored according to VA requirements.

e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

Alternate treatments for insomnia include various medications and other behavioral treatments. An alternative is not to participate.

f) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

The study treatments are forms of learning or training. Participants should be able to continue on their own if they find the treatment useful. They will be given didactic material that they can refer to after the treatment is over. In the case of the ABT-I(placebo) arm we will provide them with an introduction to CBT-I and contacts to pursue this treatment option.

g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

The study is expected to continue until all participants have completed the procedures.

3. Background

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a) Describe past experimental and/or clinical findings leading to the formulation of the study.

For more than twenty years we have investigated the efficacy of a broad range of non-drug treatments for older adults with insomnia, comparing relaxation versus sleep restriction, sleep restriction versus sleep hygiene, and bright light versus sleep hygiene. We also initiated the development of a large-scale implementation of a package of cognitive behavioral therapies for insomnia (CBT-I) in the VA Health Care system. Increasingly, the field has moved toward using a combination of various non-drug treatments. The combination therapies all share a cognitive therapy (CT) component that focuses on techniques such as systematic self-monitoring for identifying dysfunctional sleep cognitions. In addition, the combination therapies include diverse behavioral components such as sleep restriction (SR), relaxation, stimulus control, and sleep hygiene. The field has progressed to where the next stage of treatment development should move towards:
1) disaggregating the relative clinical impact of specific CBT-I components, and
2) identification of the mechanisms of action (mediators) and individual differences in response (moderators) of that effect to enable more efficient, effective, and acceptable delivery of CBT-I.

b) Describe any animal experimentation and findings leading to the formulation of the study.

Not applicable.

4. Radioisotopes or Radiation Machines

a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. More Info

Identify Week/Month of study	Name of Exam	Identify if SOC or Research

b) For research radioisotope projects, provide the following radiation-related information:

Identify the radionuclide(s) and chemical form(s).

For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.

If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).

c) For research radiation machine projects, provide the following diagnostic procedures:

For well-established radiographic procedures describe the exam.

For the typical subject, identify the total number of times each will be performed on a single research subject.

For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.

For radiographic procedures not well-established, provide FDA status of the machine, and

information sufficient to permit research subject dose modeling.

d) For research radiation machine projects, provide the following therapeutic procedures:

For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants's medical condition or whether it is being performed because the research participant is participating in this project.

For a therapeutic procedure that is not well-established, provide FDA status of the machine, basis for dosimetry, area treated, dose per fraction and number of fractions.

5. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) if they are being studied.

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.

6. Drugs, Reagents, or Chemicals and Devices

a) Please list in the table below all investigational drugs, reagents or chemicals if they are being studied.

b) Please list in the table below all commercial drugs, reagents or chemicals if they are being studied.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

No medical equipment used with the human participants is also used on animals.

8. Participant Population

a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

(i) We plan to enroll 120 participants at the VA Palo Alto Health Care Systems, a Stanford-affiliated site.
(ii) This is the only site for this project.
(iii) All participants will have a sleep/wake disturbance as defined in the Inclusion/Exclusion criteria.

b) State the age range, gender, and ethnic background of the participant population being recruited.

Age Range: 21 years old and older
Gender: Males and Females
Ethnic Background: Any race or ethnic origin

c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.

Children and pregnant women will not be recruited for this protocol.

d) If women, minorities, non-English speaking individuals, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).

There will be no participation of children in this study. The research topic to be studied is irrelevant to children because we are studying the effects of insomnia in adults.

e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.

It is unlikely that any laboratory personnel, employees, or students will qualify for participation in this study. If any do qualify and wish to participate, they will be treated the same as any other participant.

f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.

Participants should all be in fair to good physical health. We are excluding any health problems likely to exacerbate sleep problems. Risks are minimal; it is possible that patients may experience transient deterioration of sleep during the treatment, but this should improve if the participant follows the assigned protocol. Participants can contact study staff for assistance if they feel their insomnia is getting worse.

g) Describe your plan to identify and recruit potential participants including who will inform them about the study and how they will be initially contacted by the researchers (e.g., Research Engagement services; chart review; treating physician; ads including social media posts). All final or revised recruitment materials must be approved by the IRB before use. Contacting potential participants is not permitted prior to IRB approval. See Recruitment Guidance for additional information.

Veterans will be recruited at the VA Palo Alto WRIISC and PSC that are the normal clinical referral sources for TBI patients. We will also do chart reviews of Palo Alto VA patients recently seen for TBI/insomnia complaints and reach out to them with an letter introducing our study, followed by a phone call. Veterans may also be recruited from ClinicalTrials.gov. We will circulate flyers on VA campuses and around the Bay Area, and reach out to non-VA veteran groups and communities with flyers and brochures. We will also post newspaper ads and online ads on sites such as Facebook, StudyPages and Craigslist for interested participants across the US to recruit participants for Telehealth therapy.

We will be accessing participant databases provided to us by other principal investigators at the Palo Alto VA to identify potential participants for our study, in accordance with VA policies. These will be participants who have been screened or contacted by other research groups and have consented to be contacted for research opportunities. Letters will be sent to these Veterans, cosigned by the original principal investigator, with information about our current study and pre-paid response envelopes. Follow up phone calls will be made within 2 weeks after letters have been sent out.

If any VA provider notes a recent patient of theirs may be eligible for our study, we will send an introductory letter to the patient co-signed by the provider with information about our study. Alternately, providers who receive verbal consent from the participant to be contacted by us may leave a note in the

patient's CPRS medical record and co-sign a study coordinator, at which point we will reach out to the veteran directly. These methods are consistent with VA privacy guidelines.

We will also submit a DART (The Data Access Request Tracker Application) request to filter and access VA medical records based on diagnosis.

We will submit a DMDC (Defense Manpower Data Center) Request to receive contact information for retired military personnel within a 50 mile radius.

We have created a website through the Stanford School of Medicine to advertise the study and provide information for prospective participants and also for the general public: http://med.stanford.edu/sleepless-warriors.html

A pre-screen survey with basic eligibility questions will be hosted on Stanford's Redcap or StudyPages and uploaded to the study's website. Web advertisements will point to this page so interested members of the public can fill it out to determine their eligibility. If the survey determines they may be eligible for the study, the last page will prompt them to enter their name and phone number to be contacted by us.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

- Male or female Veterans of any racial or ethnic group
- Independent Living (not in nursing home or VA Extended Care facility)
- Diagnosis of insomnia using the Duke structured interview
- Male or female chronic (>3 months since injury) mild Traumatic Brain Injury (mTBI).
- Subjects with PTSD will be included in this study as long as they do not meet criteria for depression described below.
- Use of CNS active medications that could significantly impact sleep or alertness is allowed as long as the dose, timing, and formulation are stable (≥ 3 weeks).
- Stable adult onset diabetes, controlled with insulin, oral medications or diet is acceptable.
- Use of medications, drugs, herbal remedies, or hormones specifically prescribed for treating sleep disturbances is allowed as long as the dose, timing, and formulation are stable (≥ 3 weeks).
- Subjects will be assessed for sleep apnea risk by the Berlin Questionnaire. Those with responses suggestive of high risk for apnea will be referred to Pulmonary Medicine for standard clinical screening, but will not be excluded. If subjects with obstructive sleep apnea are using CPAP, we will require stable use throughout the study.

