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| **IRBNet ID:** | **1638783** |
| **Title:** | **SEdative-Hypnotic Deprescribing Assisted by a Technology-Driven Insomnia InterVEntion (SEDATIVE)** |
| **eRA Commons ID:** | **RX003732-01A1** |
| **Funding Agency:** | **VA Rehabilitation Research & Development Service** |
| **Principal Investigator:** | **Adam Bramoweth, PhD** |
| **Version Date:** | **v.7 01/24/2023** |

## Summary

Chronic insomnia is one of the most common health problems among Veterans and significantly impacts their health, function, and quality of life. Sedative-hypnotic medications are the most common treatment despite mixed effectiveness and are associated with numerous risks that can further impact Veteran function. The Clinician Operated Assistive Sleep Technology (COAST) is an efficient, scalable, and adaptable digital platform that can help providers to reach more Veterans and provide evidence-based care for insomnia that translates to improved health and function. COAST delivery of cognitive behavioral therapy for insomnia (CBT-I) will be combined with Clinical Pharmacist-led sedative-hypnotic deprescribing to integrate two previously siloed interventions to deliver efficient evidence-based care.

This is a non-randomized, single group clinical trial:

**Aim 1:** To assess the feasibility of recruiting Veterans with chronic sedative-hypnotic use to participate in a 12-week combined deprescribing and CBT-I intervention, delivered through the COAST digital platform.

**Aim 2:** To assess Veteran acceptability and usability of the COAST platform.

**Aim 3:** To assess change in Veteran sleep, sedative-hypnotic use, and function pre- to post-intervention.

**List of Abbreviations**

| | |
|---|---|
| BBTI | brief behavioral treatment for insomnia |
| BSC | Behavioral Sleep Clinic |
| CBT-I | cognitive behavioral therapy for insomnia |
| CDA | Career Development Award |
| CDW | Corporate Data Warehouse |
| CIWA | Clinical Institute Withdrawal Assessment Scale - Benzodiazepines |
| COAST | Clinician Operated Assistive Sleep Technology |
| Co-I | co-investigator |
| COVID-19 | coronavirus disease 2019 |
| CPP | Clinical Pharmacy Practitioner |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| GDR | gradual dose reduction |
| HIPAA | Health Insurance Portability and Accountability Act |
| HSR&D | Health Services Research and Development |
| ID | identification |
| IIR | investigator initiated research |
| ISI | Insomnia Severity Index |
| ISSO | information system security officer |
| M | mean |
| N/A | not applicable |
| NWAK | number of awakenings |
| PCMHI | Primary Care Mental Health Integration |
| PI | principal investigator |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PSSUQ | Post-Study System Usability Questionnaire |
| RR&D | Rehabilitation Research and Development |
| SD | standard deviation |
| SE | sleep efficiency |
| SOL | sleep onset latency |
| SPiRE | Small Projects in Rehabilitation Research |
| SQ | sleep quality |
| TIB | time in bed |
| TST | total sleep time |
| US | United States |
| VA | Department of Veterans Affairs |
| VAPHS | VA Pittsburgh Healthcare System |
| WASO | wake after sleep onset |

# Contents

# 1.0 Study Personnel

- **VA Pittsburgh Healthcare System (VAPHS)**

**Adam Bramoweth, PhD – Principal Investigator/Clinician**
Dr. Bramoweth is a Research Health Scientist/Core Investigator with the VAPHS CHERP/MIRECC and a Staff Psychologist in the Behavioral Health Service Line at VAPHS. He leads a program of research at VAPHS focused on improving access to insomnia-related care. As PI, Dr. Bramoweth will be responsible for directing and overseeing all study activities and will also serve as the insomnia clinician, responsible for the delivery of behavioral insomnia care facilitated by the COAST digital health platform.

**Amanda McQuillan, PharmD – Co-Investigator/Clinical Pharmacist**
**Brittany Spitznogle, PharmD – Co-Investigator/Clinical Pharmacist**
Drs. McQuillan and Spitznogle are Clinical Pharmacy Practitioners (CPPs) and Mental Health Clinical Pharmacy Specialists at VAPHS. Drs. McQuillan and Spitznogle will serve as the study's CPPs and will be responsible for the development, delivery, and monitoring of the participants' sedative-hypnotic taper. They will help coordinate any necessary prescription renewals and dosage changes with participants' prescribing providers.

**Carolyn Thorpe, PhD, MPH – Co-Investigator**
Dr. Thorpe is Associate Professor of Pharmacy at the University of North Carolina at Chapel Hill and a Core Investigator at the VAPHS CHERP. Dr. Thorpe will provide her expert knowledge regarding deprescribing, in collaboration with Dr. McQuillan, to design appropriate and personalized medication taper schedules for participants. Dr. Thorpe will make her contributions remotely from North Carolina.

**Megan Hamm, PhD – Co-Investigator/Qualitative Analyst**
Dr. Hamm is a WOC member of the MIRECC and will lead the qualitative analyses. Dr. Hamm's position will be supported by an IPA through the University of Pittsburgh. Dr. Hamm will help to develop the interview guide, will train the study coordinator to conduct the interviews, and will lead the rapid analysis template, summary, coding, and analysis.

- **VA Madison Healthcare System/William S. Middleton Memorial Veterans' Hospital**

**James Lickel, PhD – Co-Investigator/Clinician**
Dr. Lickel is a Staff Psychologist at the William S. Middleton Memorial Veterans Hospital (Madison VA). He serves as the Coordinator of the Behavioral Sleep Clinic (BSC). Within the BSC he coordinates referrals, develops and maintains clinic offerings, supervises psychology and other discipline trainees, and provides direct psychological services to Veterans, including CBT-I and assisting with sedative-hypnotic tapers. As a Co-I/Clinician, he will provide clinical expertise on insomnia, CBT-I, and deprescribing to Drs. Bramoweth and McQuillan, join study team meetings, and contribute to study analyses and dissemination efforts. He will also assist Dr. Bramoweth as a study clinician, delivering CBT-I through the COAST platform.

- **Consultant**

  **Anne Germain, PhD – NOCTEM COAST Consultant**
  Dr. Germain is the Founder and CEO of NOCTEM Health, Inc, a digital sleep therapeutics start-up company, and Professor Emeritus of Psychiatry at the University of Pittsburgh School of Medicine. Dr. Germain is an internationally recognized sleep researcher with a program of research emphasizing the assessment and treatment of sleep disorders within military and Veteran populations. As a study consultant and insomnia Subject Matter Expert, Dr. Germain and her team will lead training for the NOCTEM COAST digital platform and provide ongoing and as needed consultation with study staff regarding any technical issues related to COAST.

