CLINICAL STUDY PROTOCOL

TITLE:	Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken): A Randomized Controlled Trial
NCT NUMBER:	NCT04040387
PRODUCT:	NightWare Digital Therapeutic
PROTOCOL NUMBER:	NW101002
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CONFIDENTIALITY STATEMENT:	This document is confidential. It contains proprietary information of NightWare INC. Any viewing or disclosure of such information that is not authorized in writing by NightWare INC. is strictly prohibited. Such information may be used solely for the purpose of reviewing or conducting this protocol.

SPONSOR PROTOCOL APPROVAL

Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken): A Randomized Controlled Trial

Sponsor's Approval:

Brian Robertson 06/27/2023

Brian Robertson, MD
Chief Medical Officer
NightWare INC.

Date

INVESTIGATOR SIGNATURE OF AGREEMENT

Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken): A Randomized Controlled Trial

AGREEMENT

I have read and understand this protocol.
I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.
I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.
I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonization guidelines on Good Clinical Practice and with the applicable regulatory requirements.
I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.
I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

Principal Investigator's Name: _____

Principal Investigator's Title: _____

Institution Name: _____

Address: _____

_____

Principal Investigator's Signature: _____

Date: _____

Table of Contents

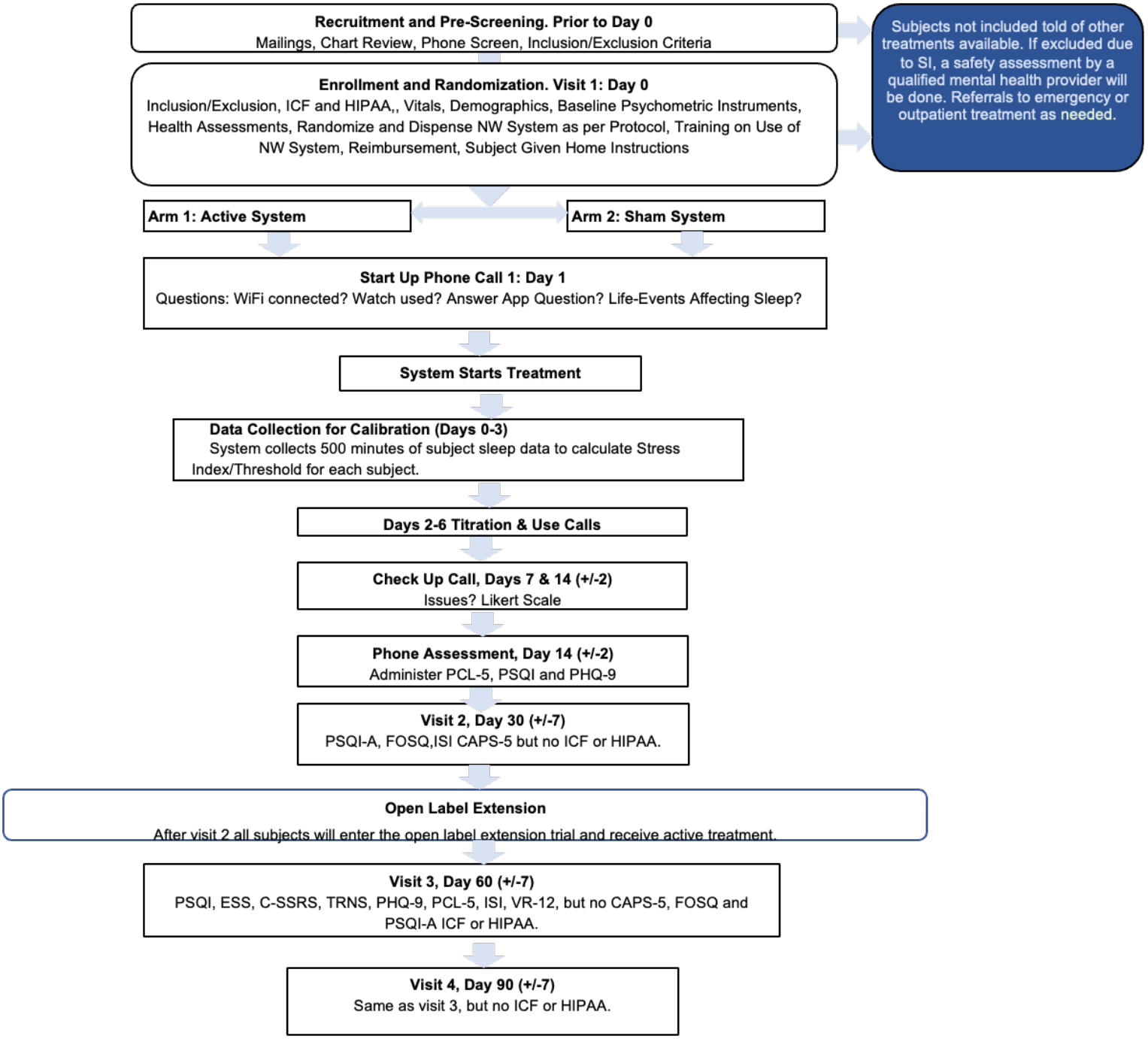
1. PROTOCOL SUMMARY

1.1. Synopsis

Title:	Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken): A Randomized Controlled Trial
Study Description:	This is a double-blinded, sham-controlled, randomized controlled trial to establish the safety and efficacy of the NightWare (NW) digital therapeutic system (NW System) which is to be used for the treatment of sleep disturbances related to nightmares associated with post-traumatic stress disorder (PTSD). This system consists of a Smartphone, a Smartwatch, and a proprietary application. This study will compare the Active System, which monitors sleep and provides tactile stimulation to terminate nightmares, to the Sham System that while it does monitor sleep, does NOT provide intervention but is otherwise identical. This study seeks to determine the safety and efficacy in treating PTSD-related sleep disturbance with the NW System as well as delineating the impact of improved sleep when using the Active System versus the Sham System. The investigators hypothesize that the Active System will significantly improve sleep quality in subjects with PTSD-related sleep disorders who are suffering from nightmares and poor sleep quality, and that the magnitude of improvement will be greater than that observed in the subjects who receive a Sham System.
Objectives:	Primary Objectives: ● Demonstrate that the Active System improves sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in participants with PTSD ● Demonstrate that improvement in sleep quality is greater for the Active System than the Sham System ● Demonstrate that the Active System does not lead to worsening of daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS) ● Demonstrate that there is not an increase in suicide risk as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) Secondary Objectives: ● Evaluate changes in the following measures between Day 0 (baseline) and Day 30: - PTSD severity [PTSD Checklist (PCL-5)] - Sleep quality [PSQI Addendum for PTSD (PSQI-A)] - Subjective sleep quality [NW Likert Scale for Sleep Quality] - Quality of life [Functional Outcomes of Sleep Questionnaire (FOSQ-10) and Veterans Rand 12 Quality of Life instrument (VR-12)] - Nightmare severity/frequency [TRNS] - Depression symptoms [Patient Health Questionnaire-9 (PHQ-9)]

	- Insomnia Severity Index (ISI)
Outcomes:	Primary Efficacy Outcomes: ● Difference between PSQI score at baseline (Day 0) and average PSQI score at the post-treatment assessment (Day 30) [i.e., PSQI change] in the Active System. ● Difference in average PSQI change scores between Active System and Sham System conditions. Primary Safety Outcomes: ● No significant increase in ESS between baseline (Day 0) and Day 30 in the Active System. ● No increase in C-SSRS severity score between Day 0 and Day 30 in the Active System. Observational Outcomes: ● Improvement in sleep quality, nightmare frequency/intensity, quality of life, PTSD severity, and depression symptoms between Day 0 and Day 30 in the Active System. ● Greater improvement in sleep quality, nightmare frequency/intensity, quality of life, PTSD severity, and depression symptoms in the Active System relative to the Sham System.
Study Population:	480 potential participants will be screened and 240 adults (120 in each arm), equal to or over the age of 22 years with symptoms indicative of PTSD and related nightmares will be enrolled into the study protocol. This is a multi-site study and will include active-duty military members, military veterans, and military family members.
Planned Number of Sites:	This study will be conducted at WRNMMC and FBCH as the two DoD sites. It is also conducted at multiple VA Hospitals.
Description of Study Intervention:	Wearable digital therapeutic system that will measure physiologic data when worn during sleep to deliver a mild vibration via the watch (i.e., haptic feedback) to elicit an arousal thereby disrupting nightmares. This detection and stimulation sequence will be performed according to NW's proprietary algorithm.
Participant Duration:	30 days in a randomized control trial followed by an additional 60-day open label extension.
Data Banking	De-identified data generated from this study will be saved for use in future studies. The site will transfer data to NightWare that does not contain individual identifiable information.