Identify exclusion criteria.

Sleep-Related
- Excessive caffeine consumption (≥ 5 cups of coffee per day) and unable to reduce to ≤ 3 cups before lunch a day for ≥ 3 weeks prior to treatment.
- Subjects working a rotating shift or an unconventional daytime shift (ending after 1700 h, expected to be rare in the age group we are studying) will be ineligible.

Neuropsychiatric
- Current or lifetime history of a psychiatric disorder with primary psychotic features.
- Current or lifetime bipolar disorder; prominent suicidal or homicidal ideation.
- Current or within the past 30 days: drug abuse or dependence (except nicotine).
- Current or expected cognitive behavior therapy for another condition (e.g. depression).
- More than one glass of wine or beer with dinner scheduled at least 3 to 4 hours before bedtime.
- Presence of any acute or unstable psychiatric condition(s) that requires referral for treatment.
- Folstein Mini-Mental State Exam (MMSE) < 24.

Medical
- 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 will be excluded.

i) Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).

Web advertisements for Telehealth participation will point participants to our study website and a pre-screening questionnaire hosted on Stanford Redcap and embedded in our website (attached in section 16).

Alternately, the company StudyPages will manage these advertising campaigns, and will set up a separate site and pre-screen questionnaire (attached in section 16). The StudyPages site and questionnaire is hosted by them, and privacy/security is addressed in section 9c.

Subjects will be screened for eligibility via a phone interview and an in-person or Telehealth evaluation. During the phone screen, respondents will be given a brief description of study procedures and research goals. If respondents are interested, the interviewer will ask further questions regarding current symptoms and medical histories to determine if we should proceed to an in-person screening evaluation. We will also request permission from the participant to review their VA medical chart to obtain further relevant information.

At the in-person or Telehealth evaluation, after reviewing the consent form and providing verbal consent, a more detailed assessment about sleep problems, and medical and psychiatric history will be completed.

Insomnia will be diagnosed using the Duke Structured Sleep Interview using DSM 5 criteria, and other sleep disorders will be screened for using DSM-IV criteria in the same interview. A medication list, Acute/Unstable Illness checklist and chart review will be used to screen for acute/unstable medical illness. The Mini Mental State Exam (MMSE) will be used to assess cognitive impairment. Mild TBI (mTBI) will be confirmed using the Boston Assessment of Traumatic Brain Injury – Lifetime (BAT-L).

Psychiatric criteria will be assessed using the Mini International Neuropsychiatric Interview Version 7 (MINI). Participants who show risk for suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). Subjects taking sleeping medications at the time of recruitment will be admitted to the study if under the supervision of their physician they remain stable on the medication for a minimum of 3 weeks before acceptance into the protocol.

j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.

We will ask the potential subject if they are participating in any other protocols on the consent form. They will be instructed not to participate in any other protocols during their involvement with our study without first getting prior authorization from both our research team and that of the other study. Overlapping participation will be handled on a case-by-case basis.

k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

Payment of $325 will be provided for all participants who complete the study, including those participating solely via Telehealth. A further $150 will be provided to in-person participants who agree to the three overnight sleep studies and subsequent urine screens.

Participants will receive:
$25 for the screening procedures
$50 for the baseline visit, and a further $50 if they choose to participate in the overnight sleep study & blood/urine test.
$25 for each of the 6 treatment visits.
$50 for the end-of-treatment visit, and a further $50 if they choose to participate in the overnight sleep study & urine test.
$50 for the 6-month follow up visit, and a further $50 if they choose to participate in the overnight sleep study & blood/urine test.

In-personarticipants will receive $10 VA canteen lunch vouchers for the longer screening, baseline and follow up visits.

If it is necessary for a participant to terminate before the end of follow-up because of the return of symptoms, they will be paid for the portion of the study they have completed.

We feel this is a reasonable amount in light of the time and effort the participant will spend in the study. The amount of this payment is similar to that paid for by other labs conducting similar studies.

l) Costs. Please explain any costs that will be charged to the participant.

No costs to the subject will arise as a result of participation in this study, other than transportation to and from the Center, and the time involved.

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The entire study should take 4 years.
(i) Screening for each participant will take approximately 2-3 hours
(ii) Each participant will actively participate in the study for approximately 32 weeks.
(iii) Analysis of participant data is estimated to take about 6-12 months.

9. Risks

a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

i. The risks of the Investigational devices.

Not applicable.

ii. The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

Not applicable.

iii. The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

Not applicable.

iv. The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Cognitive testing.
There are virtually no risks involved in the cognitive testing and psychosocial measurements other than the anxiety that can be associated with any test. Repeated evaluations of mood and mental status may be

slightly frustrating or produce fatigue and boredom.

Sleep Log and Questionnaires.
There are no harmful effects to filling out the sleep log and questionnaires, but some people may find answering the questionnaires annoying or boring.

Urine testing.
Urine testing involves no risk other than the bother involved.

EEG recording.
There is little risk to EEG recording. Participants may find the cap annoying or uncomfortable. If this occurs we will try to make them more comfortable, or stop the procedure if the participant requests.

Venipuncture.
Removal of blood by a needle and syringe poses a small risk of pain or bruising at the site of the needle stick, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the site of the needle stick.

Sleep treatments. It is possible that participants may become very sleepy under the Sleep Restriction part of the treatments. If this occurs, they will be advised to avoid driving, operating machinery, or doing activities that require close attention for the first few days of therapy.

v. The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

Not applicable.

vi. The risks of the Physical well-being.

See above procedures. No other risks to physical well-being are anticipated.

vii. The risks of the Psychological well-being.

From past experience, potential risk to participants is expected to be minimal. Specifically, questions asked that may be potentially distressing to the participants or may cause them to think about problems relating to them that may be anxiety-provoking or upsetting.

A psychiatric screening will be performed to determine whether the participant meets inclusion and exclusion criteria for the study. From past experience, potential risk to participants is expected to be minimal. Specifically, questions asked may be potentially distressing to the participants or may cause them to think about problems relating to them that may be anxiety-provoking or upsetting. Patients who develop suicidal intent will be treated following established procedures at VAPAHCS.

Cognitive Testing.
There do not appear to be any risks associated with cognitive testing other than the commitment of significant time for participation. Some participants may experience anxiety during and after the cognitive testing.

Questionnaires.
There are virtually no risks involved in filling out our questionnaires, sleep-wake cycle questionnaires and sleep logs other than the time involved.

viii. The risks of the Economic well-being.

No risks to economic well-being are anticipated.

ix. The risks of the Social well-being.

No risks to social well-being are anticipated.

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe

therapeutic agent such as the use of an FDA approved drug or device.

b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALREASEARCHFORM] International Research Form. If not applicable, enter N/A.

Not applicable.

c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.