- **Non-Financial Conflicts of Interest**

  N/A

## 2.0 Introduction

- **Scientific Background/Rationale**

  **Chronic insomnia has significant impact on Veterans' health, function, and quality of life as one of the most common health problems among Veterans.**[1–3] Insomnia impacts over 50% of Veterans[2,4] and significantly contributes to functional impairment, fatigue, and reduced alertness, memory, attention, and concentration.[5–7] Insomnia reduces quality of life and social functioning, and there is a relationship between insomnia and increased days of work missed and impaired work performance.[8,9] Insomnia also negatively affects comorbid health problems and increases risk of depression, anxiety, substance use, chronic pain, cardiometabolic disorders, and even suicide behaviors, all of which further impair function and quality of life.[10–12] Additionally, the COVID-19 pandemic continues to cause significant stress and worry about health, including increased rates of insomnia as high as 38% and increased prescriptions for sedative-hypnotic medications.[13–15]

  **Sedative-hypnotic use is highly prevalent and is not aligned with best practices for the treatment of insomnia. Furthermore, sedative-hypnotics are associated with increased risks, functional impairment, and negative quality of life and health outcomes.**[16–18] Sedative-hypnotics are commonly prescribed to treat insomnia, ranging from 5-14% in large cohort studies, and even higher rates from survey studies (upwards of 25%).[19,20] Although considered effective for the short-term treatment of insomnia, a few weeks to months, these medications are often taken well beyond one year.[21,22] Use of sedative-hypnotics, especially benzodiazepines, can result in tolerance, dependence, and/or abuse.[16] Furthermore, they only treat insomnia symptoms rather than underlying causal factors and discontinuation often results in rebound insomnia.[16] Sedative-hypnotics are also associated with risk for daytime fatigue, impaired cognitive and psychomotor functioning, falls and fractures,[17] as well as rare, yet serious, events such as sleep-driving.[18] Epidemiological research also links increased doses of sleep medication, taken for at least one year, to an elevated incidence of cancer and an increased risk of death

(controlling for prior cancer diagnosis).[23] Importantly, many Veterans don't want to take sedative-hypnotics if an alternative is available.[24] Although the most common treatment by a wide margin,[20,25] sedative-hypnotics are not the recommended treatment for chronic insomnia.[3,26,27]

**The state-of-the-science specifies that behavioral interventions, like cognitive behavioral therapy for insomnia (CBT-I), are the first line treatment.**[3,26,27] Studies within and outside the VA demonstrate that CBT-I significantly improves insomnia symptoms, nighttime sleep quality, and daytime function.[28–30] CBT-I is a multi-component evidence-based psychotherapy that includes: stimulus control,[31] sleep restriction,[32] cognitive therapy,[33] sleep hygiene,[34] and relaxation.[35] CBT-I is typically 5-8 sessions (face to face [in-person or telehealth]) conducted by psychologists or other mental health providers.[36] Randomized controlled trials and meta-analyses have established that CBT-I is effective in people with primary insomnia[37] and those with comorbid insomnia,[38] including psychiatric disorders (e.g., depression, anxiety)[38–40] and medical disorders (e.g., chronic pain).[41] A VA study, with nearly 700 Veterans, found that 60% who completed CBT-I achieved a treatment response (i.e., reduction ≥8 points per the Insomnia Severity Index [ISI]). These Veterans had a mean ISI change of 20.7 to 10.9, a large effect size (pre- to post-treatment Cohen's d=2.3).[29] In terms of long-term treatment gains, a recent review found 50% of patients responded to CBT-I and maintained treatment effects for 4-10 years.[42] CBT-I is also more effective than sedative-hypnotics at reducing sleep onset latency (SOL), and is equally effective at improving Wake After Sleep Onset (WASO) and sleep quality (SQ).[43] It is important to note, combining CBT-I and sedative-hypnotics may not improve outcomes.[44]

**Deprescribing sedative-hypnotics is recommended, but deprescribing alone may not be enough.** Deprescribing is the reduction or withdrawal of a medication managed by a healthcare professional that aims to reduce harm and improve outcomes.[45] Sedative-hypnotics are not the recommended treatment for insomnia[3] and often result in more harm than benefit, especially for high risk groups such as older adults.[46] Interventions to reduce sedative-hypnotic use range from patient-centered approaches (e.g., written instructions, relaxation strategies, therapy) to provider education and training.[47,48] A typical intervention will involve gradual dose reduction (GDR), or tapering, and is sometimes accompanied by a psychological treatment, like CBT-I.[48] Tapering approaches, including the use of telehealth,[49,50] often involve dose reductions of 25-50% every 1-3 weeks until cessation is achieved.[47] Cessation, however, has varying rates of success (27-80%). Adding psychological treatments (e.g., CBT-I) help reduce rebound insomnia and improve cessation rates compared to routine care (odds ratios: 3.38-5.96); however, the results of combining these methods has been mixed.[50,51] Two key challenges to deprescribing are rebound insomnia symptoms and the lack of personalized care (e.g., brochures).[52] Considering these barriers and the prior research on CBT-I and sedative-hypnotic tapering,[49] a personalized approach that can effectively combine CBT-I and deprescribing has promise to improve insomnia and sedative-hypnotic outcomes among Veterans.

**Access to deprescribing and behavioral interventions are necessary to provide maximum impact for Veterans.** Access to care remains a barrier – especially for a

combined insomnia treatment approach. Sedative-hypnotic use is highly prevalent, with many chronic users.[20–22,53] Although medication prescribers and clinical pharmacists can provide patient education and lead tapering efforts, they do not have training in behavioral insomnia interventions. CBT-I, despite the strong evidence to improve sleep quality and daytime function and with minimal adverse effects and long-term treatment gains,[3] continues to have limited availability. Even with significant training efforts by the VA, there is still a shortage of trained CBT-I clinicians, especially outside of urban VA Medical Centers. Additional barriers involve the location of CBT-I delivery, often in mental health clinics, which remains stigmatizing for many Veterans. CBT-I delivery can also be inflexible to meet the needs of many Veterans, requiring regularly scheduled visits (in-person or telehealth), which are not always possible for Veterans who work, have care taking responsibilities, or have transportation challenges. Considering the limitations to care due to the COVID-19 pandemic, access has changed. For some Veterans, greater access to care through telehealth has been beneficial. Flexible treatment solutions are required to provide optimal benefits for Veterans. Additionally, a novel, effective, and efficient telehealth option for deprescribing and improving sleep health and function can shift care towards telehealth for eligible Veterans and allow for increased in-person care for Veterans unable, unwilling, or not appropriate for telehealth.