1.2. Schematic



1.3. Schedule of Activities

Study Activities Table:

Study Activity	Pre-Tx	Visit 1	Calib-ration	Start Up Call	Help Calls	Check Up Call 1	Assess ment Call	Check Up Call 2	Visit 2	Visit 3	Visit 4
Study Day	**Before Day 0**	**Day 0**	**Days 0-3**	**Day 1**	**Days 2-6 (Opti onal)**	**Day 7**	**Day 14 (+/-3)**	**Day 21 (+/- 2)**	**Day 30 (+/- 7)**	**Day 60 (+/- 7)**	**Day 90 (+/- 7)**
Recruitment	X										
Chart Review	X										
Phone Screen	X										
Inclusion/Exclu sion	X	X									
ICF and HIPAA		X									
Modified Dysken l		X[a]									
AUDIT		X[b]									
DAST-10		X[c]									
Demographics		X									
Medical History		X									
Blood Pressure		X							X		
Med Reconciliation		X							X	X	X
PSQI		X					X		X	X	X
PSQI-A		X							X		
ESS		X							X	X	X
ISI		X							X	X	X
PCL-5		X					X		X	X	X
CAPS-5		X									
VR-12 (QOL)		X							X	X	X
TRNS		X							X	X	X

FOSQ-10		X							X		
PHQ-9		X					X		X	X	X
C-SSRS Lifetime		X							X	X	X
Blinding Assessment Questionnaire									X		
NW Likert Scale		X							X	X	X
Daily Use Questionnaire (Days 1-90)				X	X	X	X	X	X	X	X
Calculate Cutoffs/Eligible ?		X									
Dispense NW Devices		X									
Train Subject		X									
Activate Devices		X									
C-SSRS Since Last Contact									X	X	X
Payment of Subject(Bi weekly)	See Reimbursement Section 6.15										
Start Up Call				X							
Calibration			X								
Active/Sham Treatment			Post-Calib. [f]								
Help Calls Questionnaire (Optional)					X	X		X			
Checkup Phone Call						X		X			
Sham Cross-over to Active Treatment									X		

a—Administered DURING informed consent process to ensure subjects are capable of consent. Subjects must get all responses correct to be enrolled into the study, b-Exclude if score is equal to or greater than 8. c-Exclude if score is greater than 2. f-Only the Active System goes through calibration and on to Active Treatment.

2. INTRODUCTION

2.1. Study Rationale

Nightmares are a common problem affecting around 2-8% of the general population and a higher proportion of clinical populations. The negative consequences of untreated nightmares are significant and include impaired quality of life, sleep deprivation (often resulting in increased intensity of nightmares), insomnia, daytime sleepiness, and fatigue. Untreated nightmares can also exacerbate the symptoms of underlying psychological dysfunction in subjects with depression and anxiety, leading to poor occupational and or social functioning.[1,2]

Nightmares can be idiopathic or associated with the use (or withdrawal) of certain medications/substances, or associated with disorders including PTSD.[2]

While nightmares are readily observed and recognized by subjects and their family members, nightmare physiology is still poorly understood. Despite a limited understanding of the mechanisms of nightmares, there are treatments that show variable efficacy. The American Academy of Sleep Medicine makes two recommendations for the treatment of nightmare disorder. One is pharmacological and the other is non-pharmacological.[3]

Prazosin, an alpha 1 antagonist antihypertensive, is a medication routinely used to treat nightmares and it is thought to mediate its effects by reducing the sympathetic outflow in the brain during sleep. While there has been evidence to support its efficacy in treatment of nightmares, common side effects include orthostatic hypotension and rebound hypertension with missed doses.[3-6] Its interaction profile with other medications also limits use in clinical populations.

Image Rehearsal Therapy, a modified cognitive behavioral therapy technique, is a non-pharmacological approach that appears to be effective. It requires the subject to write down the nightmares and THEN rehearse those nightmares (inserting a positive result) prior to sleep. However, studies demonstrate poor compliance with therapy. Moreover, rehearsing the nightmares immediately prior to bed carries the risk of re-exposing the subject to their traumatic nightmare and, thus, exacerbating the symptoms of nightmares as well as increasing the frequency of nightmares.[3]

NightWare (Minneapolis, MN) has developed a novel approach to the treatment of nightmares. Through the use of a smartwatch-based application that senses physiologic parameters, the patient is aroused from sleep (without awakening the patient) so that the nightmare is interrupted prior to reaching a threshold of severity in which the patient would awaken in distress. Seconds later the patient returns to sleep without having experienced a nightmare. This approach avoids risk from pharmacological treatment, avoids exacerbation of symptoms from image rehearsal therapy and allows for a simple method with easily achieved adherence compared to existing treatments.

2.2. Background

Approximately 80% of subjects with PTSD have nightmares that begin within the first 3 months of the trauma. Although up to 50% of subjects with PTSD have resolution of their nightmares within 3 months, a substantial proportion experience lifelong nightmares.[2]

Despite their prevalence and distress, nightmares are frequently underreported and thereby undertreated. In a study published in 2015, more than 60% of subjects did not discuss clinically significant nightmares with their healthcare professional. [7]

Trauma related nightmares and accompanied sleep disturbances are thought to contribute to the development of PTSD as well as worsening symptom severity, functional impairment, distress and overall poor quality of life. [8,9,10]

Nightmares are categorized by whether they are due to a medication or substance, associated with a psychiatric disorder such PTSD, or idiopathic, meaning the cause is not readily known.

The diagnosis of nightmares is made by a clinical history and examination. Laboratory tests are not routine unless there is suspicion for a drug use disorder.

Sleep diagnostic testing using Polysomnography is not indicated for the diagnosis of nightmares, as nightmares tend to occur less frequently in a clinical sleep laboratory setting. [11] This is presumed to be due to the "first night effect" in which subjects' sleep architecture may be different than in their natural home sleep environment.

Formal Classification per the ICSD-3

The following section is included as an indicator of the issues and severity that is commonly observed in subjects with trauma-related nightmares. For a subject to actually receive a diagnosis of nightmare disorder 2 is exceedingly rare. Having a diagnosis of nightmare disorder 2 is NOT a requirement for inclusion into this study. The third edition of the International Classification of Sleep Disorders states the following minimum criteria for nightmare disorder 2:

1. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involved threats to survival, security, or physical integrity.
2. On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert.
3. The dream experience, or the sleep disturbance produced by the awakening from it, causes clinically significant distress or mental impairment in social, occupational or other important areas of functioning as indicated by the report of at least one of the following:

    a. Mood disturbance (e.g., persistence of nightmares affects anxiety, dysphoria).
    b. Sleep persistence (e.g., bedtime anxiety, fear of sleep/subsequent nightmares).
    c. Cognitive impairments (e.g., intrusive, nightmare imagery, impaired concentration, or memory.)
    d. Negative impact on caregiver or family functioning (e.g., nighttime disruption).
    e. Behavioral problems (e.g., bedtime avoidance, fear of the dark).
    f. Daytime sleepiness.
    g. Fatigue or low energy.
    h. Impaired occupational or educational function.
    i. Impaired interpersonal/social function.

While it is commonly thought that nightmares emerge from REM sleep, nightmares have also been observed to emerge from Non-REM sleep. In a cohort of 35 subjects that suffered from PTSD, an almost equal percentage of subjects were documented to have NREM and REM related nightmares. Heart rate and respiratory rate accelerations have been observed with subjects arising from nightmares. Motor behaviors preceding nightmare awakenings have been observed in stage N2 sleep.[12]

Prazosin Pharmacologic Therapy

Prazosin is an α1-adrenergic receptor antagonist. This medication was originally intended for use as an antihypertensive.[4] It is believed that Prazosin can be effective in the treatment of nightmares related to post-traumatic stress disorder by reducing noradrenergic activity in the brain; which has been found to be elevated in people diagnosed with PTSD.[6] While some evidence supports the efficacy of Prazosin in treatment of nightmares in PTSD subjects, that evidence is inconsistent, not strong, and there are common side effects that raise concern including: dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea.[5] Even more concerning is the risk of orthostatic hypotension, and the potential for syncope-related injury. The American Academy of Sleep Medicine suggests that clinicians monitor patients for potential orthostatic hypotension when prescribing Prazosin for nightmares.

