Title : Predictors of Response to Insomnia Treatments for Gulf War Veterans
Approval Period: 08/31/2024 - 08/31/2025

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Protocol Director

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
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CITI Training current				Y

Admin Contact

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
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CITI Training current				Y

Investigator

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
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CITI Training current				Y

Other Contact

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
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CITI Training current				Y

Academic Sponsor

Name	Degree (Program/year if student)	Position, e.g. Assistant Professor, Resident, etc.

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Department		**Phone**		**E-mail**
CITI Training current				

Other Personnel

Name Laura Lazzeroni		**Degree (Program/year if student)** PhD		**Position, e.g. Assistant Professor, Resident, etc.** Associate Professor
Department Psych/General Psychiatry and Psychology (Adult)	5485	**Phone** (650) 723-0947		**E-mail** Lazzeroni@stanford.edu
CITI Training current				Y

Name Arthur Noda		**Degree (Program/year if student)** MA		**Position, e.g. Assistant Professor, Resident, etc.** Software Developer, Research
Department	5550	**Phone** (650) 493-5000 ext. 64493	(650) 852-3297	**E-mail** artnoda@stanford.edu
CITI Training current				Y

Name Donn Posner		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Adjunct Clinical Associate Professor
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CITI Training current				Y

Name Beatriz Hernandez		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Data Analyst
Department Psych/Public Mental Health & Population Sciences	5550	**Phone** (650) 852-3287		**E-mail** bhernandez@stanford.edu
CITI Training current				Y

Name Pandora Lam		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.** Assistant Clinical Neuroimaging Research Coordinator
Department Psych/Sleep Medicine	5797	**Phone**		**E-mail** pal217@stanford.edu
CITI Training current				Y

Participant Population(s) Checklist **Yes/No**

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- 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 Y
- Students N
- Employees N
- Other (i.e., any population that is not specified above) N

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

  Jerome A. Yesavage, MD
- Other (Click ADD to specify details)

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) Y
- Is Stanford the coordinating institution or are you the lead investigator for this multi-site study? Y

Site Name	Contact Name	Contact Phone	Contact Email	Permission?	Engaged?
WRIISC New Jersey	Drew A. Helmer, MD	800-248-8005	drew.helmer@va.gov	Y	Y
WRIISC Washington DC	Matthew Reinhard,	800-722-8340	matthew.reinhhard@va.gov	Y	Y

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	Psy.D.				

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) Y

- Will this study be registered on clinicaltrials.gov? (See Stanford decision tree) Y
- Who will register for ClinicalTrials.gov? Y
  NCT# 03208049

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**

- 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 N

contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.

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
• Federally Sponsored Project?	N
• Industry Sponsored Clinical Trial?	N

Funding

NONE

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Funding - Grants/Contracts

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

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

Jerome Yesavage, MD. Dr. Yesavage is Associate Chief of Staff for Mental Health at the VA Palo Alto Health Care System, and Professor of Psychiatry at Stanford University. Over the past 20 years, he has conducted several studies in sleep and insomnia. He is also Director of the VA Mental Illness Research, Education, and Clinical Center (MIRECC) at VA Palo Alto Health Care System, and Professor of Psychiatry at Stanford University School of Medicine. Dr. Yesavage has tremendous experience in the design and conduct of similar studies. Dr. Yesavage will be involved in the design, execution, and analysis of this study, and will have the resources of the WRIISC to draw upon as needed.

Andrea Goldstein-Piekarski PhD is a cognitive psychologist and neuroscientist who has been studying sleep and mental health for over 8 years. As a graduate student she conducted a series of multi- dimensional studies investigating the impact of sleep loss on anxiety and affective brain function. These investigations were conducted using a combination of high-density EEG sleep recording, advanced functional and structural MRI methods, and emotion reactivity paradigms. As a postdoctoral fellow she used advanced computational modeling to understand the neurobiology contributing to anxiety and mood disorder symptomology as well as treatment response. Dr. Goldstein-Piekarski will be involved in the design, execution, and analysis of this study, and will have the resources of the WRIISC to draw upon as needed.

Art Noda, Data Manager. has 25 years of experience of doing data management and analysis for clinical studies. He has used Statistical Analysis System (SAS, Cary N.C.) software for database management, programming and data analysis for 18 years. He has developed advanced skills using SAS in database construction and management as well as proficiency in a variety of complex statistical analyses. Currently he is supporting various investigators on issues related to data management, security, analysis and presentation at VAPAHCS. In the current project, he will design and implement a database for the secure storage of all study-related data, consult on all statistical examinations of the data set, and assist with presentations and manuscript preparation.

Donn Posner, PhD brings a wealth of knowledge and research experience in behavioral approaches to sleep treatment adherence and lifestyle modification. Dr. Posner will provide input to Dr. Friedman regarding the CBT-OSA manual and related materials. Dr. Posner will be available to advise the Project Study Coordinator regarding individual participant eligibility.

Laura C. Lazzeroni, PhD has collaborated with Dr. Yesavage for the past five years, with a research focus on statistical genetics and other biostatistical issues, such as multiple hypothesis testing and simultaneous inference.

Bea Hernandez, works closely with Dr. Lazzeroni and Art Noda to help with database management and data analysis.

Grace Fischer is an administrative assistant who will be helping manage the regulatory aspects of the study.

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 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 have been 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 MIRECC / WRIISC (Mental Illness Research, Education, and Clinical Center / War-Related Illness and Injury Center) offices,, located at VA Palo Alto Health Care System, Palo Alto Division. Private interview rooms and a large conference room are available for this project, as well as office space for staff.

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 a maximum of 50 weeks in the project.
We expect to begin recruitment in late summer/fall, 2017.
The project will be completed in 5 years.

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.

Veterans will be recruited and treated at the three VA WRIISCs that are the normal clinical referral sources for Gulf War Veterans.

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.