Suicidal thoughts.
At the prescreen web survey we will ask "Did you repeatedly think about death, or have any thoughts of killing yourself, or have any intent or plan to kill yourself? Did you attempt suicide?" and include the statement "If you have had any thoughts of hurting yourself, please contact the Veterans crisis line" with corresponding info. At face-to-face screen, we will ask the same question and if the answer is positive, we will provide the participant's information to the Veteran's crisis line so they can follow up & determine risk.

Cognitive testing.
If the participant is fatigued or uncomfortable with testing, a break can be taken to rest. If a participant is unwilling to continue a testing session, they will be given the option of continuing at a later time, ending the current session, or ending all participation.

PSG and EEG.
We will make every attempt to attach sensors carefully so that they provide the minimum discomfort possible.

Data.
Paper data with PHI will be kept in locked cabinets and electronic data with PHI will be stored on physically secure and password protected computers and on the MIRECC/WRIISC server in the VAPAHCS server room (a locked facility behind the VA firewall). Computer data backups are done by VA IT. Computers are password protected. Offices are locked when unoccupied. All e-mails, texts and other unencrypted forms of communication will not involve PHI.

Sleep Log and Questionnaires.
There are no known significant risks associated with completing Sleep Logs and associated questionnaires.

Telehealth
Any study appointment conducted via Telehealth will use VA Video Connect (https://mobile.va.gov/app/va-video-connect), a program used by VA clinical and research staff. It is encrypted, and the video will be locked to anyone other than the provider and the participant. Both the study therapist and participant will use the software in a private room to ensure confidentiality. Video will not be recorded.
Invite links to Telehealth sessions will be sent to the participant via email. Participants will be able to access Telehealth via their own personal computers, or via a VA-encrypted iPad provided by the study.

Pre-screen surveys using Redcap and StudyPages
REDCap (Research Electronic Data Capture) is an application for building and managing online databases. The Stanford Center for Clinical Informatics (SSCI) runs and supports a secure, local Stanford installation of REDCap for the Stanford research community at no cost. REDCap provides a web-based interface for collecting data with data validation and includes the ability for automated export to statistical packages. The software also includes data logging for HIPAA compliance and the ability for administrators to define access rights on a per-user basis. Data stored in production REDCap databases is not automatically purged, but archiving of completed projects within REDCap is recommended. In the event the REDCap service

were to be replaced or discontinued, all project owners would be notified and plan devised that would allow ample time for owners to export their data.
StudyPages is HIPAA compliant. It is hosted and managed on Amazon Web Services (AWS), a highly scalable cloud computing platform with end-to-end security and privacy features built in. All StudyPages research staff are required to login using email/password. Only study team members with access to a study workspace can view signup details (name, email, phone number, etc.) for that study. To protect sensitive information, data at rest is encrypted with 256-bit AES encryption in the StudyPages Application Database. All data transfer in/out of the system is encrypted in-transit using 256 bit SSL and all communications with the StudyPages platform are forced to use HTTPS.

d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

The experiment will end at either the normal termination or whenever the subject decides to withdraw from the study.

e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).

Describe the following:

1. What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?

At each visit, participants will be asked about any adverse events which may have occurred since the last visit. Information about adverse events (including any injuries, illnesses, hospitalizations, etc.; this would include any adverse effects on sleep caused by study procedures) is collected at each visit by the interviewer. Any potentially serious problem is brought immediately to the Principal Investigator for review.

2. Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

The Protocol Director is the monitoring entity.

3. Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

n/a

4. Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

The Protocol Director will review all Adverse Events and Serious Adverse Events as soon as possible after the occurrence. SAEs are reported and forwarded to IRB as appropriate.

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5. If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

Information about adverse events is collected at each visit by the interviewer. Any potentially serious problem is brought immediately to the Protocol Director. All data entered into the database is monitored by the senior research associate and the database manager.

6. Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

Criteria for discontinuation of a patient in the study will include an 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. However, data from such subjects will not be included in statistical analyses since such SAEs may affect sleep. Patients will not be restarted if their sleep deteriorates meeting the above criteria and they are discontinued from the protocol.

7. Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

Serious Adverse Events are reported to the IRB using the standard reporting forms.

8. Select One:

Y The Protocol Director will be the only monitoring entity for this study.
This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.

Some participants may find that their sleep is improved.

11. Privacy and Confidentiality

Privacy Protections

a) Describe the setting and method (e.g. crowded waiting room, patient exam room, telephone or email communication) in which interactions will occur and how the privacy interests of participants will be maintained. Note, high risk data such as PHI must be sent via "Secure:" email per Stanford policy.

During screening, participants will meet in a private interview room
or via a private Telehealth session with a member of the study team
to sign the consent form, discuss the protocol, and determine suitability for enrollment. All interviews and treatment sessions will be done in a private setting. Samples will be obtained in a private setting.

With the participants consent, short email or text message
communications without PHI/PII will be sent as appointment reminders,
per VA privacy guidelines.

With the participants consent, MyHealtheVet secure messaging will be used by registered and trained research personnel. This is a portal approved by the VA for secure messaging of PHI/PII in by clinicians and research staff. Communication through regular USPS mail will be presented as an alternative.

Confidentiality Protections

b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

We are collecting the following identifiable information or PHI:
* full name,
* social security number (for VA hospital registration and payment),
* telephone number (for communication),
* mailing address (for appointment notices and to mail payment),
* date of birth (study metric),
* date of visit,
* VA CPRS medical record
* Medical history and physical examination information,
* Demographic information (gender, ethnicity, education, occupation)
* Progress notes,
* Biological specimens (e.g. blood, urine, spinal fluid),
* Diagnostic/Laboratory test results,
* Discharge summary,
* Survey/Questionnaire responses,
* Cognitive and Psychological test results.

c) You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted.

Stanford University IT approved platforms (https://uit.stanford.edu/guide/riskclassifications https://uit.stanford.edu/guide/riskclassifications) should be used for data management. Consult with your Department IT representative for more information.For data security policies and links to encrypt your devices see http://med.stanford.edu/irt/security and target=_blankhttp://www.stanford.edu/group/security/securecomputing/mobile_devices.html. Additionally, any PHI data on paper must be secured in a locked environment.

By checking this box, You affirm the aforementioned. Y

Paper data / PHI will be kept in locked file cabinets and electronic data with PHI will be stored on physically secure and password protected computer servers behind a firewall at the VAPAHCS. Computer data backups will be stored in locked cabinets. Computers will be password protected. Laptops, cell phones and removable hard drives will be encrypted. The WRIISC is located in a lockable area of Building 5 at the VAPAHCS. Offices are locked when not occupied.

All samples are stored in a locked laboratory at VAPAHCS. De-identified data are stored internally and are off-loaded to a PC via a USB cable. Some questionnaires will be administered via computer using REDcap behind the VA firewall. The CANTAB cognitive test data will be collected via password-protected iPad with participants identified only by their study code. No PHI will be transmitted by the CANTAB program.

All contact with participants will be encrypted if PHI is to be disclosed.