**Digital sleep therapeutics offer personalized, efficient, effective, and scalable treatment for insomnia.** However, there are no remote/digital interventions that combine personalized sedative-hypnotic tapering with CBT-I. Digital CBT-I platforms are available, including several developed by the VA, that have similar sleep outcomes as in-person CBT-I.[54] However, these platforms are solely self-management programs that focus only on improving insomnia symptoms. The Clinician Operated Assistive Sleep Technology (COAST) platform offers a personalized solution and can fill the gap for Veterans who can benefit from a combined approach to deprescribing and CBT-I. The COAST platform is a highly efficient and scalable digital health technology that is personalized and responsive to individual sleep behaviors.[55,56] Data from the initial development trials and recent quality improvement data from military treatment facilities show COAST significantly decreases insomnia symptoms per sleep diaries and self-report measures to a greater extent than a recent in-person CBT-I trial with active duty military.[57] COAST is built upon a patient facing mobile application and a provider dashboard. It offers safe, no-contact intervention in addition to prospective monitoring of patient-reported behaviors by a provider and assisted by the platform's technology, and offers just-in-time, HIPAA-secure communication with the treatment team. COAST's algorithms facilitate the detection of disordered sleep patterns, based on patient input, resulting in timely clinical decision making and personalized sleep interventions based on the core components of CBT-I. COAST's efficiency helps to reduce clinician time involved in treatment to <60 minutes total per patient versus 30-60 minutes per session for in-person and telehealth modalities. COAST also promotes participant engagement[58] and reduces burdensome aspects of face to face CBT-I by bringing tools and clinical expertise directly to the Veteran through their mobile device.

COAST has been iteratively refined through testing with military personnel, Veterans, healthcare providers, and key stakeholders in the Department of Defense Military Health System and academic medical settings.[56] While COAST's focus is on behavioral sleep, the

platform is flexible and can integrate interventions such as sedative-hypnotic deprescribing. The existing secure communication feature also allows for rapid feedback for potential adverse effects of the deprescribing process. If scaled appropriately, digital interventions like COAST may help reduce chronic sedative-hypnotic use, improve sleep quality, and enhance functional outcomes. Furthermore, digital platforms like COAST are highly important considering the impact of COVID-19 on health and function and the need to maintain social distancing while still accessing high quality care.

## 3.0 Objectives

- **Study Objectives**

Aim 1: To assess the feasibility of recruiting Veterans with chronic sedative-hypnotic use to participate in a 12-week combined deprescribing and CBT-I intervention, delivered through the COAST digital platform.

Aim 2: To assess Veteran acceptability and usability of the COAST platform.

Aim 3: To assess change in Veteran sleep, sedative-hypnotic use, and function pre- to post-intervention.

- **Hypotheses**

H1: It will be feasible to recruit Veterans with chronic sedative-hypnotic use to participate in the intervention.

H2: Veterans will find the COAST platform acceptable and usable.

H3: Veterans will significantly improve their sleep behaviors and function and decrease their sedative-hypnotic use.

- **Relevance to Veterans**

Chronic insomnia and sedative-hypnotic use are prevalent among Veterans. This study will test a digital health platform, COAST, to deliver a combined intervention to (1) reduce use of sedative-hypnotics and (2) improve sleep behaviors using evidence-based behavioral interventions (CBT-I). If successful, this may offer an efficient and effective treatment for Veterans as an alternative to the current standards of care in VA.

## 4.0 Resources

- **VAPHS Resources**

The primary resource utilized will be VAPHS computing resources and office space. This is a telehealth study so research procedures, especially those involving participants, will be primarily remote (e.g., Veteran not physically located at VAPHS). The COAST clinician

portal is accessible via web browser, and this will be the primary method for participant engagement from study staff. This may take place at VAPHS (e.g., ROB, clinician office) or using VAPHS resources via telework (e.g., CAG/VPN, VA issued laptop, etc.). Other resources will include various OI&T resources and computing software to manage the study and conduct analyses.

Participant data will remain confidential. Only approved study staff will have access to the study shared drive, located behind the VA firewall. Participant PHI (e.g., email, mobile device IP address) data will be collected via the COAST platform as will patient-reported outcomes (see 5.1); as needed, data may be collected directly via participant and the participant's electronic health records and documented in the study database. Participants will enter data on their personal devices through the COAST mobile app. The study data analyst/statistician will ensure that all PHI is removed from the data prior to analyses.

- **Service Line Impact**

  Co-Investigators, Drs. McQuillan and Spitznogle, are Staff Pharmacists, members of the Clinical Support Service Line; they have protected time to serve as Co-Is on this project. We also request support from service line leadership for recruitment in the form of a letter to Veterans who may be eligible based on inclusion/exclusion criteria. There is minimal service line impact, for assistance with recruitment, from Behavioral Health, Medicine (Sleep Medicine), and Primary Care.

- **Participant Payments**

  Year 1 $4,125
  Year 2 $3,750

  Funds are requested as detailed below with payment occurring after completing each task. Payment will be made by electronic funds transfer or debit card. Payment is for time and effort engaging in the study procedures.

**Year 1**

| Task | # Participants | Amount | Total |
|---|---|---|---|
| Baseline Assessment | 25 | $50 | $1,250 |
| Qualitative Interviews | 15 | $25 | $ 375 |
| Post-Treatment Assessment | 25 | $50 | $1,250 |
| 3-month Follow-Up Assessment | 25 | $50 | $1,250 |
| **Year 1 Total** | | | **$4,125** |

**Year 2**

| Task | # Participants | Amount | Total |
|---|---|---|---|
| Baseline Assessment | 25 | $50 | $1,250 |
| Post-Treatment Assessment | 25 | $50 | $1,250 |
| 3-month Follow-Up Assessment | 25 | $50 | $1,250 |
| **Year 2 Total** | | | **$3,750** |

- **Off-Site Ancillary Activities**

  A Statement of Work with NOCTEM Health, Inc has been established through the duration of the study. NOCTEM is a digital health technology company that developed the Clinician Operated Assistive Sleep Technology (COAST™) platform, built on evidence-based behavioral sleep practices, that provides efficient, flexible, and scalable delivery of behavioral sleep interventions. NOCTEM will provide a customized digital platform, COAST, to manage the collection of participant self-report data, which will be stored on HIPAA compliant, private, and secure servers; COAST is hosted on AWS GovCloud. NOCTEM will also provide all necessary technological support to the study team for COAST.