Participants will be informed of risks, using the text provided and required by the governing Institutional Review Boards. Our individual screening and test sessions will be 3 to 4 hours each at the most. In the event of discomfort experienced during the psychiatric screening and/or cognitive testing, all participants will be informed that they are free to decline to answer any questions they don't wish to answer, or to stop

the interview or testing at any time. Staff will be well-trained and supervised under the direction of experienced clinical researchers. Interviews are done at the VA Palo Alto, in the MIRECC/WRIISC offices. Assistance is available from on-site clinical psychologists and psychiatrists 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.

The VA Palo Alto site will serve as the lead site for this study, and will host the RedCap database containing all study data. All samples will be sent to VA Palo Alto, where they will be stored and analyzed. Data analysis will be done at VA Palo Alto. All therapists will be trained by the study therapist at VA Palo Alto.

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 efficacy and effectiveness of sleep restriction (SR) and cognitive therapy (CT) in Gulf War Veterans with insomnia.

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

The primary hypothesis is that the efficacy of these treatments will depend upon an individual subject's baseline characteristics. For SR we expect that baseline measures of "excessive time spent in bed" may predict response and for CT we expect that baseline measures of cognitive arousal and pain may predict response. Exploratory analyses using signal detection techniques will systematically compare and contrast the potential usefulness of a number of additional potential moderator measures. Insomnia is a serious health problem in Gulf War Veterans that is often associated with extensive prescription of sleeping medications. Although safer, even the latest "sleeping pills" can lead to cognitive impairment and risk of abuse. Thus non-pharmacological treatments for insomnia have been pursued as alternatives to medications. Cognitive Behavior Therapy for Insomnia (CBT-I) is the term widely used to describe therapies that combine behavioral and cognitive therapies for insomnia. The combined CBT-I approach has well-documented efficacy. Between 2012 and 2014 over 650 VA mental health clinicians have received extensive training in CBT-I. Although CBT-I is efficacious, the optimal target populations for its major components has not yet been well-defined for Gulf War Veterans. We propose to address this gap and develop tools for clinicians to identify the best treatment for insomnia for individual Gulf War Veterans.

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.

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.

Our hypotheses will be tested in a randomized parallel groups design. Randomization will be based on type of treatment assignment: either to SR or CT.

After screening and randomization in the 2-week baseline phase, subjects will receive SR or CT in the 6-week treatment phase. Participants will have the option to complete study sessions over telehealth for the entirety of the 6 weeks. There will be no more treatment after this point. At the end of the 6-week treatment, subjects will return to repeat many of the psychological tests administered during baseline to determine the short-term benefit. This 4-year proposal will include 100 subjects (2 groups of 50 each) with outcome, mediator and moderator measures collected at appropriate points.

All subjects will receive education about basic sleep hygiene as well as information about the science of sleep including sleep stages and sleep regulation.

Sleep Restriction Therapy (SR). The initial Time in Bed (TIB) prescription is calculated on the average total sleep time (TST) reported in the baseline sleep logs.

After one week, depending on subject's daily sleep logs, the therapist suggests a new TIB prescription. 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.

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. Similar to SR, subjects in CT are given information about relevant elements of the science of sleep and healthy sleep practices.

We will also continue to monitor progress post-treatment in the follow-up period. The complete package of outcome measures will be repeated at the follow-up session. 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 after active treatment ends.

Subjects will be screened for eligibility via a phone interview and an in person or telehealth evaluation. Subjects that learn about the study through StudyPages campaign ads and are recruited through the study landing page developed by StudyPages. They will complete a brief pre-screening survey to confirm interest and screen for initial inclusion criteria before being contacted by our study team for a full phone interview. The in-person or telehealth evaluation may be split into two visits if necessary.

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At the in-person or telehealth evaluation, after signing a consent form, a more detailed interview about sleep problems, and medical and psychiatric history will be obtained by the Duke Structured Sleep Interview, including evaluations of cognitive impairment and depression. Exclusion criteria will further be evaluated by the following given solely at the office evaluation: Acute/Unstable Chronic Illness checklist, Columbia Suicide Severity Rating Scale (C-SSRS), DUKE Structured Sleep Interview, Hamilton Depression Rating Scale (HDRS24), Life Stressor Checklist, Mini International Neuropsychiatric Interview Version 5 (MINI), Montreal Cognitive Assessment (MOCA) or MOCA-Blind, Morningness-Eveningness Questionnaire, and the Sleep Related Behavior Questionnaire. Subjects will additionally be set up with PSG equipment. The PSG will be completed in the subject's own home and be used to screen a for Obstructive Sleep Apnea and Periodic Limb Movement Disorder.

Subjects will return to the lab the next morning to have the equipment removed.

Participants will be evaluated on the Anxiety and Preoccupation about Sleep Questionnaire (APSQ), Depression Anxiety and Stress Scale (DASS-21), Epworth Sleepiness Scale, and the Insomnia Severity Index each visit during weeks 1-8, and again at week 32. Sleep logs will be done daily during weeks 1-8, and again at week 32. The following will be done at weeks 1, 8, and 32: AUA8 Noctoria; Brief Pain Inventory short form (BPI-SF); Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Clinician Administered PTSD Scale (CAPS); Dysfunctional Beliefs and Attitudes about Sleep Scale; AUA8 (DBAS); Glasgow Content of Thoughts; Glasgow Sleep Effort Scale; Multidimensional fatigue Inventory; Penn State Worry Questionnaire (PSWQ); Perceived Stress Scale (PSS); SF-36 (RAND).

Subjects will be evaluated on Functional Outcomes of Sleep Questionnaire at weeks 1, 2, 8 and 32.

Subjects will be evaluated on the Sleep Associated Monitoring Index (SAMI) at weeks 1 and 8.

Subjects will be evaluated on the Trial Making Test, Color Word Interference test, Thought Control Questionnaire Insomnia-Revised (TCQI), and the RBANS at weeks 1 and 32.

Following the completion of treatment at week 7, subjects will complete the Treatment Adherence Survey, Treatment Satisfaction Survey and Working Alliance Inventory. The Working Alliance Inventory will also be given at the second treatment session (week 3). If participants are participating in Telehealth, they will complete these questionnaires as RedCap surveys on Stanford's RedCap.