The study therapist will conduct Telehealth via a VA encrypted VA Video Connect software on a VA issued desktop or laptop. Participants will use their personal computers or study provided iPads in a private location. No PHI will be entered during their use of the device.

Survey data collected via Stanford's Redcap site will include PHI. Links to these surveys will be sent to participants via their secure MyHealtheVet messaging portal, where they will click the link to access the surveys. Surveys responses will only be associated with the participant's study ID. Their name, contact info and some demographics will be collected.

Data storage on VA's Redcap will not include any PII including no names, contact information or identifiable demographic information.

The VA Video Connect telehealth program is encrypted and secure and will be the main method of conducting Telehealth appointments with participants. Zoom, FaceTime, or Skype will be used temporarily in accordance with VA recommendations during the COVID-19 outbreak with participants consent.

d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.

Data, specimens, and computer files will be given a code and information linking code and PHI will be kept on a secure, password protected computer behind a firewall. The PI has the code key. The Data Manager is responsible for de-identification.

e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).

Members of the research team will have access to all data. The data manager has no access to any subject names or contact information. Off-site collaborators will not have access to PHI or sensitive data. If the subject requests it explicitly (in writing), we will send information about certain test results to his/her personal physician.

De-identified data will be shared with collaborating researchers at Stanford University and at other institutions. De-identified data may also be shared with collaborating researchers at other institutions in the future. No names, social security numbers, or other identifying data will be shared with anyone outside of the research team at VA.

Blood samples are collected and analyzed at various timepoints during in-person appointments by the VA Phlebotomy lab, and results are accessible through the VA's secure medical records system, CPRS.

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Blood samples for future use are labeled with the appropriate sample ID. Samples are pipetted and stored in a locked, secure freezer, and the sample ID and location is logged in the sample logbook.

Urine samples are collected at the VA and analyzed by the VA specimen collection laboratory. Urine results are accessible through the VA's secure medical records system.

f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.

A study code is assigned to a subject after they sign a consent form. This code is independent of any identifying information. A separate code is assigned to each blood sample. The participants ID and the sample ID are linked only through a password protected document on a secure, password protected computer at the VA Palo Alto.

g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.

The code will be maintained by the PI, and will be available to appropriate members of the research team but kept in a locked file cabinet or on a physically secure, password protected computer at VA Palo Alto.

h) If sharing data with others, describe how data will be transferred or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, confirm a Stanford University IT approved platform will be used (see https://uit.stanford.edu/guide/riskclassifications https://uit.stanford.edu/guide/riskclassifications) or that data will be encrypted while in transit. Additionally, confirm appropriate agreements are in place to allow for the sharing (see https://ico.stanford.edu/stanford-researchers/who-will-handle-my-agreement https://ico.stanford.edu/stanford-researchers/who-will-handle-my-agreement). If using or sharing PHI, refer to the following policies: https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.

No PHI will be transferred to anyone outside the VA/Stanford Redcap. Any electronic transfer of study information will be done using approved VA methods.

i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?

All research staff will complete and remain current with all required VA and Stanford training prior to working with human subjects. The Protocol Director will also reinforce the importance of maintaining confidentiality.

12. Potential Conflict of Interest

Investigators are required to disclose any outside interests that reasonably appear to be related/li to this protocol.

Outside Interest Tasks

Investigators	Role	Potential	Date	Date OPACS	COI Review

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		COI?	Outside Interest Answered	Disclosure Submitted	Determination
Ansgar Furst	PD	N	06/28/2024		N/A
Jamie Marc Zeitzer	OP	N	06/14/2024		N/A
Odette Althea Harris	OP	N	06/25/2024		N/A
Rachel Manber	OP	N	06/28/2024		N/A
Jerome A Yesavage	OP	N	06/04/2024		N/A

13. Consent Background

13. 1 Waiver of Documentation — Phone screen - Telehealth 021323

Check if VA related Y

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

Study personnel listed in the personnel section of this protocol will be the persons who obtain consent. Consent form will be presented in a private interview room. The potential participant will be given as much time as they would like to review the material prior to signature. They will be advised that they may take the form to discuss with a trusted family member, health care provider or other trusted person prior to signature. These steps along with moderate payment for participation are intended to minimize any undue influence to participate. No minors are participating.

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

All participants must speak and read English to participate. Please see exclusion criteria for more detail.

c) What steps are you taking to determine that potential participants have the capacity to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

All participants will be able minded adults. Basic psychological screening will take place and if there are doubts as to ability to consent then another study member will be called for consult and if doubt remains we

will forgo participation until such time as the potential participant is deemed capable of consent. Only direct consent will be obtained, no LRA consent will be obtained.

Additional VA questions:

i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.

Study personnel listed in that section of this protocol will be authorized to obtain consent. Every person has completed human subjects training and will be further trained on the specific consent for this study.

ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

Direct consent only. No LRA.

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?

We have limited payment to help prevent undue influence or coercion. Also, participants will be encouraged to take any time they need and review the consent with their own doctor or other trusted health care provider, friend or family member before deciding to participate.

iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Yes. See above.

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes.

vi) Please confirm the following:

- **a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.**
- **b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.**
- **c. A copy of the signed and dated consent document will be given to the person signing the consent document.**
- **d. The consent form is on the VA Form 10-1086.**

Select ALL applicable regulatory criteria for a Waiver of Documentation and provide a protocol-specific justification:

1)		**45 CFR 46.117(c)(1)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
2)	Y	**45 CFR 46.117(c)(1)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
3)		**45 CFR 46.117(c)(1)(iii)., if participants or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**
4)		**21 CFR 56.109(c)(1)., presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

The phone screen to determine eligibility is no more than minimal risk.

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13. 2 Waiver of Documentation Consent Form 032823

Check if VA related Y

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

i. Trained study personnel will be obtaining consent. All will be trained and knowledgeable about the study. ii. Consent will be obtained in a private room at the study center or orally during a Telehealth appointment prior to Screening procedures. Consent will be the first component of participation in this study. iii. 30 minutes is allotted to consent discussion, but it is possible that consent could take up to 60 minutes if needed. iv & v. First, the information contained in the written informed consent document is explained verbally to prospective participant in a language they can understand. Repetition is required during any learning process and is incorporated into the informed consent procedures. Special care is taken to repeatedly inform prospective participants that their participation is entirely voluntary and that they may withdraw at any time and for any reason without penalty or loss of currently existing benefits. Prospective participants are then asked to carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page, or verbally consent (if via Telehealth). The Study Staff and a witness also sign and date informed consent document, and the participant is given a copy for their records. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation. vi. n/a

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

Prospective participants are then asked to carefully read the written informed consent form, and any questions are answered. Next, the prospective participant is asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they are asked to sign and date the last page, or give verbal consent. Understanding English is a requirement for this study.

c) What steps are you taking to determine that potential participants have the capacity to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

All participants in this study must be able to independently consent to participate.

Additional VA questions:

i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.

N/A - PI only at this time. Once study personnel is hired and trained: The persons obtaining consent will be one of the investigators, the study coordinator, or a research assistant, all of whom have been trained to give informed consents. All staff will have completed the required training in Human Subjects, Good Clinical Practice, and HIPAA.

ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?

All participants in this study must be able to independently consent to participate. LAR is not applicable.

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?

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Potential participants will be encouraged to take as much time as they feel they need to make a decision about participation and to review the document with anyone whose advice they would like with regards to participation. Potential participants will be informed that choosing not to participate will in no way effect their clinical care at the VA and that participation is absolutely voluntary.

iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Potential participants will be encouraged to take as much time as they feel they need to make a decision about participation and to review the document with anyone whose advice they would like with regards to participation. Potential participants will be informed that choosing not to participate will in no way effect their clinical care at the VA and that participation is absolutely voluntary.

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?

Yes. No exculpatory language will be used.

vi) Please confirm the following:

a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.

b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.

c. A copy of the signed and dated consent document will be given to the person signing the consent document.

d. The consent form is on the VA Form 10-1086.

Select ALL applicable regulatory criteria for a Waiver of Documentation and provide a protocol-specific justification:

1) 45 CFR 46.117(c)(1)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.

2) 45 CFR 46.117(c)(1)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

3) 45 CFR 46.117(c)(1)(iii)., if participants or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

4) Y **21 CFR 56.109(c)(1)., presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

This study's procedures present minimal risk of harm to participants. This research is not FDA regulated, involves no investigational devices or drugs, collects low risk data and provides a short, low risk cognitive/behavioral intervention.

14. Assent Background (less than 18 years of age)

15. HIPAA Background

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15. 1 Waiver of Authorization for phone screen hipaa

Recruitment

a) **Describe the protected health information (PHI) needed to conduct screening or recruitment. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.**

We are collecting the following identifiable information or PHI: * full name, * social security number (for VA hospital registration and payment), * telephone number (for communication), * mailing address (for appointment notices and to mail payment), * date of birth (study metric), * date of visit, * VA CPRS medical record * Medical history and physical examination information, * Demographic information (gender, ethnicity, education, occupation) * Progress notes, * Biological specimens (e.g. blood, urine, spinal fluid), * Diagnostic/Laboratory test results, * Discharge summary, * Survey/Questionnaire responses, * Cognitive and Psychological test results.

b) Please Answer:

Y **Do you certify that the use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals?**

Y **Do you certify that the research could not practically be conducted with out the waiver?**

Y **Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**

Y **Do you certify that the research could not practically be conducted with out access to and use of the protected health information?**

c) **Please describe an adequate plan to protect any identifiers from improper use and disclosure.**

Information from the telephone screening will be protected from breach of confidentiality through several safeguards including password protected computers, locked offices, doors, and file cabinets, and secure computer networks as described previously in the IRB application.

d) **Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.**

If potential participants are found to be ineligible for or uninterested in participation in the study, records will be securely maintained until such time as their destruction is allowed by an approved and published VA schedule of record retention.

15. 2 Waiver of Authorization waiver of authorization

a) **Describe the Protected Health Information (PHI) needed to conduct the research. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.**

We are collecting the following identifiable information or PHI: * full name, * social security number (for VA hospital registration and payment), * telephone number (for communication), * mailing address (for appointment notices and to mail payment), * date of birth (study metric), * date of visit, * VA CPRS medical record * Medical history and physical examination information, * Demographic information (gender, ethnicity, education, occupation) * Progress notes, * Biological specimens (e.g. blood, urine, spinal fluid), * Diagnostic/Laboratory test results, * Discharge summary, * Survey/Questionnaire responses, * Cognitive and Psychological test results.

b) Please Answer:

Y **Do you certify that the use or disclosure of protected health information involves no more than a**

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minimal risk to the privacy of individuals?

Y **Do you certify that the research could not practically be conducted with out the waiver?**

Y **Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**

Y **Do you certify that the research could not practically be conducted with out access to and use of the protected health information?**

c) Please describe an adequate plan to protect any identifiers from improper use and disclosure.

Identifiers will be protected as described in section 11 of the protocol application

d) Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

Identifiers will be maintained until December 31, 2075 or when the research project is complete, whichever is sooner.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
TBI-CBTi final submission	07/28/2017	ajfurst	
VARQs Furst 41040	07/28/2017	ajfurst	
VA Business Card	10/15/2018	lienlwu	
Directions & Contact	10/15/2018	lienlwu	
Q&A	10/15/2018	lienlwu	
Acute_Unstable_Chronic_Illness_Checklist	10/25/2018	rayma	
BerlinSleepApnea	10/25/2018	rayma	
Boston_Lifeteime_Assessment_TBI_Questionnaire	10/25/2018	rayma	
Boston_Lifetime_Assessment_TBI	10/25/2018	rayma	
Brief_Pain_Inventory	10/25/2018	rayma	
Credibility_Expectancy_Questionnaire	10/25/2018	rayma	
Epworth_Sleepiness_Scale	10/25/2018	rayma	
Functional Outcomes of Sleep Questionnaire	10/25/2018	rayma	
Insomnia_Severity_Index	10/25/2018	rayma	
MedicationList	10/25/2018	rayma	

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MINI 7.0.2 Standard	10/25/2018	rayma	
Penn_State_Worry_Questionnaire	10/25/2018	rayma	
PTSD_Checklist_DSM5	10/25/2018	rayma	
Sleep Diary - Consensus E	10/25/2018	rayma	
Treatment_Satisfaction	10/25/2018	rayma	
Veteran's Rand 36 Item Health Survey	10/25/2018	rayma	
Working_Alliance_Inventory for Participant	10/25/2018	rayma	
Working_Alliance_Inventory for Therapist	10/25/2018	rayma	
DUKE	10/25/2018	rayma	
CANTAB Cognitive Test Security Info	10/25/2018	rayma	
PSG - Compumedics Siesta Brochure	10/25/2018	rayma	
PSG - Compumedics Quik-Cap Brochure	10/25/2018	rayma	
Morningness Eveningness Questionnaire	10/25/2018	rayma	
CANTAB Cognitive Test Overview	10/25/2018	rayma	
CBTI - A Guide to Overcoming Insomnia	10/25/2018	rayma	
CBTI - Behavioral Experiments record sheet	10/25/2018	rayma	
CBTI - Brief Positive and negative beliefs about sleep-related worry quaire	10/25/2018	rayma	
CBTI - Case Conceptualization Form	10/25/2018	rayma	
CBTI - Cognitive restructuring questions	10/25/2018	rayma	
CBTI - Definition of automatic thoughts	10/25/2018	rayma	
CBTI - Management of unwanted thought handout_vic	10/25/2018	rayma	
CBTI - monitoring examples	10/25/2018	rayma	