# 5.0 Study Procedures

## 5.1 Study Design

### Assessments

All patient-reported assessments will be conducted through the COAST platform. Additional data will be collected from participants' VA medical records (e.g., diagnoses, medications, service connection, service utilization). Assessments will occur at baseline ($T_0$/~$T_{0+1week}$), post-treatment ($T_1$), and 3-months post-treatment ($T_2$) unless otherwise specified.

Study *feasibility* will be assessed by recruitment and intervention participation. Response to recruitment letters (# responses / # letters mailed) will be assessed overall and for each stratified group (age, sex, race). Participation will be assessed by number of enrolled participants that activate the COAST app, complete baseline assessments, engage in treatment beyond the initial recommendation, and complete the intervention.

COAST *usability* and *acceptability* will be measured with the Post-Study System Usability Questionnaire (PSSUQ).[59] The PSSUQ measures perceived satisfaction with a "system" like a website or mobile app. The PSSUQ is 16-items, scored 1-7 (1-strongly agree, 7-strongly disagree) or not applicable (N/A). The usability score is the average (total score divided by number of questions answered [N/A not included]). The three sub-scales are: usefulness (items 1-6), information quality (items 7-12), and interface quality (items 13-16). Lower scores, <3, indicate higher satisfaction and above average usability. The PSSUQ will be assessed at two time points. First, after the initial sleep/wake schedule recommendation is delivered (~$T_{0+1\ week}$) as this will give participants a chance to learn the COAST platform and second, at $T_1$, to measure change over time.

To further assess usability/acceptability, 15 Veterans will be interviewed (e.g., phone, Teams, VVC) to gain context on their COAST user experience and potential changes or new features that could improve COAST. Veterans will be interviewed based on their PSSUQ scores to get a range of perspectives, if available, per score distribution (e.g., 5 low, 5 medium, 5 high).

The Insomnia Severity Index (ISI) will serve as the primary sleep outcome. The ISI is a brief measure of nighttime sleep disruption (e.g., severity of sleep onset) and daytime impact (e.g., interference with function).[60] The ISI is 7-items (0-4) with higher scores indicating greater severity or impairment. Total score (0-28) is categorized: no insomnia (0–7); sub-threshold (8–14); moderate (15–21); and severe insomnia (22–28). A reduction pre- to post-treatment ≥8 points indicate a treatment response and a post-treatment score ≤7 indicate remission. The ISI will be assessed at $T_0$, $T_1$, $T_2$ as well as weekly during treatment.

*Sedative-hypnotic medication* will be measured by participant self-report, as part of a daily entry in COAST (e.g., "What sleep medication and dose did you take today?"). The daily COAST entry will also involve assessments for adverse effects and/or withdrawal symptoms (i.e., Clinical Institute Withdrawal Assessment – Benzodiazepines [CIWA-B]). Outcomes will include post-treatment ($T_1$) medication dosage, relative to starting dose at baseline ($T_0$), and binary outcomes of ≥50% reduction (yes/no) and total cessation (yes/no). Also, medication information from participants' VA health records will be used to help validate their self-report of sedative-hypnotic use throughout the study. Additional information will be collected from the VA electronic health records (e.g., medical and psychiatric diagnoses, service utilization [e.g., insomnia-related care, behavioral health/sleep medicine appointments, sleep medicine pharmacy data]).

Additional *sleep* outcomes will be measured with a daily sleep diary.[61] Sleep diaries provide information about a participant's sleep behaviors, such as bedtime, rise time, total time in bed (TIB), total sleep time (TST), sleep onset latency (SOL), number of nighttime awakenings (NWAK), duration of wake after sleep onset (WASO), and sleep efficiency (SE). Sleep diaries will be completed daily from baseline ($T_0$) through post-treatment ($T_1$) and for 7-days at 3-month follow-up ($T_2$). Daily sleep diary data is used by COAST's algorithms to generate personalized recommendations for each participant.

Secondary clinical and functional measures will come from the Patient-Reported Outcomes Measurement Information System Adult Profile (PROMIS 29+2). It includes measures of Physical Function, Social Roles, Anxiety, Depression, Fatigue, Sleep Disturbance, Pain Interference, Pain Intensity, and Cognitive Function. Each construct is scored individually (4 items, range 4-20) except Cognitive Function (2 items, range 2-10), with higher scores indicating more of the construct being measured. Raw scores are translated to a T-score with a mean of 50 and SD of 10. When all constructs are scored together, a preference score is calculated, representing health-related quality of life ranging from 0 (as bad as dead) to 1 (perfect or ideal health).[62]

## Screening

- Via phone or video telehealth (e.g., MS Teams, VVC) to confirm inclusion/exclusion criteria

*Inclusion Criteria*

- VAPHS Veterans ≥18 years
- Medical record documentation and self-report of active sedative-hypnotic use ≥3 days/week for ≥3 months: z-drugs (zolpidem: ≤10mg IR, ≤12.5 SR; zaleplon: ≤20mg; eszopiclone: ≤3mg); trazodone (≤400mg); temazepam (≤30mg); hydroxyzine (≤100mg); Veterans on higher doses may be eligible on a case-by-case basis
- A desire to reduce or stop using sedative-hypnotics
- Access to a mobile device

*Exclusion Criteria*

- A self-report of a medical and/or psychiatric disorder that would significantly impair participation (e.g., cancer, uncontrolled pain, severe depression)
- A self-report of a medical and/or psychiatric disorder that can be exacerbated by changes in sleep (e.g., seizure disorder, psychotic disorders, bipolar I disorder)
- A self-report of an active substance use disorder
- High risk of suicide per the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Currently engaged in an evidence-based, time limited, psychotherapy (e.g., prolonged exposure, cognitive processing therapy, cognitive behavioral therapy for depression, cognitive behavioral therapy for insomnia, etc.)

## Interventions

*Pharmacist-led Deprescribing*

This up-to 12-week intervention, sedative-hypnotic deprescribing integrated with CBT-I, will be delivered through the COAST platform.[55] For the deprescribing intervention/taper, the study's Clinical Pharmacist will develop a personalized taper for each participant based on their medication, dosage, and factors such as anxiety about the taper, duration of use, and insomnia severity (see Appendix—Deprescribing Summary for more information). The study's CPPs will, as needed for the personalized taper, place appropriate orders for different doses and/or new medications in CPRS for the Veteran participant's VAPHS prescribing provider to review/approve.