Blood will be drawn to measure levels of C-reactive protein (CRP). Urine samples will be collected at during each of the 3 study phases to monitor abstain from drugs of abuse, except for medical marijuana used less than four times a week. Samples will be collected by nurses at the VA Clinical Studies Unit and analyzed by the VA lab. Blood samples will be taken at the same time to be analyzed for C-reactive protein. Remaining blood will be banked to be analyzed for genetic factors.

Due to the COVID-19 pandemic, we are adding the option for participants to complete all study sessions through telehealth. We will utilize Zoom and send questionnaires as RedCap surveys on Stanford's RedCap. This will allow the participants to move forward in the study while also not deviating from the study timeline. We will still collect adverse events and study measures at each treatment session. After the COVID-19 shut-down is over, we will still offer telehealth as an option to our veterans to be flexible to their scheduling needs and keep consistency with the measures taken during

this crisis. Under normal circumstances, we will allow the veterans to choose if they would like to utilize telehealth or in-person treatment session and would complete all therapy sessions through the selected delivery method. We will document each individual who started therapy sessions in-person and switched to telehealth so that we can do analyses to see if their data is viable.

Additionally, we are adding the option for veterans to do their screening, baseline, and follow-up sessions via telehealth. For these individuals, we will not collect the following measures: urine screen, blood draw, Trial Making Test, Color Word Interference test, and overnight PSG (currently only available at Palo Alto). All other measures can feasibly be done through telehealth. As stated above, we will continue to offer this option for the remainder of the study.

Palo Alto will be the main site for virtual national recruitment. We will recruit participants nationally and also take referrals from the other sites. If the other sites have a waitlist or are unable to screen new participants, they will refer the participants to the Palo Alto site to be consented and screened at our site. The Palo Alto site will not share PHI with any other sites. The Washington, DC WRIISC site will share PHI (name, mailing address, phone number) with the Palo Alto site if the participant consents to this. These data will be shared via an encrypted AZURE email between VA email addresses from the Washington, DC WRIISC study team to a study team member working at the Palo Alto VA. The Palo Alto site would then call the participant to complete the phone screen. The other sites can also refer participants to our site by giving the participants our recruitment flyer/phone number and having the participant call our site or through warm transfers. If a warm transfer is being conducted, no PHI will be shared prior to this call. The other site will call the participant and ask if they would like to participate at our site or remain on their site's waitlist. If they would like to be transferred, a lab member from our site will be added to the telephone call and then left with the participant to complete the telephone screen.

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).

No deception will be used.

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.

Audio recordings will be done for quality control purposes. All recordings will be stored in locked cabinets and destroyed at the end of the VA-required holding period (currently 6 years). Sessions done through telehealth will have audio and video recorded.

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. Cognitive Behavioral Therapy is available from clinicians and therapists at VA hospitals and in most communities.

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

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

Insomnia in Veterans is a serious problem often associated with extensive prescription of sleeping medications.

Although safer, even the latest "sleeping pills" are not without risks. Lack of safe and effective treatment for insomnia has notable economic impact on society and patients alike. Thus, nonpharmacological treatments for insomnia have been pursued as alternatives to medications with some suggesting they should be the "first line of therapy". In two studies published in 1998 the prevalence of insomnia in GWVs was 30 and 31% compared to 11% in Veterans deployed to Germany during the same period. Of particular import is a 2014 study performed by colleagues at our VISN21 MIRECC documenting poor sleep quality in GWVs twenty years after deployment. This study found that sleep disturbance was also associated with abnormalities in brain volume. Finally, Gehrman and associates have documented that insomnia is a serious problem for many Veterans and is associated with medical and psychiatric comorbidities other than those problems related with over-medication. Cognitive Behavior Therapy for Insomnia (CBT-I) is the term widely used

to
describe psychological therapies that combine a broad range of non-
pharmacological treatments for insomnia. The combined CBT-I approach
has
well-documented efficacy. Under the direction of the VISN 21 MIRECC,
over
650 VA mental health clinicians have completed extensive training in
CBT-
I.
Components of CBT-I may include behavioral interventions (e.g.,
stimulus
control, sleep restriction, relaxation training), cognitive therapy,
and
sleep hygiene education. Stimulus control is based on the concept
that
following a set of instructions will re-associate the bed and bedroom
with
sleep and reestablish a consistent sleep/wake pattern.

Sleep restriction (SR) is designed to reduce "excessive time spent in
bed"
to the actual amount of the subject's sleep time, thereby increasing
sleep
pressure that leads to higher quality sleep. Cognitive therapy (CT)
for
insomnia, like CT for other disorders, focuses on changing
maladaptive
cognitions, intrusive thoughts and perception of pain that interfere
with
sleep. Harvey et al. suggest that a broad range of cognitive
processes
such
as beliefs, attributions, and expectations are relevant to
understanding
insomnia. CT challenges maladaptive and/or inaccurate cognitions
about
sleep
and insomnia. CBT-I combines CT with one or more of the behavioral
therapies. Both SR and CT include a sleep education component that
provides
an understanding of basic sleep regulation and sleep hygiene
instructions.
Background to Insomnia Treatments in Gulf War Veterans. A National
Academy
of Sciences Workgroup has recognized insomnia in Gulf War Veterans to
be
associated with Chronic Multisymptom Illness (CMI). CBT-I is
recognized
to
be a "Best Practices" recommendation for the treatment of insomnia
associated with CMI. Although this Workgroup identifies several pain
syndromes associated with Gulf War syndrome, their extensive
literature
review did not discover any studies discussing the comorbidity of
pain

syndromes with insomnia in Gulf War Veterans.

Nonetheless, the appended CBT-I manual used in current training of VA therapists specifically addresses CT strategies for dealing with pain syndromes including those seen in Gulf War Veterans. Similar strategies have been used in the past to treat insomnia in patients with fibromyalgia and other syndromes with chronic pain. In sum, there is little data on how pain experienced by Gulf War Veterans may affect their response to treatments for insomnia.