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handout			
CBTI - Monitoring for information about sleep	10/25/2018	rayma	
CBTI - Monitoring for monitoring form	10/25/2018	rayma	
CBTI - Personalized case conceptualization	10/25/2018	rayma	
CBTI - Questions and Answers about Guidelines	10/25/2018	rayma	
CBTI - Reasons for Feeling Tired	10/25/2018	rayma	
CBTI - Safety behaviors examples handout	10/25/2018	rayma	
CBTI - safety behaviors correction form	10/25/2018	rayma	
CBTI - safety behaviors questionnaire_32 items	10/25/2018	rayma	
CBTI - SAMI_quaire for monitoring attentional bias	10/25/2018	rayma	
CBTI - Sleep Alteration Instructions	10/25/2018	rayma	
CBTI - Sleep and Wake and the Daily Temperature Pattern	10/25/2018	rayma	
CBTI - Sleep Hygiene	10/25/2018	rayma	
CBTI - Sleep regulation slide	10/25/2018	rayma	
CBTI - Sleep Restriction figure	10/25/2018	rayma	
CBTI - Spielman_Three P Model	10/25/2018	rayma	
CBTI - Staying Awake Until Your Scheduled Bedtime	10/25/2018	rayma	
CBTI - Things to do if you are awake_update	10/25/2018	rayma	
CBTI - Thinking traps handout	10/25/2018	rayma	
CBTI - Thought Control Questionnaire Insomnia	10/25/2018	rayma	
CBTI - Treatment Goals Form	10/25/2018	rayma	
CBTI - Trouble with estimating sleep handout	10/25/2018	rayma	

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CBTI - Why questions handout	10/25/2018	rayma	
Study Visual Diagram - For Participants	10/25/2018	rayma	
Participant Contact - Appointment letters	10/25/2018	rayma	
Participant Contact - Appointment schedules	10/25/2018	rayma	
Treatment_Adherence_Questionnaire_ABTI	10/29/2018	rayma	
Treatment_Adherence_QuestionnaireCBT	10/29/2018	rayma	
CBTI - Sleep Need Questinnaire	10/29/2018	rayma	
CBTI - Action plan for addressing future insomnia	10/29/2018	rayma	
ABTI - 8_Item_Hierarchy	10/29/2018	rayma	
ABTI - Brief_Assessment_form	10/29/2018	rayma	
ABTI - Brief_Initial_Assessment_Script	10/29/2018	rayma	
ABTI - Healthy_Sleep_Habits	10/29/2018	rayma	
ABTI - Instructions_For_Practicing_Desensitization	10/29/2018	rayma	
ABTI - Rationale_for_Treatment	10/29/2018	rayma	
ABTI - Sleep_Education	10/29/2018	rayma	
Marijuana_Use_Discussion_Tool	10/29/2018	rayma	
Understanding alcohol effects on the body	10/29/2018	rayma	
Debriefing Script 10/30	10/30/2018	rayma	
Duke - annotated	11/02/2018	rayma	
Trail_Making Instructions	11/02/2018	rayma	
Trail_Making_AB_scoring_and_sheets	11/02/2018	rayma	
Columbia_Suicide_Severity Rating Scale	11/02/2018	rayma	

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Recruitment Form with Consent for Chart Review	12/11/2018	rayma	
Introductory Letter	02/04/2019	rayma	
NewspaperAd	02/04/2019	rayma	
Recruitment Letter Cosigned by Provider	02/04/2019	rayma	
Recruitment letter from Dr Bayley	04/01/2019	rayma	
Duke screening form	04/01/2019	rayma	
Caffeine chart	04/01/2019	rayma	
VA Flyer v2	05/07/2019	rayma	
VA postcard	05/07/2019	rayma	
Waiver of HIPAA Authorization for Research	05/07/2019	rayma	
Study Business card - 053119	06/03/2019	rayma	
Sleep Diary - One night PSG	06/03/2019	rayma	
PSG participant info sheet	06/03/2019	rayma	
Study postcard 060619	06/06/2019	rayma	
PSG Disconnect Form	06/10/2019	rayma	
Participant Eligibility Form	06/11/2019	rayma	
CBTI - Things to do if you are awake	07/31/2019	rayma	
CBTI - Changing your thoughts about sleep	07/31/2019	rayma	
Brochure_v2	01/07/2020	rayma	
Information_Card_Participants	01/07/2020	rayma	
Alternative_Treatments_Letter	01/07/2020	rayma	
Introductory Letter_Concussion_v2	01/17/2020	rayma	
PHQ9_noScore	01/17/2020	rayma	
Headache_Impact_Test_noScore	01/17/2020	rayma	
DBAS	01/17/2020	rayma	
Duke Checklists	02/11/2020	rayma	

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ImportantInfo_forParticipants	03/16/2020	rayma	
VA Telehealth Memo - COVID19	03/25/2020	rayma	
FinalContactLetter	06/25/2020	rayma	
Suicidality Protocol - Telehealth	06/25/2020	rayma	
Suicidality Protocol - Phone calls	06/25/2020	rayma	
AdverseEvents - 062520	06/25/2020	rayma	
WebAdvertisingMockups	06/25/2020	rayma	
Web_PreScreen	07/06/2020	rayma	
ImportantInfo_ForTelehealth	07/06/2020	rayma	
VAVideoConnectHandout	07/06/2020	rayma	
HIPAA Waiver of Consent	07/24/2020	rayma	
Participant_Telehealth_Instructions	09/11/2020	rayma	
Telehealth Recruitment Letter from Wes	09/11/2020	rayma	
Telehealth_Introductory_letter	09/11/2020	rayma	
Text Email Secure Message templates	11/09/2020	rayma	
01042021SleeplessWarriorsStudyCampaignCreative	01/06/2021	rayma	
Text Email Secure Message templates 010621	01/06/2021	rayma	
Telehealth flyer 010621	01/06/2021	rayma	
Alternative Treatment Resources - National	08/10/2022	rayma	
Sleep Diary - updated	02/09/2023	rayma	
Demographics 2023	02/13/2023	rayma	

Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB

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- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical principles, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised
- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook,
http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data)

APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.

Statistical Analysis Plan
In testing Hypotheses 1 and 2, treatment response will be evaluated in terms of improvement in the Insomnia Severity Index (ISI) from baseline to end of the 6-week treatment.

Primary Hypothesis 1: Efficacy of CBT-I compared to a manualized active control condition, Arousal Based Therapy for Insomnia (ABT-I). To test the hypothesis that CBT-I will show efficacy for insomnia in TBI patients at the end of the 6-week treatment period, compared to the control condition (ABT-I) we will regress change in ISI on treatment (CBT-I versus ABT-I; 6 weeks vs. baseline). We will run analogous models to test for persistent treatment effects at the 16 and 24-week follow-up points. In each set of models the dependent variable will first be the change relative to baseline in our primary outcome measure of insomnia change defined by the ISI scores. We will covary for comorbid PTSD severity and amount of medication use (SSRIs) as required, if the frequency of such differs by treatment group.

Secondary Hypothesis 2: Moderators and Mediators of response. Our previous design separated Sleep Restriction (SR) and Cognitive Therapy (CT) components of CBT-I, however, we feel that although the design of the study has been changed, we can still gather some preliminary data on likely moderators and mediators of CBT-I, SR and CT while conducting the clinical trial and testing our Primary Hypothesis. Thus, we can still determine whether changes in potential moderators and mediators of SR and CT might also moderate or mediate the effects of the entire CBT-I package.