As needed, the taper can be extended to 12-weeks, and if necessary, participants can be referred to their VAPHS prescribing provider for further deprescribing assistance after the intervention and post-treatment assessment is complete ($T_1$). At any point during the intervention the taper can be paused if the participant is struggling to adjust or experiences withdrawal symptoms. All withdrawal symptoms will be reported through the COAST

platform and will be responded to within one business day by a study team member; outside of business hours (M-F, 0800-1630 EST), if necessary, participants can contact emergency services. The study's CPPs will communicate the deprescribing plan to each participant through COAST's secure messaging and the initial deprescribing plan will also be discussed verbally (e.g., phone, Teams, VVC).

*COAST Delivered CBT-I*

As deprescribing begins, so too will CBT-I through the COAST platform. The COAST algorithms, based on participant data (e.g., sleep diary, self-report measures), will generate treatment recommendations after approximately one week of participant data entry.[56] COAST's treatment recommendations are based on the core components of CBT-I—stimulus control, sleep restriction, cognitive therapy, and relaxation—with additional strategies targeting nightmares and daytime fatigue as needed. Weekly assessments and daily sleep diaries help the COAST algorithms make recommendations. A unique feature of COAST is that the study clinician must review and approve, or change, all recommendations before they are sent to the participant. This tailored approach allows for modification of COAST's recommendations based on clinician expertise and knowledge of the participant (e.g., a recent stressor that indicates slowing or pausing treatment). To further enhance the treatment process, the clinician is available by secure message (i.e., in-platform texting) to provide rapid support and/or schedule an appointment as needed (e.g., phone, Teams, VVC). These features offer personalization for each participant, consistent with case-conceptualization based on Veteran's sleep needs.

The study clinician/Sleep Psychologist may be located at either VAPHS or the William S. Middleton Memorial Veterans Hospital (Madison VA). The goal of this research study is all interactions with study clinicians will be done remotely, primarily using the COAST platform, but as needed by video telehealth or telephone. However, if Veteran participants need to see a study clinician in-person, that visit will occur at VAPHS. For an in-person visit with a Sleep Psychologist, Veteran participants will see the Sleep Psychologist at VAPHS.

The COAST recommendations are based on CBT-I and the rationale that modifying behaviors and cognitions impact the homeostatic and circadian drives. Modifying sleep and daytime behaviors helps regulate wakefulness, which can increase the homeostatic sleep drive, and restructures and optimizes sleep and wake times to reinforce the circadian drive. Modifying cognitions can help reduce worry that can result in the failure to inhibit wakefulness and contribute to physiological arousal.

Stimulus control limits the bed to sleep and sexual activity only, which strengthens the association between bed and sleep. Staying in bed while awake and engaging in non-sleep activities perpetuates the cycle of wakefulness, frustration, and arousal. When unable to sleep, it is recommended to get out of bed and go to another room until sleepiness returns.

Sleep restriction matches sleep opportunity, or prescribed time in bed (TIB), to average total sleep time (TST) so that the homeostatic and circadian drives can become better aligned. A consistent wake time is a) the most important cue for setting the biological clock, b) regulates exposure to morning light, and c) helps increase the homeostatic sleep drive

for subsequent nights. Going to bed only when sleepy, but not before a prescribed bedtime, increases the sleep drive and the likelihood of falling asleep quickly.

Cognitive therapy helps to reduce nighttime stress and worry through the identification and challenging of dysfunctional beliefs. Learning strategies to overcome negative thoughts and promote positive attitudes can reduce racing thoughts at night and the wake/frustration cycle during awakenings.

Relaxation strategies help reduce physical and cognitive arousal that can perpetuate wakefulness. Breathing exercises, guided imagery, and progressive muscle relaxation help to reduce arousal and feel ready to sleep.

*NOCTEM COAST*

The patient-facing app is available for iOS and Android:

- https://apps.apple.com/us/app/noctem-coast/id1512674928
- https://play.google.com/store/apps/details?id=com.noctem.coast&hl=en_US&gl=US

The clinician portal is accessible through web browsers:

- https://portal.noctemhealth.com/login

**Risks and Benefits**

*Potential Risks*

The trial involves two interventions, sedative-hypnotic deprescribing and CBT-I, both of which are regularly delivered interventions to Veterans in the VA clinical environment.

Deprescribing/withdrawal risk. Deprescribing is the reduction or withdrawal of a medication managed by a healthcare professional that aims to reduce harm and improve outcomes. Veterans regularly engage in deprescribing for a variety of medications, including sedative-hypnotics, under the guidance of their health care providers (e.g., PCP, Clinical Pharmacist, etc.). When deprescribing sedative-hypnotics, rebound insomnia is common and expected. However, there is some risk for other withdrawal symptoms, which will be assessed daily (see below). For this study, deprescribing for each participant will be managed by study CPPs, licensed Clinical Pharmacy Specialists at VAPHS.

The deprescribing of sedative-hypnotics, while a common outpatient procedure, does impose risks such as rebound insomnia, the potential for more serious withdrawal symptoms, and psychological discomfort. As noted above in the inclusion/exclusion criteria, we have limited the sedative-hypnotics in this study to z-drugs (i.e., zolpidem, zaleplon, eszopiclone), trazodone, temazepam, and hydroxyzine as these represent the most commonly used medications for insomnia at VAPHS. Veterans who use other prescription medications to improve their sleep will not be excluded from this study; however, only z-drugs, trazodone, and temazepam will be targeted for deprescribing. Veterans who use over the counter medications for sleep will be managed on an individual basis. Also, for

Veterans taking zolpidem, trazodone, and temazepam at greater doses than is typically recommended,[63] their inclusion will be determined on a case by case basis. Any Veteran excluded but still interested in reducing their use of sedative-hypnotics will be referred to their prescribing provider for assistance. The study's CPPs will be responsible for the management of participants' sedative-hypnotics, including collaborating with participants' prescribing providers about who will enter the order in CPRS, communicating detailed instructions to participants and coordinating with them on the pick-up/delivery of medications, and, if necessary, the return of excess medication in higher doses. As needed, the study's CPPs will utilize clinical tools at her disposal to assist with an individualized taper, such as the VA Academic Detailing Benzodiazepine Tapering Calculator located on the VA Academic Detailing SharePoint.