Gaps in the Literature of Insomnia Treatments in Gulf War Veterans to be Addressed by the Proposed Research. It is unknown how chronic pain associated with CMI might affect outcome from either SR or CT. Although CBT-I has well-documented efficacy and is recommended for use in Gulf War Veterans, the optimal target populations for the SR or CT components has not been well-defined for this cohort. We propose to address this gap with the research described here. Such knowledge, could lead to rational allocation of resources and not waste either patient or therapist time applying interventions that are not likely to be of benefit.

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.

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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.

5. 1 Device Name : Compumedics Safiro? ambulatory PSG system

Describe the device to be used.

We will use the Compumedics Safiro? ambulatory PSG system. This includes monitoring of the electroencephalogram (EEG; C3-A2 or C4-A1, O2-A1 or O1-A2), electrooculogram (EOG; ROC-A1, LOC-A2), chin and anterior tibialis electromyograms (EMG), heart rate by two-lead EKG, snoring intensity (anterior neck microphone), nasal pressure (nasal cannula), thoracic and abdominal movement (inductance plethysmography bands), and oxygen saturation (pulse oximetry).

Manufacturer Compumedics

IDE Exemption

Y **This is a legally marketed device being used in accordance with its labeling.**

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 equipment is 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.

Please note: Our original targets changed due to COVID-19 as a result of the pandemic we are no longer expecting to meet the full recruitment target.
(i) We plan to randomize and enroll 20-25 participants at the VA Palo Alto Health Care Systems, a Stanford-affiliated site. We plan to consent 50-60 participants total to adjust for the attrition rate of 36% (20/.36 = 55.6).
(ii) A total of 50-55 subjects are expected across all sites. There are 3 sites, at WRIISC California, located at VA Palo Alto, WRIISC New Jersey, located at VA New Jersey, and at WRIISC Washington DC, at Washington DC VA. Since the study will now have a telehealth option, the study will be open to veterans across the country.
(iii) Participants will be Gulf War Veterans with insomnia.

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

Age Range: we expect the ages of gulf war veterans to be within the ages of 42-80.
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, pregnant women, economically and educationally disadvantaged, decisionally impaired, and homeless people 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 military Veterans of the Gulf War.

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.

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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.

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 and treated at the three WRIISCs that are the normal clinical referral sources for Gulf War Veterans, through chart reviews, and through articles in local newspapers, relevant newsletters, flyers, and online forums such as reddit, facebook and craigslist. We will also use the DMDC recruitment database, WRIISC database, and the Gulf War Registry Database to identify potential participants. We will send letters and call possible participants from these three databases.

Participants will be recruited nationally at the Palo Alto site.

If the other sites have a waitlist, they will refer participants to participate in the study virtually at Palo Alto. They will be screened and consented at Palo Alto. The other sites can refer participants to our site by giving the participants our recruitment flyer/phone number and having the participant call our site or through warm transfers. Before the warm transfer, no PHI will be shared. The other site will call the participant and ask if they would like to participate at our site or remain on their site's waitlist. If they would like to be transferred, a lab member from our site will be added to the telephone call and then left with the participant to complete the telephone screen. The Palo Alto site will not share PHI with any other sites. The Washington, DC WRIISC site will share PHI (name, mailing address, phone number) with the Palo Alto site if the participant consents to this. These data will be shared via an encrypted AZURE email between VA email addresses from the Washington, DC WRIISC study team to a study team member working at the Palo Alto VA. The Palo Alto site would then call the participant to complete the phone screen.

Veterans will also be recruited through the StudyPages outreach campaign that will utilize a targeted social media campaign through Facebook. Interested participants can be redirected to the study landing page if they click on the links on the campaign ads. We will call possible participants using the phone number they provide through the pre-screening survey if they agree to share their information in order to be contacted about the study.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

o Male or female Gulf War Veterans of any racial or ethnic group
o Independent Living (not in nursing home or VA Extended Care facility)
o Subjective complaint of insomnia on the Insomnia Severity Index (ISI) ≥ 10
o Subjects with PTSD will be included in this study as long as they do not meet criteria for depression described below.
o 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).
o Stable adult onset diabetes, controlled with insulin, oral medications or diet is acceptable.
o Access to a device with video capabilities and ability to have the video on during study visits

Identify exclusion criteria.

o Sleep-Related
- Excessive caffeine consumption (≥ 4 cups of coffee per day) and unable to reduce to ≤ 3 cups before lunch a day for ≥ 3 weeks prior to treatment.
- Subjects will be initially screened by the Berlin Questionnaire (for sleep apnea) and those with

responses suggestive of high risk for sleep apnea, will be referred to Pulmonary Medicine for standard clinical screening including polysomnography. Those in which apnea is primarily responsible for their sleep complaints should be excluded.

- Subjects working a rotating shift or an unconventional daytime shift (ending after 1830 h, expected to be rare in the age group we are studying) will be ineligible.
- Subjects who have received CBT-I treatment within the past year will also be excluded due to potential carry over effects to the current treatment.

o Neuropsychiatric

- Hamilton Depression Scale (HDRS ≥ 24) and classified as high risk on the Columbia Suicide Severity Scale (C-SSRS) in the past month. Individuals are considered high risk if they have endorsement of either of the following on the C-SSRS:

a) A positive endorsement, relative to the past 30 days, in the "Suicide Thoughts" section of item #4 (Have you had these thoughts and had some intention of acting on them) or item #5 (Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

b) A positive endorsement, relative to the past 90 days, in the "Suicide Behavior" section of item #6 (Have you ever done anything, started to do anything, or prepared to do anything to end your life?)

- Current or lifetime history of a psychiatric disorder with primary psychotic features.
- Current or lifetime bipolar disorder; prominent suicidal or homicidal ideation.
- Current exposure to trauma, or exposure to trauma in the past 3 months.
- 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).
- Excessive alcohol consumption (>14 drinks per week or > 4 drinks per occasion)
- Presence of any acute or unstable psychiatric condition(s) that requires referral for treatment.
- Montreal Cognitive Assessment (MOCA) < 20 or Montreal Cognitive Assessment Blind(MOCA-BLIND) < 15.

o 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).