Image Rehearsal Therapy

Image rehearsal therapy is a form of cognitive behavioral therapy in which the subject later recalls a nightmare, then consciously imagines changes in the theme, storyline, ending, or any part of the dream, to a more positive and tolerable one. The intended outcome would be that when a subject has the rehearsed dream during sleep, they will replace the disturbing content with the positive and tolerable content imagined during the day. The subject will commonly practice the rehearsal of these dreams for 10 - 20 minutes per day. While this has been demonstrated to be generally effective in the treatment of nightmare disorder in subjects with PTSD, reports have described increased nightmare frequency and exacerbation of PTSD symptoms during image rehearsal therapy.[3] Likewise, sleep logs that subjects use to document the frequency and content of nightmares have been associated with subject reluctance to fill out the logs for fear of re-exposure [6]. For these reasons, not to mention the specialized staff training and time for repeated clinic visits, image rehearsal therapy has low potential to have a large population-level impact on PTSD-related nightmares.

NightWare Digital Therapeutic

For the purposes of this study, we will be using only the Apple (Cupertino, CA) 3rd generation smartwatch and the Apple iPhone. As described above, the NW System consists of a Smartphone (a functionality-limited iPhone), Smartwatch (a functionality-limited Apple Watch 3) and proprietary software application. NOTE: Since the phones and watches will be provided to research staff PRE-IMAGED and with much of the functionality disabled, they will be referred to throughout this document as “research equipment, research phone, and/or research watch”. The NW System has been effective in focus groups when used on both Apple smartwatches and Motorola smartwatches. The NW System utilizes physiological markers obtained via the smartwatch to determine, by proprietary algorithm, whether a subject is in the early stages of a nightmare but has not yet awoken in distress. As directed by the algorithm, the smartwatch then applies varying degrees of vibratory stimulation to the wrist over variable lengths of time with the intention of arousing the subject from sleep without eliciting an awakening.

There are three levels of intervention:

Low: Vibration is least intense, of short duration.
Medium: Vibration is slightly higher, duration is short (same as for "low").
High: Vibration level is the same as for "medium, duration is increased.

The threshold for these interventions can be manually titrated, if needed, in response to a specific person's symptoms.

Background information regarding sleep patterns: Sleep architecture has been explored extensively by the use of EEG's (Electroencephalography). Normal sleep physiology includes micro-arousals. These micro-arousals consist of EEG shifts of the brainwaves to a higher frequency and last from 3-10 seconds. They can be elicited through environmental stimuli such as noise. No definitive limits have been defined as to what is considered a pathologic frequency of micro-arousals. However, during routine clinical practice, micro-arousals of up to 15 times per hour are considered to be within normal limits.

EEG shifts lasting ten seconds, or more are considered **brief awakenings.**

The NW System cannot be used for detection of brain waves, therefore, no brainwave data (EEG) will be collected or analyzed.

Every person has their own sleep pattern that is almost as unique as a fingerprint. The NW System adjusts to a person's usual sleep pattern by going through an observation-only calibration stage. Usual sleep information is gathered during the first 500 minutes of sleep after the person begins wearing the NW System. The system then calculates an individual "arousal index" based on that sleep information for each subject. Once this arousal index has been calculated, the NW System goes into Active Treatment mode. Every time the arousal index for that person is exceeded, the system will intervene by applying a vibration through the smartwatch. The system uses only enough intervention (see intervention levels, above) to generate a micro-arousal and bring the person out of the nightmare.

In a 2004 study measuring EEG sleep changes elicited by vibratory tactile plus simultaneous auditory stimuli, microarousals were significantly more frequent than awakenings. This suggests that non-painful tactile stimuli can be used to elicit arousals and shift sleep stages without awakening subjects.[13]

The vibrations (0-3 seconds) being delivered by the NW System are intended to be brief enough that they reduce the chances of awakenings and the subsequent memories of the stimulation. The subject continues sleeping, and the smart watch arousal derails the generation and processing of the potential nightmare. Even in the uncommon event that the subject is awakened briefly, nightmare processing should still be curtailed.

Our hypothesis is that by abating these nightmare events people can improve the sleep quality and overall quality of their lives without major adverse consequences.

2.3. NW System Description

The NW System's proprietary application directs the smartwatch to monitor the wearer's movements and heart rate during sleep to detect the onset of a nightmare. When physiologic symptoms of a nightmare are detected (increased movements, fast movements, increased heart rate), the smartwatch provides gentle stimulation to minimally arouse but not fully awaken the wearer and therefore prevent the nightmare from fully developing and causing significant awakenings and/or sleep disturbance.

Once the smartwatch has been properly fitted to the individual and activated the Active System goes through a learning phase/calibration period. During this time the system monitors the subject's movements and heart rate to delineate the usual low, medium, and high-stress points, termed the "stress index" (threshold) (i.e. system determines the wearer's usual sleep patterns). The application then calculates the "stress index" (threshold) for that individual. When the upper end of this "stress index" (threshold) is exceeded, the system is activated and directs the smartwatch to gently vibrate leading to a slight arousal of the subject to interrupt the development of the nightmare without waking them and allow for a more restful sleep. The Sham System monitors the wearers' sleep patterns and calculates a "stress index" (threshold) but does NOT provide any interventions. The calculated "stress index" (threshold) will be used for subsequent data analysis only. The stress index (threshold) will be set manually on the Sham System to be so high that it will NEVER be activated. Data is collected throughout, and a stress threshold is initially calculated during the initial phase, though the subject isn't aware of this or shown it in any way. The stress threshold is continually calculated in both groups. The sham group never receives treatments regardless of stress threshold

Graphically, this learning/intervention strategy for nightmares is shown below (Active System, only).

Figure 2: NightWare User Interface and Data Flow

Active Intervention Description

The Active System captures heart rate and movement data from the wearer via sensors in the smartwatch (gyroscope, accelerometer, and heart rate monitor). This data is transmitted to the smartphone where the proprietary NW application algorithms calculate the individual's stress index (threshold) and learn how best to intervene in that person's nightmare development. This data is also transmitted by the smartphone to the secure NW server. This data is accessible only to NW Study staff and is used to monitor each subject. Monitoring will be used to ensure that each subject is wearing the NW System every night and to manually change the titration threshold and intervention strength parameters as necessary to provide the best sleep possible. If the subject is not wearing the NW System every night, the subject will be contacted to ask why the NW System is not being utilized. The Sham System will also be monitored to ensure that the system is being used nightly, but as the system is NOT active, no changes to the parameters will be made.

Sham Intervention Description

Subjects randomized to the Sham System will receive a research phone and research watch (as did those randomized to the Active System) and a version of the NW Application that has the threshold set extremely high (so high that it will NEVER be activated) will be installed. The Sham System will have the same user interface on the smartwatch (start button is enabled and is indistinguishable from the user interface present in active mode). The Sham System (as well as the Active System) will vibrate whenever the subject hits the "START" button. The Sham System will monitor the wearer's sleep pattern, as the active system does but will not provide any interventions during the night.

3. OBJECTIVES AND OUTCOMES

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
Primary Efficacy		
To demonstrate that the NW digital therapeutic improves sleep quality in subjects with PTSD	Difference between average PSQI score at baseline (Day 0) and average PSQI score at post-treatment (Day 30) assessment	The NW digital therapeutic is expected to improve sleep quality. PSQI is a validated measure of subject-reported sleep quality
Primary Safety		
To assess the potential risk of worsening sleep quality	Difference between average Epworth Sleepiness Scale (ESS) at baseline (Day 0) and ESS at Day 30.	The Epworth Sleepiness Scale is a validated measure of daytime somnolence.

To assess the potential worsening of suicidal risk	Difference between the average Columbia-Suicide Severity Rating Scale (C-SSRS) at baseline (Day 0-Lifetime and Recent version) and C-SSRS at Day 30 (Since Previous Contact version)	The Columbia-Suicide Severity Rating Scale is a validated measure of suicide risk.
Secondary: Observational		
To evaluate changes in subjective sleep quality.	Difference in PSQI-A and NW Likert Scale for Sleep Quality between baseline (Day 0) and post-treatment (Day 30) in the Active System.	May show improved sleep quality on scales other than PSQI.
To evaluate changes in PTSD and/or depression symptoms.	Difference in PCL-5 and PHQ-9 between baseline (Day 0) and post-treatment (Day 30) in the Active System.	The NightWare digital therapeutic may improve PTSD and/or depression symptoms. Therefore, this is an observational endpoint.
To evaluate changes in quality of life	Difference in FOSQ-10 and VR-12 between baseline (Day 0) and post-treatment (Day 30) in the Active System.	Improved sleep quality may improve quality of life
To evaluate changes in nightmare severity and frequency	Difference in TRNS between baseline (Day 0) and post-treatment (Day 30) in the Active System.	The TRNS is a validated measure of nightmare frequency and severity.
To evaluate changes in insomnia symptoms	Difference in ISI between baseline (Day 0) and post-treatment (Day 30) in the Active System	Decreased sleep latency and reduced sleep disturbance were noted as major areas of improvement in sleep quality on interim and secondary analyses of current data. Treatment of nightmares may improve insomnia symptoms.