Exploratory analyses will compare the predictive usefulness of all measures listed in Table 5. In more detail, we will fit regression models for change in ISI on treatment, the continuous moderator and the treatment by moderator interaction. Baseline Medication use and PTSD should be similar across groups due to randomization and use of the blocking procedures (Section 2.a.3.b.5). The analysis may be adjusted for other covariates (age and alcohol use) if they are significantly different between groups at baseline despite randomization. We will use percentile, bootstrap confidence intervals to determine the moderator value, if any, at which there is a change in the optimal choice of treatment (i.e. the point of intersection at which one treatment first surpasses another). Our results will allow us to choose the optimal treatment based on individual moderator values and estimate the comparative advantage of one treatment over another given a specific moderator value. The confidence intervals will also show the moderator values, if any, for which the difference between treatments is statistically or clinically insignificant.

Secondary Hypothesis 2: Mechanisms of Action (Mediators). As in the case of moderators of treatment response, since our design has changed mediators of treatment response are reduced in prominence in this proposal. Nonetheless, we feel some exploratory analyses may be carried out. For example, we hypothesize that changes in TIB with its associated increase in homeostatic pressure for sleep may account for some of the effects of SR and that changes in measures of worry and pain may explain some of the effects of CT. In the package of combined SR plus CT (CBT-I) this may still be the case for the group as a whole. Therefore, we will conduct secondary analyses using the bootstrap strategy for mediator analysis formulated by Preacher and Hayes [98] to address this possibility. Specifically, we will fit three separate regression models to estimate the indirect effect of treatment through the mediator: 1) Change in ISI on treatment; 2) Change in mediator on treatment; and 3) Change in ISI on treatment plus change in mediator. Each model will be adjusted for the same covariates described above. We will estimate the indirect effect as the product of the treatment effect in (2) and the mediator

effect in (3). We will compare the indirect effect to the total effect of treatment, estimated in (1), to determine how much of the total effect of treatment is accounted for by the mediator. Due to the non-normality of the estimates, percentile bootstrap confidence intervals for the mediator effects will be computed and their statistical significance assessed. We propose to use multiple imputation [99, 100] and an analyses based on total ISI change over the course of the study. Additional mediator analyses will be performed for relevant measures listed in Table 5.

Likelihood of Obtaining Useful Results. For our primary hypothesis we considered a target power of 80% with a two-tailed test at 5% significance in an Intention-to-Treat (ITT) analysis. We will require 60 subjects per group (for a total of 120 in the two groups) to detect a main effect of treatment group with an effect size that increases R-squared by 6% or more, with respect to the continuous outcome variable (ISI improvement). Thus we feel that the sample of 60 per group is adequate. Power analyses were computed using G*Power Version 3.1.9.2 [101].

Considerations Regarding Sleep Medication Changes During the Study. Tentatively, we would consider patients who required a sleep medication increase a treatment failure and they would be scored accordingly. We would interpret a decrease in medications a sign that therapy was working and assume that the ISI ratings would reflect a treatment success. We plan to monitor these assumptions with our statistical team and adjust our analyses appropriately.

Other analyses. The above is meant to be a brief outline of our analytic approach. Other analyses will be conducted including examination of secondary outcomes such as Quality of Life measures.

IRB Use Only
Approval Date: July 31, 2023
Expiration Date: July 31, 2024

Title of Study: Non-pharmacological treatments for insomnia in chronic traumatic brain injury	ePrototcol #41040
Principal Investigator: **Ansgar J. Furst, PhD**	VAMC: VA Palo Alto HCS

Non-pharmacological treatments for insomnia inchronic traumatic brain injury

PURPOSE OF RESEARCH

You are invited to participate in a research study of non-drug treatments for insomnia in Veterans with chronic traumatic brain injury. We hope to learn which of two treatments works best for adults with specific sleep problems. Specifically, we will compare and contrast Cognitive Behavioral Therapy with Arousal-Based Therapy for Insomnia. You were selected as a possible participant in this study because you may have insomnia.

This project plans to enroll about 120 research study participants with insomnia to participate in this study. The study will be conducted at VA Palo Alto Health Care System by the Principal Investigator, Dr. Ansgar Furst.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to. You have the right to refuse to answer particular questions.

DURATION OF STUDY INVOLVEMENT

Participation in this study will require two sessions for initial evaluation, six sessions for treatment - once per week for six consecutive weeks - one session at end of treatment and one session approximately six months after completion of the treatment for follow-up. Study participation will take place across a total of approximately eight months.

PROCEDURES

If you decide to participate in the study, you will go through a series of screening steps to determine the nature of your sleep problem. The order of these steps may vary. If at any point during the screening portion of this study, we determine that our treatments are not appropriate for your sleep problem, we will end your participation in this study and suggest possible referral resources.

Screening Session

The initial evaluation begins with a screening session to determine if you are a good fit for the study. During this screening session, we will ask you to complete several interviews and questionnaires to gather information about your sleep and general health You will also have a chance to bring up issues you believe are relevant to your sleep problem.

Medications

Participants may take medications, drugs, herbal remedies, or hormones specifically prescribed for treating sleep disturbances while participating in the study. Sleep medications are acceptable if stable (at least 3 weeks of same dose/timing/formulation) at the time of recruitment. Other medications, including those with sleep side-effects, are acceptable if stable (at least 3 weeks of same dose/timing/formulation) at the time of recruitment.

Once enrolled in the study, changes to these medication (starting, stopping or changing the dose) may result in delays in treatment or your withdrawal from this study. Please inform us immediately of any recent or expected changes to your medications.

Your responses to questions concerning illegal drug use will be kept confidential by us, but could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement of the consent, we do not intend to disclose this information.

Other Psychological Therapies and Interventions

Concurrent psychotherapy is allowed in most cases. If you decide to start another new therapy or research study at the time of your enrollment in this study, your participation may be delayed or you may be withdrawn from this study. Please inform us of any recent or expected changes to other therapies.

Sleep Logs.

During the first session, we will show you how to complete daily sleep reports. A sleep report is designed to gather information about your daily sleep pattern. You will be asked to keep a daily sleep report for the two weeks of initial evaluation, the entire six-week treatment period and for one week at the six-month follow-up.

When you have completed the screening session described above, we will determine if our study is appropriate for you. If so, you will have a fifty percent chance to be assigned to one of two treatments: Cognitive Behavioral Therapy or Arousal-Based Therapy for Insomnia.

Baseline Session

Before treatment begins, you will meet with study staff to complete some additional interviews and questionnaires about the nature of your sleep problem and general health. We will also ask you to complete some tasks to test your memory and attention. Prior to this appointment, we will ship you an iPad for you to borrow which you will use to complete these memory and attention tasks. You can also use this iPad to fill out surveys and meet with study staff on video calls. The iPad will need to be returned at the end of treatment.

Treatment

You will have a fifty percent chance to be assigned to one of two treatments: Cognitive Behavioral Therapy for Insomnia (CBT-I) or Arousal-Based Therapy for Insomnia (ABT-I). The two therapies teach you different skills and techniques to help reduce insomnia symptoms.