StudyPages Prescreening: Consent to complete the pre-screening survey will be obtained electronically on the survey through the study landing page. Interested subject will reach the study landing page by clicking the link on the StudyPages online posting/advertisements. The study landing page will contain a description of the study purpose, procedures, requirements, and study staff contact information. Interested subjects will need to select the "See if you may qualify" button on the study landing page so that the initial prescreening survey prompt box appears which will instruct subjects that they should call the clinical coordinators using the study phone number if they have any questions and review the consent and HIPAA information for the prescreening survey questions, and then that by clicking "Next" on the pre-screening survey, they are i) consenting to participate in the pre-screening questionnaire, ii) agreeing with the information they read regarding the prescreen survey and how their information will be used/protected, iii) agreeing to proceed to the prescreening questions, and iv) that all of their information is confidential. Interested subjects will only be able to proceed if they click "Next" after reviewing the consent form information before the next page appears that allows them to respond to the prescreening questions (included in the StudyPages document in section 16). Upon completion an successful submission of their responses, subjects will be notified that the study team will reach out to them regarding their eligibility. The study team will then review the

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prescreening responses and call interested subjects and follow the screening procedures listed below.

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.

Subjects will be screened for eligibility via a phone interview and an in person or telehealth evaluation. The in-person or telehealth evaluation may be split into two visits if necessary. At the in-person or telehealth evaluation, after signing a consent form, a more detailed interview about sleep problems, and medical and psychiatric history will be obtained by the Duke Structured Sleep Interview, including evaluations of cognitive impairment and depression. Exclusion criteria will further be evaluated by the following given solely at the office evaluation: Berlin Questionnaire, Life Stressor Checklist, Columbia Suicide Severity Rating Scale (C-SSRS), Acute/Unstable Chronic Illness checklist, Mini International Neuropsychiatric Interview Version 5 (MINI), Morningness-Eveningness Questionnaire, Montreal Cognitive Assessment (MOCA) or MOCA-Blind, Thought Control Questionnaire Insomnia-Revised (TCQI), and the Mini-Mental State Exam (MMSE). If the session is conducted in-person, subjects will additionally be set up with PSG equipment. The PSG will be completed in the subject's own home and be used to screen for Obstructive Sleep Apnea and Periodic Limb Movement Disorder. Subjects will return to the lab the next morning to have the equipment removed.

At that time a brief physical exam will be conducted including cardiopulmonary and neurological status. Potential subjects will complete 1 week of daily sleep logs, which will serve as a further screening to insure that subjects' insomnia severity meets our entry criteria. Baseline sleep logs will also serve to screen for certain disorders such as a non-24-h sleep-wake syndrome or an irregular sleep-wake pattern (i.e., ≥ 3 sleep episodes during a 24-h period indicating an absence of a circadian rhythm). Potential participants will also undergo relevant psychological tests, and medical, psychiatric, and medication histories will be gathered and evaluated. 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.

Participants who complete a screening session via telehealth will not undergo a physical but will complete all other screening measures.
Participants from other sites can be referred to Palo Alto for screening. They will be given our phone number and told to contact us. We will follow the remote screening procedures outlines above for these participants.

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, and document this 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

Participants will receive $150 for the screening procedures including the PSG. If the participant is determined to be eligible for the study, s/he will receive stipends of $25 for each of the 6 treatment visits thereafter and $25 for the follow up visit 7 x $25 = $175. Participants who complete all treatment visits and the follow up, which includes a second PSG overnight, visit will receive a $150 completion bonus. Thus, participants who complete all the study visits will receive a total of $475.
If a participant completes the study through telehealth, they will receive $50 for the screening procedures. If the participant is determined to be eligible for the study, s/he will receive stipends of $25 for all 6

treatment visits thereafter and $25 for the follow up visit (7 x $25 = $175). Participants who complete all treatment visits and the follow up visit will receive a $50 completion bonus
These stipends are intended to encourage compliance with the research protocol without adding undue influence.

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 about 4 years.
(i) Screening for each participant will take approximately 5 hours
(ii) Each participant will actively participate in the study for approximately 32 weeks.
(iii) Analysis of participant data is taking longer than anticipated and will estimate an additional 12 to 24 months for data analysis to be completed at this time.

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.

Ambulatory Overnight Sleep Recording (Compumedics Safiro ambulatory PSG).
The electrodes used for the ambulatory overnight recording have a risk of causing a minor skin irritation (rash) underneath the electrode. If this were to happen, we will suggest that the subject put normal skin lotion on the affected area.
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.

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 Therapies. There are virtually no risks involved in the cognitive therapies (CBT and SR). Some participants may feel sleepy during the Sleep Restriction therapy. They will be instructed to nap if needed.

Cognitive and psychosocial 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.

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, Washington DC VA Medical Center and VA NJ Health Care System.

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. Both the BDI and the Columbia Suicide Severity Rating Scale will be administered to assess for SI. Any responses to questions that would indicate suicidal thoughts will be referred to the PI (a psychiatrist) for review and appropriate action as soon as possible. The PI will determine appropriate immediate action, and the participant will be referred to appropriate therapy.
Before each telehealth session, study staff will collect an emergency contact and the address that the participant is located. If the clinician deems the participant to be at acute risk of suicide during a risk assessment and the participant leaves the Zoom session or the clinician cannot contact the participant, they will reach out to the emergency contact. If the clinician cannot reach the emergency contact, they will call local emergency services to initiate a welfare check.
We will provide information for contacting the Veterans Crisis Line at the top of each survey page. We have an alert in RedCap to notify study staff immediately via email if a participant endorses suicidal ideation on a survey.

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.

Ambulatory Overnight Sleep Recording 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 PAVA 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.

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

Venipuncture. Experienced medical personnel will handle all the blood drawing procedures and sterile conditions will be maintained.

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.