4. STUDY DESIGN

This is a prospective, randomized, controlled, multi-center clinical trial to evaluate the effectiveness and safety of the NW System for the treatment of nightmare disorder secondary to post-traumatic stress disorder.

4.1. Treatment Assignment

Any subject meeting all inclusion and no exclusion criteria is eligible for enrollment in the study. Subjects are considered enrolled in the study once the informed consent form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) form have been executed.

All subjects will receive a NW System (research phone, research watch, and NW proprietary application-set to either an active mode or a sham mode). 240 subjects will be enrolled into the study. Subjects will be randomly assigned to receive either the Active System or Sham System. There will be 120 subjects in each arm. None of the subjects will be aware of whether they have received an Active System or a Sham System. For further details of treatment assignment procedures, go to the "Randomization" section of this protocol.

5. STUDY POPULATION

Veterans and active-duty service members that meet the inclusion and exclusion criteria will be enrolled in the study.

5.1. Inclusion Criteria

Inclusion Criteria

- Either Diagnosis of PTSD via American Psychiatric Association PTSD diagnostic criteria in the fifth edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or having symptoms consistent with PTSD (subject must score at least 25 on the PTSD Checklist-5 to qualify for the study).
- Equal to or older than 22 years of age.
- Proficient in both reading and writing in the English language.
- Pittsburgh Sleep Quality Index (PSQI). Potential participants would need to score 10 or more to qualify.
- ESS: On question #8 any score above "0" will prompt an additional question:
    - Do you drive ("get behind the wheel") when you are drowsy?
        - Answer must be "No" to be enrolled in the study due to safety concerns.
- Have repetitive nightmares contributing to disrupted sleep as reported by the subject
- Wireless Internet and two power outlets where they sleep
- Prazosin use; if yes, subject may be included if willing to be tapered by prescribing provider.
    - Taper must be completed, and the subject must be off prazosin for 2 weeks prior to enrollment.
- Alpha blocker use; if yes, subject may be included if willing to be tapered by prescribing provider. Taper must be completed, and the subject must be off all alpha blockers for 2 weeks prior to enrollment.

5.2. Exclusion Criteria

- Patient Health Questionnaire-9 (PHQ-9) score greater than or equal to 20 indicates that the subject is too depressed to be included in this study.
    - Score of 1 or more on the suicide ideation item (question #9) of the PHQ-9 will trigger a risk assessment by the principal investigator or qualified co-investigator.
- Responses on the C-SSRS that indicate High Suicide Risk.
    - Study staff will contact a licensed Behavioral Health Provider to assess any subject who reports any symptoms that fall into the High-Risk categories or are having current (within the last month) suicidal ideation.
- Uncontrolled atrial fibrillation
- Current use of varenicline
- Current use of beta-blockers (unless ophthalmic solutions). See "Excluded Medications List" in Appendix A.
- Current use of non-dihydropyridines. See "Excluded Medications List" in Appendix A.
- Current use of Prazosin for the treatment of nightmares (can include subjects 2 weeks post-taper and discontinuation). This would be coordinated with the prescribing provider.
- Current use of alpha blockers (can include subjects 2 weeks post-taper and discontinuation under guidance from prescribing provider).
- Circadian rhythm disruption on a regular basis (shift work)
    - Including regularly scheduled overnight care of very young, elderly, or sickly family members
- Known diagnosis of OSA
- Diagnosis of an active disorder of arousal from non-rapid eye movement sleep
- Diagnosis of rapid eye movement sleep behavior disorder
- Diagnosis of narcolepsy
- Alcohol Use Disorders Inventory Test (AUDIT) (score equal to 8 or higher)
- Drug Abuse Screening Test-10 (DAST-10) (score greater than 2)
- Suspicion of nightmares being secondary to substance abuse or withdrawal
- Diagnosis or suspicion of dementia
- Previous or foreseeable legal proceedings involving nightmares or trauma
- Nocturia that causes awakening from sleep
- Known sleep walking
- Wrist tattoos on the both arms where the watch will be worn, that prevent detection of heart rate by the device watch.

5.3. Screen Failures

Subjects that are screened but do not meet inclusion or exclusion criteria will not be enrolled or followed in the trial. Screen failures will be informed of other possible treatments available. Persons that failed screening due to Suicidal Ideation or having Moderate- to High-Risk on the C-SSRS will be assessed by the PI and, if deemed necessary, referred to a qualified Behavioral Health Provider immediately and provided appropriate referrals for emergency or outpatient treatment as indicated by risk assessment.

6. STUDY METHODS

6.1. Pre-recruitment

We will request a HIPAA Waiver and a Waiver of the Informed Consent Form (ICF) for purposes of recruitment. Note that no participants will be enrolled in the study without full written consent. The HIPAA Waiver will allow us to request that a computer search be done so that veterans and active-duty service members who meet the basic inclusion/exclusion criteria can be found. The Waiver of Informed Consent will also allow us to call and speak to the possible subject and to conduct a phone screen.

6.2. Recruitment

1. Subjects will be recruited using fliers and referrals from areas like the PTSD Clinic, VA Hospital CBOCs, Non Clinical counseling veteran centers, and mental health and behavior health clinics. Invitation letters will be sent to all veterans and active-duty service members compiled from the computer search, asking them to call the study coordinator if they are interested in study participation.
2. If the subject has not contacted study staff within two weeks after the recruitment letter is mailed, the subject may be called and/or texted by study staff.
    a. Study Staff has requested a IRB-Approved Cell Phone to assist in contacting and interacting with potential/enrolled subjects. (See Cell Phone/Text message content document submitted with this protocol).
3. Recruitment letters/Fliers will specify that if the veteran calls and either speaks to study staff or leaves a voicemail (secured) expressing interest, that their medical charts will be checked to determine eligibility.
4. If study staff answer the phone when the veteran calls, the veteran will be told about the study requirements and, if interested, phone screened.
5. Based on the phone screen results, those veterans and active-duty service members who appear to qualify will be told that their chart will be checked to make the final determination of their eligibility.
6. Study staff will call and/or text veterans and active-duty service members who leave messages after their chart has been checked for inclusion/exclusion criteria. If the veteran and active-duty service member appears to qualify, the phone screen will be conducted, and the veteran and active-duty service member will know his/her eligibility at the end of the call.
7. Veterans and active-duty service members that pass both chart review and phone screening will be invited to come in for an enrollment visit.
8. Veterans and active-duty service members and active-duty service members who do not qualify for the study will be told of other treatment options. These options are on the Handout "Post-Study Resources for Participants". Contents of Handout may be read to the veteran and active-duty service member over the phone and/or the Handout mailed to the veteran and active-duty service member as requested.

6.3. Pre-Screening

A trained study staff member will pre-screen interested veterans and active-duty service members for basic eligibility requirements (see above for inclusion criteria and exclusion criteria) and schedule consent and eligibility/baseline assessment appointments with site RA. (See Phone Screen submitted with this protocol for details.)

Based on the answers to this phone screen questionnaire, this subject:

1. **Subject does not qualify.**

    a. Subject will be thanked for their time and the phone call terminated.

    b. If the subject did not qualify due to recent suicidal ideation, if deemed necessary by the PI (a licensed Neurologist), a licensed Behavioral Health Provider will be contacted to provide appropriate follow up care.

    c. Subject will be informed of other options for care. These options are on the Handout "Post-Study Resources for Participants". Handouts may be read to veteran and active-duty service members over the phone and/or mailed to the veteran and active-duty service member if requested.

2. **Subjects who do not clearly fail, or meet, the study criteria** will be told that the rest of the study team will need to be contacted to determine if the subjects are eligible or not. Subject will then be contacted to be told the team's decision.

3. **Veterans and active-duty service members who pass the phone screening** will be asked to come in for an enrollment visit.

6.4. Enrollment: Visit 1, Day 0

Those who pass the telephone pre-screening will be scheduled for an Enrollment Visit (Visit 1, Day 0).