Veterans will be assessed for withdrawal symptoms and psychological discomfort (e.g., irritable, restless, anxious, fatigue) on a daily basis as part of the daily sleep diary entry through the COAST platform. First, Veterans will be asked if they are experiencing any unexpected symptoms (other than increased trouble sleeping, which is expected with medication reduction)? If so, Veterans will be prompted to complete the Clinical Institute Withdrawal Assessment – Benzodiazepines (CIWA-B) for more detailed information. Any participant report of withdrawal symptoms, psychological distress, and adverse effects will be reviewed by the study staff daily (during weekdays). If symptoms are reported outside of business hours, Monday-Friday (0800-1630 EST), reports will be reviewed on the next business day. After review of symptom reports, the study Clinical Pharmacist and/or Clinical Psychologists will contact the Veteran through the COAST platform's secure messaging to collect more information and provide feedback. As the study staff are only available during regular VA business hours (M-F, 0800-1630 EST), Veterans enrolled in the study will be instructed to contact emergency services if they ever feel they are experiencing emergent symptoms, study related or not. All Veterans will be provided the Veterans Crisis Line information as well. This approach to symptom management is similar to typical outpatient care at VAPHS.

CBT-I risk. CBT-I is an evidence-based, multi-component psychotherapy regularly delivered within the VHA. CBT-I is the recommended first line treatment for insomnia per the VA/DOD Clinical Practice Guidelines, the American Academy of Sleep Medicine, and the American College of Physicians among other professional societies.[12,25,40] Furthermore, there are several online and/or mobile app-based, self-management CBT-I interventions that have good evidence to improve symptoms with similar outcomes as in-person treatment.[3] The CBT-I intervention delivered through COAST uses proprietary algorithms to develop personalized recommendations based on the patient-reported data from users. COAST treatment recommendations are always reviewed by providers prior to being delivered to the participant. For this study, Dr. Bramoweth (PI), a licensed psychologist with expertise in insomnia/behavioral sleep medicine, will review all COAST treatment recommendations prior to their delivery to participants and make changes based on clinical expertise and knowledge of each participant as needed.

Suicide risk. Regarding suicidal ideation/behaviors, Veterans who are at high risk per the Columbia-Suicide Severity Rating Scale (C-SSRS) will be excluded and referred to the

appropriate resources following VAPHS guidelines. Specifically, Veterans with active suicidal ideation with intent and/or plan will be excluded. Veterans with ideation but no current intent or plan, but with a history of suicide attempts (including preparing for, interrupted, or aborted attempts) or self-injury in the past year will also be excluded. For Veterans who are eligible, those with suicidal ideation without method, plan, or intent will be monitored weekly with the C-SSRS through the COAST platform. If a Veteran meets elevated criteria for suicide risk (e.g., ideation with intent, plan, behaviors), they will be withdrawn from the study and referred for appropriate care per VAPHS guidelines.

Breach of confidentiality. There is minimal risk of breach of confidentiality. All Veteran participants will be assigned a unique research ID in COAST; the only PHI collected via COAST is the participant's email address and mobile device IP address, both of which are necessary for this study and this information will not be transferred to the PI/VAPHS as part of the regular data transfers. Furthermore, the study's data analyst will ensure that all data received from COAST (see Data Sharing below) is deidentified and all PHI are removed prior to data review and analysis by the study team. In sum, the risks for Veterans are not considered to be different than risks associated with engaging in clinical care related to sedative-hypnotic deprescribing and/or engagement in CBT-I.

This study will use the COAST platform to combine the clinical interventions of deprescribing and CBT-I to efficiently deliver treatment to participants in a remote manner. However, should any adverse events occur, they will be reported according to the VAPHS Human Subjects Research Reportable Events Guidelines.

*Protections Against Risks*

As noted above, we have plans in place to assess aspects of risk related to sedative-hypnotic withdrawal and psychological discomfort, medication tapering and management, and suicide risk.

Regarding protections against a breach of confidentiality, all data collected and obtained during the study will be confidential with access limited to approved study team members. Data collection and management will be conducted in strict accordance with the policies and procedures set forth by the VA Office of Research and Development. All participants will be assigned a unique ID that will be used throughout the study. COAST has several privacy and security measures in place (see Data Security below).

*Potential Benefits*

There is potential benefit for Veterans directly and VA broadly, as the reduction of sedative-hypnotic use and the improvement of insomnia and sleep quality may improve Veteran function and clinical outcomes. These improvements can potentially improve overall Veteran health, function, and quality of life, and reduce utilization of VA health care services. The long-term objective of this proposal is to develop a larger clinical trial to test the effectiveness of the intervention in an appropriately powered and diverse sample. If effective and able to be broadly implemented in VA, there is potential to benefit Veterans

who use sedative-hypnotics to reduce their use of these medications, improve their sleep quality, and overall improve function, quality of life, and health.

Veterans who engage in this deprescribing and insomnia intervention have the potential to directly benefit from improved function and sleep quality due to the impact of the intervention. Both deprescribing and CBT-I are evidence-based interventions. Secondary benefits may include the reduction of symptom severity of comorbid psychiatric disorders that are commonly linked with insomnia, such as depression, anxiety, and posttraumatic stress disorder; reduction of these symptoms may also improve Veteran function and quality of life.

For Veterans who participate, they may have the opportunity to gain access to a treatment they may otherwise not have access to, a combined deprescribing and remote CBT-I intervention. Also, Veteran participants may benefit from participating as it allows them the opportunity to engage in research designed to help other Veterans, providing a sense of satisfaction knowing that they are contributing to improved Veteran function and health broadly.

### Alternatives

Both sedative-hypnotic deprescribing and CBT-I are available treatments at VAPHS; however, they are typically available as separate treatments and not delivered via a digital platform. Participants interested in either interventions outside of participating in this study will be referred to the appropriate clinical service—their prescribing provider (e.g., PCP, Psychiatrist) for deprescribing and/or the Behavioral Health Service Line (Insomnia Consult) for CBT-I. The research team is not aware of other research studies that would provide a similar intervention.

## 5.2 Study Population, Recruitment Methods, and Informed Consent Process

### Study Population/Inclusion and Exclusion Criteria

*Inclusion Criteria*

- VAPHS Veterans ≥18 years
- Medical record documentation and self-report of active sedative-hypnotic use ≥3 days/week for ≥3 months: z-drugs (zolpidem: ≤10mg IR, ≤12.5 SR; zaleplon: ≤20mg; eszopiclone: ≤3mg); trazodone (≤400mg); temazepam (≤30mg); hydroxyzine (≤100mg); Veterans on higher doses may be eligible on a case-by-case basis
- A desire to reduce or stop using sedative-hypnotics
- Access to a mobile device

*Exclusion Criteria*

- A self-report of a medical and/or psychiatric disorder that would significantly impair participation (e.g., cancer, uncontrolled pain, severe depression)
- A self-report of a medical and/or psychiatric disorder that can be exacerbated by changes in sleep (e.g., seizure disorder, psychotic disorders, bipolar I disorder)
- A self-report of an active substance use disorder
- High risk of suicide per the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Currently engaged in an evidence-based, time limited, psychotherapy (e.g., prolonged exposure, cognitive processing therapy, cognitive behavioral therapy for depression, cognitive behavioral therapy for insomnia, etc.)