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 we would want to make sure that nightmares 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

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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 with a member of the study team to sign the consent form, discuss the protocol, and determine suitability for enrollment. All interviews will be done in a private setting. Samples will be obtained in a private setting.
Telehealth sessions will also be private. Study staff will confirm with each participant that they are in a safe and private location before beginning each session.
Study staff will use the program AZURE to send secured emails from VA email addresses to the participant's email.

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.
*Emergency Contact: name and phone number

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 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. Custom software analyzes breathing data and derives AHI, as well as apnea and hypopnea indices.

StudyPages is a cloud-based HIPAA compliant SaaS platform. 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. Only the personnel authorized to have access to participant PHI on our study team will have password protected access to sign up information.

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. Collaborators at other sites will not have access to PHI from the Palo Alto site. Palo Alto will receive PHI (name, mailing address, phone number) from the Washington, DC WRIISC site via an encrypted AZURE email between VA email addresses. Participants will be referred to Palo Alto and give contact information for our site.

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.

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.

Data transfer will be between VA hospitals, using secure VA protocols behind the VA firewalls.

The DC WRIISC site will transfer PHI (first and last name, mailing address, phone number) to Palo Alto via a VA AZURE encrypted email between VA email addresses. This data will then be stored on physically secure and password protected computer servers behind a firewall at the VAPAHCS with all other PHI for this study. The Palo Alto site will not transfer any PHI to the other sites.

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 COI?	Date Outside Interest Answered	Date OPACS Disclosure Submitted	COI Review Determination
Jerome A Yesavage	PD	N	08/05/2024		N/A
Andrea Nicole	COP	N	08/05/2024		

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Goldstein	D				N/A
Laura Lazzeroni	OP	N	08/05/2024		N/A

13. Consent Background

13. 1 Consent 22-AUG-2022 Gulf War Insomnia Consent

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) The persons obtaining consent will be one of the investigators, the study coordinator, or a research assistant, who have been trained to give informed consents. (ii) The consenting interview is always done after the potential research subject has been presented with a description of the study and indicated interest in participating, and before any information is collected, or any questionnaires answered. The consenting interview typically takes place in one of the private interview rooms in the Aging Clinical Research Center. For telehealth sessions, the consent process will be completed through Zoom. Study staff will review the consent with the participant. If the participant agrees, they will sign the consent form through a fillable PDF form in Adobe. Study Staff will share the screen with participants and participants will take control of the screen to sign the form. Participants will be sent a copy of the signed consent form. If the participant is unable to attend the consenting interview on a computer, multiple copies of the consent form will be mailed to them in advance. The participant will have the physical consent form in front of them while the study staff reviews the consent form. The participant will be provided a pre-paid return envelope to mail one signed copy of the consent form back to the VA. (iii) Enough time will be allowed for the consent discussion for the potential participant to make an informed decision, and to ask any and all questions they may have and discuss the study with the researchers. We estimate this will take between 30 minutes and one hour. (iv) The potential participant may take the consent home to discuss with family or others, and return later to sign it if they so desire. (v) Every attempt will be made to ensure the participant does not feel coerced. Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others. We believe that the payment offered for participation is not great enough to entice a person to participate if they do not want to do so. (vi) Not applicable.

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.

The potential subject will be asked questions about the study to make sure they understand. All participants will have a good understanding of English, since the standardized forms, questionnaires, and tests used are not currently available in other languages. Hearing impairment severe enough to impair comprehension is an exclusion criteria for a similar reason.

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.

We expect all persons who meet inclusion criteria will have capacity to give informed consent.

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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.

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 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?

Consent will be obtained from the participant.

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?

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the signing of the consent is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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)?

All information presented to the participant, including anything they must sign, has been approved by the IRB.

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.**

13. 2 Waiver of Documentation GulfWar Insomnia Remote Phone Screen04-MAR-2021

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) The persons obtaining consent will be one of the investigators, the study coordinator, or a research assistant, who have been trained to give informed consents. (ii) The telephone interview is always done after the potential research subject has been presented with a description of the study and indicated interest in participating, and has given verbal consent. (iii) Enough time will be allowed for the consent discussion for the potential participant to make an informed decision, and to ask any and all questions they may have and discuss the study with the researcher. (iv) The potential participant may take the time to discuss with family or others, and call back later to complete the interview if they so desire. (v) Every attempt will be made to ensure the participant does not feel coerced. Participants are allowed as much time as needed to discuss the project with the research staff. (vi) Not applicable.

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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.

The potential subject will be asked questions about the study to make sure they understand. All participants will have a good understanding of English. Hearing impairment severe enough to impair comprehension is an exclusion.

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.

If there is any question about a potential participant's capacity to give consent, he or she will be evaluated by a staff psychiatrist or psychologist at an in-person or over a Zoom interview instead of a telephone screen.

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.

The persons obtaining consent and administering the telephone screen will be one of the investigators, the study coordinator, or a research assistant, all of whom will have been trained to give informed consents. All staff 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?

Consent for the phone screen will be obtained from the person answering the telephone interview questions.

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?

Participants are allowed as much time as needed to discuss the project with the research staff. If desired by the participant, the telephone screen is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others. The participant is urged to call back after discussing the study with family or friends.

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

The researcher will explain the interview to the potential participant, and answer any questions they may have. The potential participant is free to end the interview and disconnect at any time.

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)?

The attached phone script will be followed by the interviewer.

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.

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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:

See attached phone script.

13. 3 Waiver of Documentation StudyPages_Prescreen_Consent_JULY-2021

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) Consent to complete the pre-screening survey will be obtained electronically on the survey through the study landing page. The study landing page will contain a description of the study purpose, procedures, and requirements. Interested subjects will be instructed that by clicking “Next” on the pre-screening survey, they are consenting to participate in the pre-screening questionnaire and that all of their information is confidential. (ii) Contact with interested subjects is minimal until completion of the pre-screening questionnaire. Interested subjects will be led to the study landing page after selecting one of the social media study ads. Then after reviewing the study information, they may choose to select the button on the page which will bring up the pre-screening survey. Consent to complete the pre-screening survey will be obtained after the participant reads the instructions and consent/HIPAA information regarding the pre-screening survey questions provided for them, and after they select “Next” to advance to the pre-screening questions. (iii) The interested subjects will be able to review the information in the study landing page and pre-screening survey consent page for as long as needed and be instructed to contact the study coordinator with any questions they may have before filling out the pre-screening survey. (iv) The potential participant may take the time to discuss with family or others, and return to the survey whenever they feel ready to proceed. (v) Every attempt will be made to ensure the participant does not feel coerced. Participants are instructed to reach out if they have any questions before agreeing to answer any questions and are allowed as much time as needed to discuss the project with the research staff. (vi) Not applicable.