Procedures to be done at this visit include:

1. Re-check of inclusion/exclusion criteria prior to signing enrollment forms.
2. Signing of Informed Consent Form (ICF) and HIPAA
3. Completion of a Demographics Form
4. Baseline Psychometric Instruments:
    a. Pittsburgh Sleep Quality Index (PSQI)
    b. PSQI Addendum for PTSD (PSQI-A)
    c. PCL-5 Checklist (past 1 month)
    d. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)
    e. Patient Health Questionnaire-9 past 1-month version (PHQ-9) (Score greater than or equal to 20 indicates severity of depression too great for this study. Score of 1 or more on the suicide ideation item [question #9] to trigger a risk assessment by PI and a licensed Behavioral Health Provider.)
    f. Epworth Sleepiness Scale ESS: On question #8 any score above "0" will prompt an additional question:
        1. Do you drive ("get behind the wheel") when you are drowsy?
            a. Answer must be "No" to be enrolled in the study due to safety concerns.
    g. DAST-10: Exclude if score is greater than two (2).
    h. AUDIT: Exclude if score is equal to, or greater than, eight (8).
    i. Functional Outcomes of Sleep Questionnaire (FOSQ)
    j. Insomnia Severity index (ISI)
    k. Trauma Related Nightmare Scale (TRNS)

   l. VR-12 Quality of Life (VR-12)
   m. NW Likert Scale for Sleep Quality (NW Likert) 7-day
   n. Columbia-Suicidality Severity Rating Scale, Lifetime and Recent version (C-SSRS) (responses in the High-Risk range will make the subject ineligible).
      i. After further assessment with the PI, Study Staff will contact the healthcare provider that has been trained to perform a suicide assessment for all subjects with a rating greater than "LOW".
   o. RedCAP collection questionnaire: What type or types of traumas led to your PTSD? (Choose the primary type of trauma that applies) 1) Combat/blast trauma 2) Sexual Trauma/Rape/Sexual Assault 3) Natural Disaster 4) Childhood physical abuse 5) Accident, such as a car accident 6) Other (a secondary choice would appear for free text).
5. Baseline health assessments
   a. Blood Pressure-Blood pressures should be taken while the patient is in a sitting position with their feet flat on the ground after at least 5 minutes of rest. A minimum of 2 blood pressures should be taken 30-60 seconds apart. The average of these two blood pressures should be recorded.
   b. Height and Weight to calculate BMI
   c. Complete a Health Questionnaire
   d. Medication Reconciliation (compare to EHR, add any over the counter medications)
6. Determination of subject's eligibility for randomization:
   a. Based on each subject's scores and answers to the previous questionnaires/questions the subject will either be:
      i. Randomized.
         1. The enrollment visit will continue.
      ii. Told that he/she does not qualify.
         1. Enrollment visit ends.
         2. Subjects are reimbursed for their time/assessments.
         3. Subject given contact information for behavioral health services.
         4. No further contacts/visits will be scheduled.
7. Randomization.
   a. Eligible subjects with scores equal to or more than 16 (PSQI High stratum), will be randomized separately from subjects whose scores were equal to a minimum of 10 to a maximum of 15 (PSQI Low stratum).
      i. Both the 16 and over scoring group and the 15 and under scoring group will have 50% of their group given the Active System and 50% will get the Sham System.
   b. PSQI Low stratum subjects will have assigned ID #'s ending in 001 to 499.
   c. PSQI High stratum subjects will have ID #'s ending in 500 to 999.
8. NW System provided to subject
   a. Systems will be pre-prepared by NW Corporate.
   b. Pre-prepared Systems will be labeled with the study ID number used.
   c. Subjects will then be randomized using the randomization procedure delineated in section 6.1.
   d. Once the subject is randomized, the system will be set to sham or active mode by NW technical staff.
      i. These staff are not located at the study site.
      ii. Neither the subject nor the study staff will have access until data is unblinded.
9. Subject training on NW System:
   a. Subjects will be instructed on the proper use and care of the phone and watch.
   b. Subjects will be shown how to Access and Use the NW Application.

   c. Verify that participant understands how to use the NW System
   d. Send participant home with directions "Home Instruction Sheet"
      i. The Contact Number for Study Staff is included in the Home Instruction Sheet, so if there is/are any issue(s) prior to the Checkup Call the subject may obtain help solving the issue(s)
10. Complete the NW Call and Visit Schedule (included in this submission).
   a. Subjects will fill-in their own copy of the form and take it home with them.
11. Stress to subject that ANY ISSUES with the phone and/or watch must be reported promptly to Study Staff so that they can be corrected.
12. Inform subjects that Study Staff may call DAILY from days 2-6 (optional—dependent on subject understanding, connectivity issues, etc.). These calls have been named "Help Calls".
13. Enrollment status and subject ID will be placed into a spreadsheet that indicates Study ID #, name, last 4, contact phone, address, and the serial number of the pre-prepped System that was provided to the subject.
   a. This spreadsheet will NOT be shared with NightWare personnel as it contains PHI.
14. A second spreadsheet will keep track of all pre-prepared phones and watches received from NW.
   a. Phone and watch passcodes as well as the NW Application log-in key code will be tracked upon receipt.

6.5. Calibration of System (Days 0-3, approximately)

Once the NW Active System has been installed on the watches of those participants randomized to receive study intervention, a calibration period consisting of the recording of approximately 500 minutes of normal (non-intervention) sleep will occur. This calibration allows for a Stress Index (Threshold) to be assigned for the participant. Sham Systems will not go through a calibration phase, nor will they ever provide study interventions.

6.6. Treatment Operation (Study Intervention, Post-Calibration, Daily Use Questionnaire)

After the calibration period, the Active System enters active treatment (study intervention) on approximately days 2-3. The Sham System will never go into this mode.
Subjects will also receive a daily use questionnaire Deployed via RedCAP

1. RedCAP deployed Daily Use questionnaire (Day 1-90)
   a. How was your sleep quality? 0 = Refreshing, 1 = Average, 2 = Poor
   b. Was the device disruptive? 0 = Did not feel it, 1= Mildly disruptive, 2 = Uncomfortable
   c. How many nightmare-related awakenings? 0 = none, 1 = 1-2, 2 = 3 or more

6.7. Day 1: Startup Phone Call

This call will be to see if subjects have gotten the NW System connected to their home WiFi and were able to set things up and use the system during the night
Administer:

1. NW Start up Call Questionnaire.

Any issues that arise will be dealt with by Study Staff (help with calling participant's internet service provider to get the System synced with the participant's home WiFi, additional education on how to wear the watch and use the application, etc.).

6.8. Days 2-6 and others if needed: Help Calls/Texts (Optional)

After doing the Start Up Call on Day 1, research staff will conduct additional calls/texts on days 2-6, and on other days, as needed. During these calls/texts, research staff will address any issues arising with WiFi connectivity, misunderstandings and the proper use of the devices, as well as any other issues that may arise. Administer the following questionnaire (as needed): Help Calls.

6.9. Day 7: Checkup Phone Call

Study staff will call on Day 7 (+/- 2 days) to determine how the participant is doing with the NW System. Administer:

a. NW Help Calls Questionnaire

6.10. Day 14: Patient Questionnaire Assessment

Participants will complete questionnaires on Day 14 (+7 days). Study coordinator will contact participants on Day 16 if the questionnaires have not yet been completed. Questionnaires to be completed:

a. Administer the PCL-5.
b. Administer the PHQ-9
c. Pittsburgh Sleep Quality Index (PSQI)

6.11. Day 21: Checkup Phone Call

Study staff will call on Day 21 (+7 days) to determine how the participant is doing with the NW System. Administer:

a. NW Help Calls Questionnaire

6.12. Day 30: Visit 2 - In person follow up

The following events/assessments will occur at the in-person 30-day (+ 7 days) visit.
Health assessments

2. Psychometric Instruments:
    a. Pittsburgh Sleep Quality Index (PSQI)
    b. PSQI Addendum for PTSD (PSQI-A)
    c. PCL-5
    d. Insomnia Severity Index (ISI)
    e. (PHQ-9) (Score of 1 or more on the suicide ideation item [question #9] to trigger a risk assessment by a licensed Behavioral Health Provider if deemed necessary by the PI.)
    f. Epworth Sleepiness Scale ESS
    g. Functional Outcomes of Sleep Questionnaire (FOSQ)
    h. Trauma Related Nightmare Scale (TRNS)
    i. VR-12 Quality of Life (VR-12)
    j. NW Likert Scale for Sleep Quality (NW Likert)
    k. Columbia-Suicidality Severity Rating Scale, Since Last Contact version (C-SSRS)
        i. If deemed necessary by the PI, Study Staff will contact a healthcare provider that has been trained to perform a suicide assessment if there is any risk of suicide.
    l. Blinding Assessment Questionnaire
3. Health assessments

a. Blood Pressure- Blood pressures should be taken while the patient is in a sitting position with their feet flat on the ground after at least 5 minutes of rest. A minimum of 2 blood pressures should be taken 30-60 seconds apart. The average of these two blood pressures should be recorded.
b. Height and Weight to calculate BMI
c. Medication Reconciliation

Every effort will be made to get the subject to the Study Site for an in-person visit. However, if the participant absolutely cannot come in, the assessments can be made by phone or mail and a deviation recorded. Blood pressure and BMI assessments will not be able to be done.