The treatment part of the study lasts six weeks and you will complete a sleep report for each day during treatment. During the treatment, you will meet with the therapist for a total of six sessions: once per week for six consecutive weeks. Each session lasts approximately 60 minutes.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

This therapy addresses thoughts and behaviors that can interfere with sleep. Thoughts and behaviors that develop in response to insomnia can result in heightened anxiety about sleep and the development of coping strategies that can ultimately worsen insomnia. This therapy aims to alter behaviors that contribute to sleep problems, and correct the beliefs that drive those behaviors. Therapy will also include sleep education.

Arousal-Based Therapy for Insomnia (ABT-I)

This therapy addresses the heightened state of alertness or anxiety that can occur when experiencing difficulty sleeping. This heightened state of arousal develops over time in response to insomnia, and can make falling asleep more difficult. Since this response is learned, it can also be unlearned. This therapy teaches skills to reduce the heightened arousal that contributes to insomnia. Therapy will also include sleep education.

Audio Recording.

We will make an audio recording of each treatment session, which will be evaluated by a research psychologist for quality control. All audio recordings will be kept in a locked cabinet for the VA-required period of 6 years after study closure, then destroyed.

_____ Yes, I give permission for audio recordings to be made, as set forth above.

_____ No, I do not give permission for audio recordings to be made.

End of Treatment Follow-up

At the end of the 6-week treatment period, you will be asked to complete a 7-day sleep log, and then attend another meeting to repeat some of the interviews and questionnaires that you completed at the beginning of the study. You will also be asked to complete the same memory and attention tasks at this appointment that you completed at the Baseline appointment. The iPad and charger shipped at the beginning of the study will need to be returned after you complete the End of Treatment Follow-up.

6-Month Follow Up

We expect the benefits of your treatment to continue and improve with time, thus we encourage you to continue practicing the treatment instructions to maintain your progress. Six months after you have completed the treatment, we will ask you to complete a 7-day sleep diary and an updated medication list. We will ask you to meet us to complete the interviews and questionnaires for a third and final time. An iPad will be shipped to you once more to use for the memory and attention tasks completed at this visit. The iPad and charger should be shipped back after completing the 6-Month Follow Up visit.

PARTICIPANT RESPONSIBILITIES

As a study participant, your responsibilities include:

- Follow the instructions of the investigators and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigators or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigators or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Keep your sleep diaries as instructed.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigators or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for any condition.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling the research assistants at 650-852-3426 or the Principal Investigator, Dr. Ansgar Furst, at 650-493-5000 extension 68652.

If you withdraw from the study for any reason, you must return any study-related equipment still in your possession.

The investigators may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the investigators and/or study staff.

- The investigators decide that continuing your participation could be harmful to you.
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Principal Investigator if you have any questions. This study involves the following risks, discomforts, and possible inconveniences:

Evaluation and testing. There are virtually no risks involved in the cognitive testing and psychological measurements other than the anxiety that can be associated with any test. It is possible that you might become tired or frustrated by some of our testing. You may find answering the questionnaires annoying, boring, or repetitive. If this happens, please tell us and we will take a break or skip a particularly difficult test. Evaluations of mood and mental status may be slightly frustrating or produce fatigue and boredom. If the research staff has reason to believe you may be having suicidal thoughts, you will be asked to speak to a clinician trained in suicidality risk assessment.

Sleep Log and Questionnaires. There are no harmful effects to filling out the sleep log and questionnaires, but you may find answering the questionnaires annoying or boring. All paper data collected will be stored in a locked cabinet at the Palo Alto VA accessible only by study staff. De-identified data from web-based surveys and tests will be stored on server to which only approved study staff will have access.

There is always the possibility that your sleep might get worse during treatment. In general, most patients benefit from the proposed treatments, but it is always possible that an individual can experience unwanted changes in their sleep pattern.

Non-pharmacological treatments for insomnia like Cognitive Behavioral Therapy and Arousal-Based Therapy may lead you to challenge some of your thoughts and concerns about the way you sleep. The treatment may lead you to adopt a more flexible cognitive stance regarding your sleep. Some people may find this uncomfortable. In addition, you may feel overly sleepy, cranky, or disoriented during the first few days of treatment. It is recommended that you avoid driving, operating machinery, or doing activities that require close attention for the first few days of therapy. Sleep efficiency training has been known to trigger seizures in people with seizure disorders and to have possible negative effects on mood in people with bipolar disorder. For this reason, people with these disorders are not eligible for this study.

POTENTIAL BENEFITS

There may be no direct benefits to you for participation in this study. Your sleep may improve. Your participation may help us to learn more about the causes of insomnia.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY DIRECT BENEFITS FROM THIS STUDY.

ALTERNATIVES

You do not have to participate in this research study in order to receive treatment for any medical condition. There are other behavioral treatments for sleep problems, as well as various drug treatments for sleep problems, that are not included in this study. A study clinician can discuss any alternatives with you before you agree to participate in this study.

PARTICIPANT'S RIGHTS

Your participation is voluntary. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

We will keep your name and all the information you tell us in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

If you decide to participate in other studies at the VA or Stanford Sleep Center, data about you from this study may be combined with data about you collected for other studies.

It is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide, physical or sexual abuse) to the appropriate authorities.

FUTURE USE OF PRIVATE INFORMATION

Research using private information is an important way to try to understand human disease. You are being given this information because the investigators want to save private information for future research.

Identifiers might be removed from identifiable private information and, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

FINANCIAL CONSIDERATIONS

Payments. You will receive $25 for the screening session. If you are determined to be eligible for the study, you will receive an additional $50 for completing the baseline session. You will receive stipends of $25 for all 6 treatment visits thereafter (6 x $25 = $150) and $50 each for the 2 follow up visits. If you complete all the study visits, you will receive a total of $325.

You will need to provide your Social Security Number to receive payment.

Costs. You will not have to pay anything to be in this study.

Sponsor. The Department of Veterans Affairs is providing financial support for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for Veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the principal investigator, Dr. Ansgar Furst, at 650-493-5000 ext. 68652. You should also contact the principal investigator or any member of the research staff at any time if you feel you have been hurt by being a part of this study.

Appointment Contact: If you need to change your appointment, please contact the research assistants at 650-852-3426.

If in the event of a medical emergency that may or may not be related to participation in the study please call 911 and notify your primary care physician.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL PARTICIPANT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Title of Study: Non-pharmacological treatments for insomnia in chronic traumatic brain injury	eProtocol #41040
Principal Investigator: **Ansgar J. Furst, PhD**	VAMC: VA Palo Alto HCS

Current Participation in Other Studies:

Are you participating in any other research studies? _____ Yes _____No

Contact for Future Research Studies:

May we contact you (by phone or letter) about related studies that may be of interest to you?

_____ Yes. I would like to be contacted for future research opportunities.

_____ No. Do not contact me about future research opportunities.

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

Print Name of Participant Date

_____ **Participant provided verbal consent in lieu of signature.**

Person Obtaining Consent:

Signature of Person Obtaining Consent Date

Print Name of Person