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.

The potential subject will be provided with the study coordinators contact information multiple times on the study landing page and the pre-screening survey. This will include instructions to reach out if they have any questions. This is done to ensure they understand that by filling out the survey they assert their interest in participating in the study and to be contacted by the study team to determine their eligibility to enroll in the study. All participants will have a good understanding of English. Hearing impairment conditions are not applicable at this stage.

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.

Interested subjects will require the use of an electronic device and social media in order to reach our study landing page and follow the prompts to complete the survey. Their ability to give consent will be further assessed over the phone interview and if there is any question about a potential participant's capacity to give consent, he or she will be evaluated by a staff psychiatrist or psychologist at over a Zoom interview instead

of a telephone screen.

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.

The language and procedures for obtaining electronic consent will be the same across all interested subjects that reach our study landing page. Additionally, the persons overseeing the use of the study landing page will be one of the investigators, the study coordinator, or a research assistant, all of whom will have been trained to give informed consents. All staff 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?

Consent for the pre-screening survey and to be contacted will be obtained from the possible participant (person completing the survey questions).

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?

Participants are allowed as much time as needed to discuss the project with the research staff if needed. If desired by the participant, the electronic pre-screen is delayed for as long as needed to allow participants to discuss the project with family, personal health care providers, or others.

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

The study landing page and pre-screening survey will have multiple prompts/instructions that explain the pre-screening procedures to the potential participant, and instructs them to call the study coordinators to answer any questions they may have. The potential participant is free to end the survey and disconnect at any time.

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)?

The attached pre-screening script will be presented on the study landing page.

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.**

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Rationale for above selection:

We are collecting a brief online prescreen questionnaire with minimal risk to participants. They will be provided with full study description and consent information with HIPAA related to use of their prescreen questionnaire responses.

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

15. HIPAA Background

15. 1 Authorization — **gulfwarinsomnia va hipaa auth**

15. 2 Waiver of Authorization for Recruitment — **waiver of authorization for 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.

Chart reviews will be conducted to assist in identifying prospective participants. Additionally, contact information (name, mailing address, phone number) from the Gulf War Registry, WRIISC, DMDC databases, and DC WRIISC site of this study, and the StudyPages outreach campaign will be utilized to identify and recruit participants. In addition, the Washington, DC WRIISC site will share contact information (name, mailing address, phone number) with the Palo Alto site for recruitment. We will send letters and call possible participants from these three databases as well as from the Washington, DC WRIISC and StudyPages list of interested participants. We are requesting a waiver of authorization for the chart review and also for the StudyPages Prescreening: Consent to complete the pre-screening survey will be obtained electronically on the survey through the study landing page. Interested subject will reach the study landing page by clicking the link on the StudyPages online posting/advertisements. The study landing page will contain a description of the study purpose, procedures, requirements, and study staff contact information. Interested subjects will need to select the “See if you may qualify” button on the study landing page so that the initial prescreening survey prompt box appears which will instruct subjects that they should call the clinical coordinators using the study phone number if they have any questions and review the consent and HIPAA information for the prescreening survey questions, and then that by clicking “Next” on the pre-screening survey, they are i) consenting to participate in the pre-screening questionnaire, ii) agreeing with the information they read regarding the prescreen survey and how their information will be used/protected, iii) agreeing to proceed to the prescreening questions, and iv) that all of their information is confidential. Interested subjects will only be able to proceed if they click “Next” after reviewing the consent form information before the next page appears that allows them to respond to the prescreening questions (included in the StudyPages document in section 16). Upon completion an successful submission of their responses, subjects will be notified that the study team will reach out to them regarding their eligibility. The study team will then review the prescreening responses and call interested subjects We are collecting the following identifiable data during recruitment and the pre-screen: full name, mailing address, social security number, telephone number, age, Health information about the participant pertaining to inclusion/exclusion criteria, including information about general health (sleep disturbance or insomnia, sleep disorders, general medical conditions, medications, therapy, height, weight, etc.) related to medical treatments and care they receive.

b) Please Answer:

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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.

All information from VA affiliated sites will be kept in locked cabinets in locked offices, or on computer servers behind the VAPA firewall. Information from the StudyPages outreach campaign will be encrypted with 256-bit AES encryption in the StudyPages Application Database. A copy of this data will be stored on computer servers behind the VAPA firewall.

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.

Information will be kept or destroyed following current VA requirements.

16. Attachments

Attachment Name	Attached Date	Attached By	Submitted Date
GulfWarInsomnia Egrant	07/22/2016	emilyg	
Berlin Questionnaire	09/28/2016	emilyg	
BRIEF PAIN INVENTORY	09/28/2016	emilyg	
Columbia_Suicide_Severity_Rating_Scale	09/28/2016	emilyg	
Dysfunctional Beliefs about Sleep	09/28/2016	emilyg	
Epworth Sleepiness Scale	09/28/2016	emilyg	
HAMD	09/28/2016	emilyg	
Life_stressor_Checklist_Revised	09/28/2016	emilyg	
Penn_State_Worry_Questionnaire	09/28/2016	emilyg	
Sleep Diary	09/28/2016	emilyg	
Protocol 38548 VARQs_APP1m-1	09/28/2016	emilyg	
Anxiety_and_Preoccupation_about_Sleep_Questionnaire	03/29/2017	emilyg	
AUA8_Nocturia	03/29/2017	emilyg	