6.13. Day 60: Visit 3 – Patient Questionnaire Assessment

Participants will complete questionnaires on Day 60 (+7 days). Study coordinator will contact participants on Day 62 and after if the questionnaires have not yet been not completed.
Procedures to be done during the call: Questionnaires to be completed:

1. Psychometric Instruments:
    a. Pittsburgh Sleep Quality Index (PSQI)
    b. PCL-5
    c. (PHQ-9) (Score of 1 or more on the suicide ideation item [question #9] to trigger a risk assessment by the PI, and if necessary, a licensed Behavioral Health Provider.)
    d. Epworth Sleepiness Scale ESS
    e. Trauma Related Nightmare Scale (TRNS)
    f. Insomnia Severity index (ISI)
    g. VR-12 Quality of Life (VR-12)
    h. NW Likert Scale for Sleep Quality (NW Likert)
    i. Columbia-Suicidality Severity Rating Scale, Since Last Contact version (C-SSRS)
        i. Study Staff will immediately contact the PI, and if necessary, a healthcare provider that has been trained to perform a suicide assessment if there is any risk of suicide.

6.14. Day 90: Visit 4 – Patient Questionnaire Assessment

Participants will complete questionnaires on Day 90 (+7 days). The study staff will contact participants on Day 92 and after if the questionnaires have not yet been completed. When all questionnaires are completed, the study staff will call or text the participants to confirm that their involvement in the study is complete and to reiterate the instructions on returning the study device.
Questionnaires to be completed:
Health assessments

1. Psychometric Instruments:
    a. Pittsburgh Sleep Quality Index (PSQI)
    b. PCL-5
    c. Insomnia Severity index (ISI)
    d. (PHQ-9) (Score of 1 or more on the suicide ideation item [question #9] to trigger a risk assessment by the PI, and if necessary, a licensed Behavioral Health Provider.)
    e. Epworth Sleepiness Scale ESS
    f. Trauma Related Nightmare Scale (TRNS)

g. VR-12 Quality of Life (VR-12)
h. NW Likert Scale for Sleep Quality (NW Likert)
i. Columbia-Suicidality Severity Rating Scale, Since Last Contact version (C-SSRS)
    i. Study Staff will immediately contact the PI, and if necessary, a healthcare provider that has been trained to perform a suicide assessment if there is any risk of suicide.

Subjects will be allowed to keep the device at the end of the study, but will be given a $100 reimbursement if they return it. The device can only be used for NightWare. No other applications are enabled on the device.

6.15. Reimbursement Plan

Subjects will receive $50 for enrolling and completing study-related surveys at their baseline visit.

At each two-week interval during the Study (Day 15, 30, 45, 60, 75, & 90) study participants will receive $25 for continuing to participate in the study.
Study participants will also receive an additional $25 every two weeks (Day 15, 30, 45, 60, 75, & 90) for wearing the device for ≥70% or 10 of the 15 nights in a two-week period.

Subjects will also receive $100 upon returning the device and completing study-related surveys.

In total, participants will receive between $200-$450 for participating in the Study, which averages up to $5/day.

Study participants will also be reimbursed for any travel expenses if required.

Compensation Table

Study Day	Base Amount	Incentive Amount	Condition of incentive Amount
1	$50		
15	$25	$25	Study device use in 10 of last 15 days
30	$25	$25	
45	$25	$25	
60	$25	$25	
75	$25	$25	
90	$25	$25	
Return of study device		$100	
TOTAL	$200	$250	

7. Statistical Considerations

7.1. Randomization Procedure

The study will use stratified randomization based on study site and whether the participant has a baseline PSQI score equal to or less than 15 versus scores that are equal to 16 or more. This will result in four study strata (groups). See Table #2, below.

Table #2: Assigned ID numbers for different strata-schema

NW RCT Assigned ID's	Study Protocol #	Site Number	1st ID for stratum (low/high PSQI score)	Last ID for stratum	Final ID assigned numbers by stratum
Minneapolis (Mpls) Low PSQI	2	1	001	499	21001-21499
Mpls High PSQI	2	1	500	999	21500-21999
Tampa Low PSQI	2	2	001	499	22001-22499
Tampa High PSQI	2	2	500	999	22500-22999
Walter Reed Low PSQI	2	3	001	499	23001-23499
Walter Reed High PSQI	2	3	500	999	23500-23999
Cleveland Low PSQI	2	4	001	499	24001-24499
Cleveland High PSQI	2	4	500	999	24500-24999
Low PSQI	2	n	001	499	2n001-2n499
High PSQI	2	n	500	999	2n500-2n999

As explained below, throughout the study the Active and Sham Systems will be well balanced in the number of participants from each study stratum. The rationale for imposing balance (equal numbers of participants in each stratum as delineated in table #2, above) based on baseline PSQI score, is that participants with a higher baseline PSQI will have a greater potential for PSQI-score reduction during follow-up, while participants that begin the study with lower scores, will have a correspondingly lower potential for PSQI-score reduction. If these strata were NOT imposed there is a real risk that a higher proportion of participants with LOW starting PSQI-scores would be given the Active System and the HIGH starting PSQI-scores would receive the Sham System. Upon analysis of the strata in this example, any effect that was due to having the Active System would be severely blunted. This would make it seem that the NW System is not as effective as it really is. If, conversely, the Active System was assigned to more baseline HIGH PSQI-scorers, the effect of the NW System could show a much-greater effect than there really is. As explained in the journal JAMA[17]:

The permuted block technique randomizes patients between groups within a set of study participants, called a block. Treatment assignments within blocks are determined so that they are random in order but that the desired allocation proportions are achieved exactly within each block. In a 2-group trial with equal allocation and a block size of 6, 3 patients in each block would be assigned to the control and 3 to the treatment and the ordering of those 6 assignments would be random. For example, with treatment labels A and B, possible blocks might be: ABBABA, BABBAA, and AABABB. As each block is filled, the trial is guaranteed to have the desired allocation to each group.

Participant ID's will be linked to a randomization schedule to be accessed by the unblinded NightWare programmers (who keep the randomization results secret) so that each participant's NW System may be remotely programmed accordingly as either Active or Sham. This remote programming will occur before the subject arrives home with the study device.

The randomization schedule for each of the four study strata will be generated randomly using permuted blocks (as described above) of size two, four, or six. When, for example, a block size of two is used, one participant will be assigned Active and the other will be assigned Sham; for a block size of four, two will be assigned Active and two will be assigned Sham; and for a block size of six, three will be assigned Active and the other three will be assigned Sham. The assignment order within the block will be randomly chosen with equal probability. For example, the assignment order for a block size of two may be Active, then Sham or Sham, then Active; whereas for a block of four the assignment order is realized in six possible ways, and for a block of six the assignment order is realized in twenty possible ways. Due to the many possible randomization schemes possible it will be difficult to predict the next arm assignment, even for someone who is unblinded to the previous assignments and strata information. After each block of participants has been enrolled in a particular study stratum, the two arms will necessarily have the same number of participants from that study stratum. To generate the randomization schedule for each stratum, a string of block sizes, along with their assignment order, will be randomly selected using the software statistical package R v 3.5.1 and subsequently imported into the randomization document to be accessed by the unblinded NightWare programmers as needed.

7.2. Statistical Hypothesis Testing

The primary hypothesis is that NW will improve sleep quality as measured by the Pittsburgh Sleep Quality index (PSQI) relative to sham. On average, compared to the sham, NW will provide a greater reduction in PSQI score measured on day 30 relative to baseline on day 0

Let Y_{ij} denote the PSQI score for the i-th participant at their j-th assessment, j=0,1,2, where j=0 denotes baseline, and i=1,…,n. Let $D_i = Y_{i0} - Y_{i1}/2$, i.e., the difference between the i-th participant's PSQI score at baseline (Y_{i0}) and their average PSQI score across the post-treatment initiation assessment (Y_{i1}). The trial will test the hypotheses

$$H_0: \mu_{Active} \leq \mu_{Sham} \text{ versus } H_A: \mu_{Active} > \mu_{Sham},$$

where μ_{Active} and μ_{Sham} respectively reflect the average difference with NW and sham.

We will evaluate the statistical hypotheses using an equal-variances, two sample t-test. If the equal variance assumption is untenable, we instead will use an unequal-variances, two sample t-test, i.e., Welch's t-test. We will reject the null hypothesis (H_0) that change in PSQI from baseline to day 30 resulting from the active NW system is no better than sham when the two-sided p-value is less than or

equal to 0.05 and the direction of the difference favors NW over sham. In this way, the proposed test controls the one-sided type I error rate at 2.5%.