*Inclusion of Women, Minorities, and Children*

Women and minorities will be included in this study. Children (i.e., under the age of 18) will not be enrolled in this study. Also, no prisoners or currently hospitalized Veterans will be enrolled. Veterans with severe and/or unstable medical/psychiatric illnesses will also be excluded from this study (see Inclusion/Exclusion Criteria above) as will Veterans at high risk for suicide. No exclusion criteria shall be based on race, ethnicity, gender, religion, or HIV status.

*Master List*

A master list of enrolled participants will be maintained. A Veteran is considered enrolled after completing the informed consent process. The master list will be stored on the secure VA study drive and only accessible by approved study staff.

**Recruitment Methods**

The goal is to recruit and enroll 50 Veterans from VAPHS and affiliated CBOCs. Rather than recruiting in clinic and in-person, as is common for intervention trials such as this, to expand the pool of eligible participants we will primarily recruit through mail. The study team will mail a letter (see Recruitment Letters) to potentially eligible Veterans, based on inclusion and exclusion criteria, utilizing data from Veteran medical records. These letters will be sent from service line leaders at VAPHS—Behavioral Health, Primary Care, and Medicine (representing Sleep Medicine). A pre-screen list of potentially eligible Veterans will be generated by the study's data analyst, through VA's Corporate Data Warehouse, and stratified by sex (male/female), race (White/non-White), and age (<65/≥65) as an attempt to recruit a diversified sample. Then, letters will be mailed weekly to potentially eligible Veterans randomly selected from each stratified group (e.g., ~20-25/group). Letters will be sent until the goal of 50 Veterans have been enrolled.

Letters will ask Veterans to call the study coordinator for more information or they can return a letter indicating their interest. Interested Veterans who contact the study team will then schedule an eligibility screen (e.g., phone, Teams, VVC) with the study coordinator.

If feasible, depending on COVID-19 restrictions, recruitment will take place in VAPHS clinics (e.g., Primary Care, Behavioral Health, Sleep Medicine) in addition to the mail recruitment campaign. This may involve clinicians describing the study to their patients and providing study contact information as well as IRB approved fliers posted through VAPHS.

| | White | | Non-White | | Total |
|---|---|---|---|---|---|
| | <65 | ≥65 | <65 | ≥65 | |
| Female | 82 | 24 | 29 | 2 | 137 |
| Male | 346 | 859 | 48 | 65 | 1318 |
| Total | 1311 | | 144 | | 1455 |

As part of the proposal, a preparatory to research data query found VAPHS has n=1,455 Veterans who used sedative-hypnotic medications >14 doses/month for ≥3 months from 01/01/2019 to 01/31/2021 without diagnoses that would exclude them from participating. A new CDW query, using updated inclusion criteria, will update the pool of potential participants as of 1/31/2023. If feasible, depending on COVID-19 restrictions, recruitment will take place in VAPHS clinics (e.g., Primary Care, Behavioral Health, Sleep Medicine) in addition to the mail recruitment campaign. Clinicians familiar with the study can also notify the research team of interested, potentially-eligible participants via a research specific CPRS consult, so that a study member can contact a Veteran directly. This will minimize the burden on the clinician and help recruitment in clinical settings be more efficient.

**Informed Consent Process**

Interested Veterans who respond to the letter recruitment (or other methods) will be scheduled to undergo a screen (e.g., phone, Teams, VVC, in-person [only if necessary]) to confirm inclusion/exclusion criteria. The study team will also review their electronic medical record to confirm aspects of inclusion/exclusion criteria. If eligible, they will be invited to undergo the informed consent process via remote procedures (e.g., phone, Teams, VVC) or in-person if requested. For remote consent, Veterans will sign the ICF + HIPAA using DocuSign. If in-person, the Veteran will complete a written ICF + HIPAA.

Following consent, participants will be instructed on how to download the patient facing COAST app to their mobile device. Once downloaded, it will be activated with a unique code to prevent the app being used on another mobile device. Once the app is activated, the participants will be assigned a unique ID number, will undergo a brief training on how to use COAST, including instructions on how to access and navigate to the content areas, how to enter data for measures, how to use the sleep diary, and how to use the secure messaging. Previous testing of the COAST app by military Veterans and Service Members found its usability to be excellent and it received high scores for ease of use and learnability.[55] Since the initial development, the user interface has been further improved to meet the needs of users. Also, any technical issues with the app will be rapidly responded to by the study/Noctem team. After the app training, participants can then complete the baseline assessment in the COAST app.

## 5.3 Data Analysis

This study is focused on the feasibility of recruitment and participation, usability and acceptability of COAST, and estimates of change in Veteran sleep and sedative-hypnotic use. The findings from this SPiRE will inform the study design of a larger clinical trial (e.g., RR&D Merit). A meta-analysis of digital CBT-I (2016) found a hedge's g of 1.09 (95% CI 0.74-1.45) when evaluating pre-post change on the Insomnia Severity Index (or similar measures).[54] The only study, to date, using NOCTEM COAST found a pre-post Cohen d of 1.93 for the ISI.[56] While there are few studies specifically looking at CBT-I plus sleep medication deprescribing, they show large effect sizes for change on the ISI (Cohen d = 1.98-2.26).[49,64,65] Given the estimates from prior work conducted, we can expect an effect size range for pre-post ISI between 1.09 and 2.26 with an average effect size of 1.73 (large effect sizes). Given 50 recruited and accounting for a 25% drop out (i.e., 37 completers), we will still have 95% power to be able to detect an effect size of 0.65.

Prior to analyses for each aim, participant characteristics will be evaluated with descriptive statistics (e.g., age, sex, race). Distributions will be examined for normality, outliers, and missing data. Continuous variables (means/SD) and categorical variables (frequency/percentage) will be reported.

**Aim 1.** *Feasibility* will be evaluated in two ways. The first is by participant recruitment—how many participants contact the coordinator, undergo the study screen, and provide consent. The second is by treatment participation—how many participants download and activate the COAST app, complete baseline assessments, engage in treatment beyond the initial recommendation, and complete the intervention. Chi-square analyses will be used to determine group differences (age, sex, race) in recruitment response and participation rates.