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BAI	03/29/2017	emilyg	
BDI	03/29/2017	emilyg	
Color_Word_Interference_D-KEFS	03/29/2017	emilyg	
DASS-21	03/29/2017	emilyg	
Functional_Outcomes_of_Sleep_Questionnaire	03/29/2017	emilyg	
Glascow_Content_of_Thoughts	03/29/2017	emilyg	
Glasgow_Sleep_Effort_Scale	03/29/2017	emilyg	
MOCA	03/29/2017	emilyg	
Multidimensional_Fatigue_Inventory	03/29/2017	emilyg	
Perceived_Stress_Scale	03/29/2017	emilyg	
RBANS	03/29/2017	emilyg	
SF-36_RAND	03/29/2017	emilyg	
Trail_Making_Test	03/29/2017	emilyg	
Treatment Adherance Questionnaire_BT_5.5.14	03/29/2017	emilyg	
Treatment Adherance Questionnaire_CT_5.5.14	03/29/2017	emilyg	
Treatment Satisfaction Survey	03/29/2017	emilyg	
WAI participant	03/29/2017	emilyg	
WAI Therapist	03/29/2017	emilyg	
Gulf War Insomnia Certificate of Confidentiality	03/31/2017	emilyg	
CAPS past month	05/29/2017	agoldpie	
CAPS worst month	05/29/2017	agoldpie	
Credibility/Expectancy Survey	05/29/2017	agoldpie	
DUKE	05/29/2017	agoldpie	
Insomnia Severity Index	05/29/2017	agoldpie	
MEQ	05/29/2017	agoldpie	
SAMI	05/29/2017	agoldpie	
TCQI	05/29/2017	agoldpie	
Goldstein CITI	06/02/2017	agoldpie	

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Approved AmendedCoC	08/29/2017	emilyg	
Brochure_091317	09/13/2017	agoldpie	
Flyer_091317	09/13/2017	agoldpie	
Flyer_withNibs_091317	09/13/2017	agoldpie	
Buisness_Cards_091317	09/13/2017	agoldpie	
Newspaper_ad_091317	09/13/2017	agoldpie	
Recruitment Letter Prior Study 041818	04/18/2018	agoldpie	
Recruitment Letter New Contact 041818	04/18/2018	agoldpie	
DC Site IRB Approval 2018	09/05/2018	agoldpie	
NJ Site IRB Approval 2018	09/05/2018	agoldpie	
Additional Demographics questions	02/01/2019	agoldpie	
NJ site approval 2019	08/28/2019	kohora	
DC site approval 2019	08/30/2019	kohora	
2019FlyerQR	09/05/2019	kohora	
2019FlyernoQR	09/05/2019	kohora	
DSMB2020	08/25/2020	kohora	
GW_national_recruitment_postcard	08/25/2020	kohora	
GW_national_recruitment_poster_v5_no_email	08/25/2020	kohora	
RecruitmentLetterNewContact082420	08/27/2020	kohora	
SocialMedia_ad_082420	08/27/2020	kohora	
GW_national_recruitment_poster_v7_no_email	10/06/2020	amorehse	
NJ site IRB Approval 07-JAN-2020	10/27/2020	amorehse	
DC site IRB Approval 15-APR-2020	10/27/2020	amorehse	
Fillable 102720 Gulf War Insomnia Consent	10/27/2020	amorehse	
TheCoRonavIruSHealthImpactSurvStable	11/05/2020	amorehse	
TheCoRonavIruSHealthImpac	11/05/2020	amorehse	

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tSurvChange			
DSMB_2021	02/09/2021	amorehse	
MoCA-BLIND	02/09/2021	amorehse	
Fillable 09-FEB-2021 Gulf War Insomnia Consent	02/12/2021	amorehse	
GW Letter Remote 24-FEB-2021	03/03/2021	amorehse	
GW_national_recruitment_poster_for_DC	03/15/2021	amorehse	
WRIISC_GW Letter Remote 11-MAR-2021	03/15/2021	amorehse	
Fillable 04-MAR2021 Gulf War Insomnia Consent clean	03/15/2021	amorehse	
Waiver_of_Auth_of_recruit_GW_05-MAR-2021	03/15/2021	amorehse	
GW_national_recruitment_poster02APR21	04/02/2021	amorehse	
Fillable 02-APR-2021 Gulf War Insomnia Consent	04/02/2021	amorehse	
DC_DUA_Internal_7April2021 signed	06/10/2021	amorehse	
GW_ScreeningPacketCoverLetter_14-JUN-2021	06/15/2021	amorehse	
05052021_Gulf War study_CampaignCreative	07/28/2021	mlopez3	
05052021_Gulf War study_Prescreen_Survey	07/28/2021	mlopez3	
2021-01-07_NJ_Approval	08/20/2021	amorehse	
02-JUN-2021_DC_Approval	08/23/2021	amorehse	
Waiver_of_Auth_of_recruit_GW_12-AUG-2021	08/26/2021	sutm	
GW_DSMB_29-JUN-2022	07/22/2022	amorehse	
31-JAN-2022_DC_Approval	08/19/2022	acirelli	
NJ_IRB_annual protocol check in_2022_acknowledgement	08/22/2022	acirelli	
DSMB closing report 2023	07/10/2023	agoldpie	
DC_IRB_Project Closure Form CBTI study 10Jan2023	07/20/2023	acirelli	

DC_Reinhard Transition Letter (signed)	07/20/2023	acirelli	
NJ_annual protocol check in_2022_acknowledgement	07/20/2023	acirelli	
GW_Consent_Audit_report_email_25-JUL-2023	07/28/2023	acirelli	
GW_Consent_Audit_July_2023_1	07/28/2023	acirelli	
Reinhard 01858 IRB Closure-Signed	08/22/2024	eileenf1	
VANJHCS IRB Closure Letter 2024 0410 (1)	08/22/2024	eileenf1	

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
- 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.

Title : Predictors of Response to Insomnia Treatments for Gulf War Veterans
Approval Period: 08/31/2024 - 08/31/2025

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.