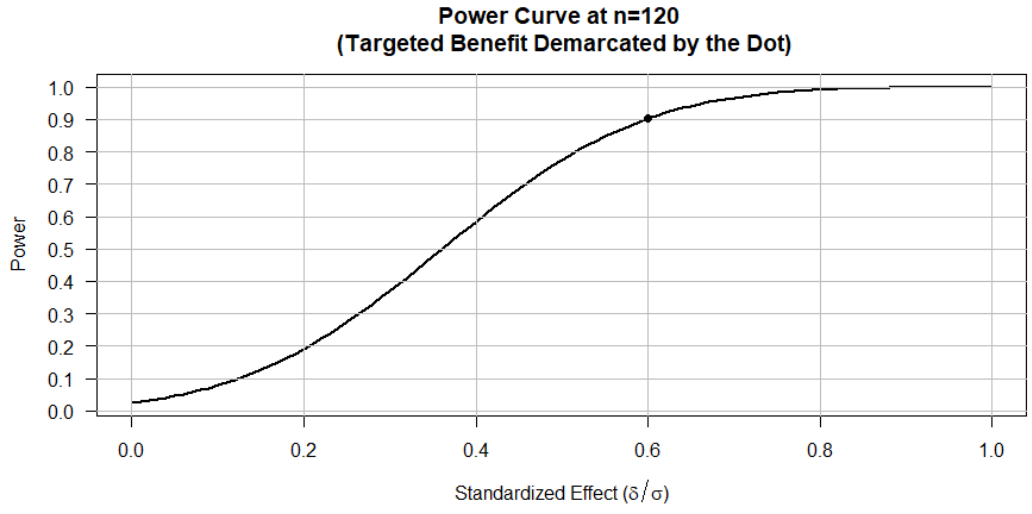
Data will be presented as mean(standard deviation) or median (interquartile range), as appropriate for continuous variables. Categorical variables will be presented as frequency (percentage). Continuous data will be assessed for normality, and transformed as appropriate (e.g. log transformation, square root transformation, etc.). Patient demographics and characteristics will be listed and compared. Continuous
variables will be analyzed by category, intervention vs control, by two-sided t-test or Mann-U Whitney, as appropriate. Categorical variables will be compared by Chi-Square test or Fisher's Exact test as appropriate. The change in PSQI score from baseline to day 30 will be tested via repeated measures tests as determined appropriate by a trial statistician.
Time-to-event analyses will be conducted to determine time to a reduction of PSQI over the longevity of the study (baseline, visit 2, day 30, day 60, day 90). These analyses may be Kaplan Meier survival curves to determine the time to the median population attaining the 3 point decrease. If appropriate,

univariate cox regression models will be used to determine the hazard ratios of PSQI scores. Additionally multivariable, adjusted, models will be evaluated. All analyses will be conducted at = 0.05 to alleviate type II errors.

7.3. Sample Size Determination

A total of 240 veterans and active-duty service members will be enrolled (consented) into the study so that even with attrition of up to 50% of study subjects, we can ensure that the study is completed by a MINIMUM of n = 120 participants (60 in each arm) to reach 90% power for rejecting the null hypothesis under the targeted benefit of $\delta = \mu_{Active} - \mu_{Sham} = 3$ points with an equal standard deviation of $\sigma = 5$ points in each of the two arms. Figure 1 (see below) depicts the power of the trial as a function of the true standardized reduction (δ/σ) in the population assuming we enroll and **retain** a MINIMUM of 60 participants in each arm of the proposed trial. If we get more than 60 participants (i.e. less than a 50% attrition rate) this will just make the study results even more powerful.

Figure 4: Power Curve (total completers- n=120, 50% for each arm)



The rationale for powering the trial to detect a 3-point reduction is two-fold. First, a 3-point reduction constitutes a clinically relevant benefit as this may reflect, for example, a change from 3 (most severe) to 0 (least severe) on a particular item of the PSQI, or a 1-point reduction on three items of the PSQI. Second, assuming a 5-point standard deviation, the targeted 3-point reduction is equivalent to a 0.6 standardized effect, which is plausible as evidenced by a meta-analysis[20] for the observed benefit in previous clinical trials evaluating cognitive behavioral therapies for treating nightmare disorder using the difference between PSQI score at baseline and post-treatment follow-up assessment in which the estimated standard effect size was estimated to be 0.68 (0.34, 1.03). Furthermore, a more recent open-label trial[21] reported a standardized effect size of 1.06. Therefore, the targeted 3-point reduction or 0.6 standardized effect constitutes both a plausible and clinically meaningful benefit in this context.

7.4. Interim Monitoring

The trial will incorporate two interim analyses after 20 and 40 participants in each arm have completed the first 30 days of the trial. Statistical monitoring guidelines will be based on two-sided O'Brien-Fleming boundaries. This conservative interim monitoring plan demands a negligible increase in sample size, so with a MINIMUM of 120 total participants completing, the trial will still be powered at 90% for the targeted benefit. The interim analyses will assess only patient demographics and primary endpoint.

7.5. Primary Safety Analyses

The hypothesis for the primary safety endpoint is that the Active NW System will not lead to worsening of daytime sleepiness as measured by the Epworth Sleepiness Scale, which provides a score between 0 and 24 with higher values indicating a higher degree of sleepiness. Specifically, the hypothesis is that on-average a user of NW will have a mean ESS score measured at 30 days following the start of NW digital therapeutic system use that is not higher than their ESS score measured at baseline. This hypothesis will be tested similarly to the primary efficacy hypothesis using a one sample t-test.
The hypothesis for the secondary safety endpoint is that the Active NW System will not lead to an increase in suicide risk as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline (Day 0) to Day 30. C-SSRS has ratings of "none", "low", "moderate", and "high". Those possible participants rated as "high" on the C-SSRS at Visit 1 will NOT qualify for the study and, if deemed necessary by the PI, will be given immediate assessment by a licensed Mental Health Provider, who will determine the next therapeutic steps. This hypothesis will be tested similarly to the primary efficacy hypothesis using a one sample t-test.

7.6. Secondary/Exploratory Analyses

Secondary and Exploratory analyses will be carried out with appropriate regression modeling techniques and hypothesis tests. In particular, we will use longitudinal data analysis methods, such as generalized estimating equations and generalized linear mixed models, to assess temporal variation in the longitudinal outcome measures, and we will carry out two sample t-tests of the secondary hypotheses.

At the conclusion of the trial, the data will be assessed as both intention to treat (ITT) and per protocol. The effect sizes at the conclusion of the analyses will be compared using standard techniques. If the effect size of the per protocol analysis is greater than 10%, data will be reported as intention to treat to decrease probability of type I errors. Both analyses will follow the outline below:

Secondary outcomes, data will be presented as mean(standard deviation) or median (interquartile range), as appropriate for continuous variables. Categorical variables will be presented as frequency

(percentage). Continuous data will be assessed for normality, and transformed as appropriate (e.g. log transformation, square root transformation, etc.). Patient demographics and characteristics will listed an compared. Continuous variables will be analyzed by category, intervention vs control, by two-sided t-test or Mann-U Whitney, as appropriate. Categorical variables will be compared by Chi-Square test or Fisher's Exact test as appropriate. Longitudinal data will be analyzed by repeated measures tests as appropriate for the variables.

Repeated measure ANOVA will be used to determine the difference in responses at the time points between groups for all survey types and questions, as appropriate. If determined inappropriate Poisson regression models will be used to determine the univariate, univariable, effect size.

Upon secondary outcomes analysis , multivariable, adjusted, models will be used to determine controlled effect sizes. Each variable with a p-value of 0.25 or less in standard distribution test will be included in the model. Backward stepwise regression modeling may be used to best fit the model.

Time-to-event analyses will be conducted to determine time to survey effects over the longevity of the study (baseline, visit 2, day 30, day 60, day 90) for all survey results within the secondary outcomes. Univariate Cox regression models may be used to determine hazard ratios for the survey scores if appropriate.

Correlation coefficients (i.e. Spearman, Pearson) may be used to determine the inter-survey reliability. If determined to be reliable, multivariate analyses may be conducted for surveys.

7.7. Implementation

All statistical analyses will be carried out by the Principal Investigator and/or a PhD Biostatistician.

8. Subject Accountability

Subjects who meet the eligibility criteria and agree to participate will be given written informed consent approved by the center's Institutional Review Board (IRB).

All subjects who meet eligibility criteria and complete the informed consent form are considered enrolled in the study. Screening tests that are part of Standard of Care (SOC) can be used to determine pre-eligibility. Subjects enrolled in this investigation must be followed per this investigational protocol.