**Aim 2.** *Usability* and *acceptability* of COAST will be evaluated by the PSSUQ measure. Usability/acceptability will be measured early in treatment ($T_{0+1\text{-week}}$) and at post-treatment ($T_1$) as well as change over time ($T_1 – T_{0+1\text{-week}}$). Change will be assessed using an intent-to-treat (ITT) approach and fitting mixed effects linear models that tests change in usability/ acceptability (change on PSSUQ scores over the course of treatment) that includes a main effect of time ($T_{0+1\text{-week}}$ to $T_1$) and random effects for the Veteran.

Audio-recorded qualitative interviews will help to gain more nuanced information on COAST usability/acceptability. The interviews will be interpreted using the rapid qualitative inquiry[66,67] to ensure that results are delivered in a timely manner to be meaningful to the study. Interviews will be summarized by the study's qualitative analyst into a template of categories that reflect topics of interest. The summaries will be coded by two analysts to develop the basis of content and thematic analyses.

**Aim 3.** Veteran clinical and functional outcomes will be evaluated with an ITT approach. We will fit mixed effects linear models that test change pre-post treatment (ISI, sleep diary, PROMIS) that includes a main effect of time ($T_0$-$T_1$, $T_0$-$T_2$, and $T_1$-$T_2$) and includes random effects for the Veteran (multiple measurements during treatment). Sedative-hypnotic change will be a determined by an ITT approach and fitting a mixed methods logistic model that tests for dose reduction (≥50%, yes/no) and cessation of medication (yes/no) over the

course of treatment that includes a main effect of time ($T_0$-$T_1$, $T_0$-$T_2$, and $T_1$-$T_2$) and random effects for the Veteran. Additional analyses will compare completers vs. non-completers and responders vs. non-responders.

The study data analyst/statistician will lead quantitative analyses and the study qualitative analyst will lead qualitative analyses. The PI and Co-Is will also be involved in study analyses and interpretation.

### 5.4 Withdrawal of Subjects

This study is voluntary, and participants may withdraw from the study at any time. If so, they may not be eligible for study payment depending on when they withdraw. Participants may withdraw from the study but may be eligible to continue in the follow-up assessments; if so, study staff will only communicate with the participant to schedule and complete the follow-up assessments.

If it becomes known that a participant meets exclusionary criteria (e.g., high risk for suicide, active substance abuse), they may be withdrawn from the study.

If a participant chooses to begin a new sedative-hypnotic or increases a dose of a sedative-hypnotic that is not part of the study's Clinical Pharmacist taper plan, they may be withdrawn from the study.

If a participant chooses to begin a new evidence-based psychotherapy, they may be withdrawn from the study.

If a participant withdraws or is withdrawn, with their permission, current sedative-hypnotic information and taper plan will be communicated to their prescribing provider.

## 6.0 Data Safety Monitoring

A data and safety monitoring plan will be implemented to ensure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. The PI, investigators, study personnel, and the clinical coordinators involved in the study will meet at least monthly to discuss the study (e.g., study goals, progress, modifications, documentation, recruitment, retention, data analysis and confidentiality) and address any issues or concerns at the time. These meetings will be overseen by the PI. Any instances of adverse events, protocol deviations, or other problems identified during the meetings will be reported as soon as possible within the required reporting timeframes using the standard forms and/or procedures set forth by the IRB. In addition, clinical coordinators may review study documentation and/or consent forms to ensure that participant's confidentiality is maintained.

This study does not have a DMC or DSMB.

## 7.0 Privacy and Confidentiality

PHI will only be disclosed for necessary study procedures, including recruitment via a CDW data query for VAPHS Veterans who may be eligible (only accessed by study data analyst) and as needed for the informed consent process and for participant payments.

All participants will have unique research ID numbers that will be used in lieu of PHI (e.g., names, date of birth, SSN, etc.) for data collection and storage. The research ID numbers are unrelated to any potentially identifiable numerical series, such as social security number, medical record number, or date of birth. Study data will be kept strictly confidential, and participants' identities will not be revealed in any publication. Electronic data collected via COAST will be reviewed for completeness and uploaded into the study database at NOCTEM. Both NOCTEM AWS GovCloud-based databases and VA databases are protected by several procedures, including password protection and a firewall around the networks.

Data collected by NOCTEM via COAST will be transferred to the PI/VAPHS. After participant enrollment, data collection will primarily be through COAST and managed by the NOCTEM team; interview data will be conducted by study staff using approved methods (e.g., digital audio recorder, MS Teams, audacity). There will be a regular (e.g., quarterly) data review and a secure data transfer between NOCTEM and VAPHS. Once data is at VAPHS, the PI will oversee aspects of data management with support from the study data analyst. VAPHS databases and necessary data entry forms will be developed by study data analyst and data will be stored on a VA server maintained by OI&T in a study-specific shared drive with access limited to the VAPHS study team.

All research data will be stored according to the VA Record Control Schedule.

Data collected in this study, if approved by the participant, will be stored in a repository (VAPHS Research Repository (MIRECC)). However, data will not be used in other studies unless using approved VAPHS ORD guidelines (e.g., new IRB protocol; approval by repository PI).

## 8.0 Collaborative/Multisite Research

VAPHS is the primary research site and will also serve as the coordinating site. The Madison VA (Co-I, Lickel) will serve as the participating site. To facilitate communication, an MS Teams will be created for the SEDATIVE study so all team members can be kept up to date for all study procedures. This included ensuring the study protocol is followed and to avoid any study non-compliance; any non-compliance that occurs will be reported in accordance with VHA Directive 1058.01.

The study will utilize a VAPHS shared drive (R:\Bramoweth_1638783_SEDATIVE) to ensure document version control; Madison VA will not have a separate study drive. This will also prevent data from being stored at multiple study sites, further protecting study data per VA information security policies.

Similarly, all IRB approved study documents (e.g., ICF, HIPAA, IRB/R&D approval) will be available on the study shared drive and IRBNet. Prior to the initiation of any study procedures,

the PI will ensure that all approval documents, from VAPHS and Madison VA, are up-to-date. For any amendments, a similar procedure will take place, with the PI ensuring that all approved documents are in place at both sites.

Should any serious adverse events (SAEs) occur, they will be documented on the adverse events log (shared drive) and reported according to VA ORD policies. Study investigators, at both participating sites, will be notified as well.

If VAPHS (IRB of record) determines that Madison VA is NOT to be engaged in research, the PI will inform Dr. Lickel, who will inform his local facility Director, who has the authority to approve/disapprove the conduct of research activity. Furthermore, when Madison VA no longer needs to be engaged in research, the PI will inform Dr. Lickel.

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