8.1. Withdrawal

All subjects enrolled in the clinical study, including those withdrawn from the clinical study or lost to follow-up, shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. Reasons for withdrawal include, but are not limited to:

- Subject found not to meet eligibility criteria
- Subject choice to withdraw consent
- Investigator discretion
- Enrollment ceiling met
- Lost to follow-up, despite best efforts to locate the subject
- Death (see Section 8.3 for reporting requirements)

If a subject withdraws from the clinical investigation, the reason(s) shall be reported in a study data collection system. Data up to the point of withdrawal will be collected. All open adverse events should be closed or documented as chronic.

8.2. Enrollment Controls

Investigational sites will monitor the number of subjects enrolled and will notify NW when the enrollment goal is close to being reached. Once enrollment ceiling is reached, site staff shall discontinue study enrollments.

9. Safety

9.1. Risk/Benefit Assessment

9.1.1. Known Potential Risks

There are no predicate devices used specifically to treat nightmares. However, there are many variations of over-the-counter applications and wearable devices that vibrate to signal the wearer. The same risks known to over-the-counter wearable fitness devices apply to this device.
The NW digital therapeutic is designed to interrupt during a nightmare, but not awaken the individual. The device may instead awaken, or incorrectly diagnose a nightmare and alarm (false positive). Therefore, worsening sleep quality is a potential risk of this device intervention.

9.1.2. Known Potential Benefits

Potential benefits are currently unknown. Uninterrupted sleep due to interrupting nightmares by arousing the subject without waking them, resulting in a more restful sleep, as measured by the PSQI. Improved sleep quality and duration can improve overall psychological effects of sleep deprivation.

9.1.3. Assessment of Potential Risks and Benefits

Study inclusion and exclusion criteria were designed to only include subjects already suffering from sleep disorder and therefore most likely to benefit from the intervention.

Since the intervention is delivered through a non-invasive smartwatch, study participants may simply discontinue wearing the watch if the intervention is contributing to deteriorating sleep quality.

The trial includes a primary safety endpoint designed to evaluate worsening sleep quality:

1. Epworth Sleepiness Scale

The trial also includes a secondary safety endpoint designed to evaluate worsening suicidal risk:

1. Columbia-Suicide Severity Rating Scale (C-SSRS LT) will be administered at the beginning and end of the study.
    a. The Lifetime and Recent version will be used to determine if the subject is suitable for this study.
        i. Potential Subjects that have a rating of “High” will be excluded from this study.

ii. Since a "High" rating is an imminent safety risk, study staff will immediately call/page the PI, and if needed, a licensed staff member to conduct a safety assessment.
    1. If there isn't a licensed staff person available, the subject will be TAKEN to the Hospital Emergency Room.

b. At the 30, 60, and 90 day visits(+7 days), the subject will take another C-SSRS, the Since Last Contact version.
    i. Either an increase in or a "High" score is an imminent safety risk, so study staff will immediately call/page licensed staff member to conduct a safety assessment.
        1. If there isn't a licensed staff person available, the subject will be TAKEN to the Hospital Emergency Room.

9.2. Unanticipated Problems

9.2.1. Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). For this clinical trial, unanticipated problems include, but are not limited to, significant changes in the sleep environment which may impact sleep quality.

9.2.2. Unanticipated Problem Reporting

The principal investigator (PI) will report unanticipated problems (UPs) to the site Institutional Review Board (IRB) and to the sponsor. The UP report will include the following information:

- Report date, IRB Study number, Study Title, Study Staff Contact Information, Date UP occurred, and date PI was notified about the UP.
- Description of the Unanticipated Problem which occurred during the conduct of the research.
- Provide an explanation for why this Unanticipated Problem occurred.
- Characterize the impact of the Unanticipated Problem on the study.

- Describe the steps which have been taken to resolve the reported occurrence.
- Describe the plan implemented to avoid or prevent future occurrences.
- Inform other study participants as necessary.
- Name all other entities to which this UP has been reported.
- Determine if the UP will require modification of the currently approved study and/or consent form.

9.2.3. Serious Adverse Event (SAE) Reporting

A Serious Adverse Event (SAE) is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome (VHA Handbook 1058.01§4.r and 21 CFR 312.32(a)).

Only adverse events and deaths occurring at the site that are 1. serious **and** 2. unanticipated **and** 3. related or probably related to the research need to be reported to the IRB (VHA Handbook 1058.01 §6.a. & 6.b.)

If the event satisfies ALL three of these criteria the event must be reported to the IRB **within 5 business days** of learning of the event. The study sponsor will also be notified within the same time frame.

9.2.4. Adverse Event Reporting

Adverse Events are unfavorable changes in health that occur in trial participants during the clinical trial or within a specified period following the trial.
For this clinical trial, adverse events include any adverse event that occurs as a result of the use or potential use of the study device. An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse events, no later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)). A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

9.3. Death Reporting

Death is reported as is stated in section 8.2.3 Serious Adverse Event (SAE) Reporting.
A death that meets all three criteria for an SAE, as above, shall be reported by Study Staff to the IRB within 5 business days of learning of the death.
A detailed narrative or death letter may be requested by the sponsor including date of death, place, circumstances, cause of death, and whether the death was witnessed or not.

10. Informed Consent

Subject participation in this clinical study is voluntary. Formal Consent is required from each subject and consists of a signed IRB-Approved ICF and signed IRB-Approved HIPAA. The Investigator is

responsible for ensuring that such Formal Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local IRB. The ICF must be accepted by the sponsor and approved by the site's IRB.

The IRB will provide a template of both the ICF and HIPAA documents to investigators participating in this study. Study staff will complete the templates incorporating study-specific information.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to a subject that has the equivalent of a high-school education,
- provide ample time for the subject to consider participation and ask questions, if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.
- The subject will be made aware that they may be in the sham arm of the trial and not receive treatment.

11. Protocol Deviations/Unexpected Problems Reports

A protocol deviation is any noncompliance with the clinical trial protocol. It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity (if the deviation/UP is discovered immediately). All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

Protocol deviations must also be reported in the study data collection system.

12. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigator and study sponsor (if sponsor is NOT the terminating party). If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, and, as necessary, the Institutional Review Board (IRB), and/or the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to their study visit schedule.
terminate
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

13. Data Management

13.1. Data Collection and Handling

Subject data will be recorded on REDCap electronic case report forms. MyCAP, a companion application for REDCAP, will be installed on study device phones and used by the participants to complete questionnaires throughout this study. Data will be entered with a de-identified subject indicator, with a crosswalk file to the subject identifier to be maintained by the investigating site. The electronic files will be maintained as the original study documents. All paper forms will be maintained in a locked office before being entered in the database. Once entered, the paper files will be destroyed.

De-identified data will be entered from REDCap into an SPSS database to perform data analysis.

13.2. Study Records Retention

The Office of Research Development/ Office of Research Oversight (ORD/ORO" Records Control Schedule Guideline (DAA-0015-2015-0004) states:

> All Protocol Files related to the review and oversight of human subjects' research protocols submitted by principal investigators to the IRB shall have a cutoff at the end of the fiscal year after the research project has been completed or terminated. Records will be retained for 6 years after the cutoff.
> Records include, but are not limited to, the application to the IRB; research protocol and amendments; case reports forms; informed consent template and HIPAA Authorization template; reports of adverse events, complaints, and deviations from IRB-approved protocol; data and safety monitoring reports; research findings to date; and all relevant documents and related correspondences between the IRB and the investigators in the review of an associated protocol.

No records will be destroyed without the written consent of the sponsor, if applicable.

14. Abbreviations

The list below includes abbreviations utilized in this protocol.

Abbreviation	Description
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
C-SSRS (LT)	Columbia-Suicide Severity Rating Scale-Lifetime
C-SSRS (SLC)	Columbia-Suicide Severity Rating Scale-Since Last Contact
DAST-10	Drug Abuse Screening Test - 10
DCC	Data Coordinating Center
EEG	Electroencephalogram
EHR	Electronic Health Record
ESS	Epworth Sleepiness Scale
FOSQ-10	Functional Outcomes of Sleep Questionnaire
Ha	Alternate hypothesis
HIPAA	Health Insurance Portability and Accountability Act of 1996
Ho	Null hypothesis
ICF	Informed Consent Form
ICSD-3	International Classification of Sleep Disorders – 3rd Edition
IRB	Institutional Review Board
IRT	Image Rehearsal Therapy
ISI	Insomnia Severity Index
NCT	National Clinical Trial
N-T-F	Note-to-file
NW	NightWare
OSA	Obstructive Sleep Apnea

PCL-5	PTSD Checklist -5
PHQ-9	Patient Health Questionnaire - 9
PI	Principal Investigator
PSQI	Pittsburgh Sleep Quality Index
PSQI-A	PSQI-Addendum for PTSD
PTSD	Post-Traumatic Stress Disorder
VR-12	Veterans Rand 12 health and quality of life survey
REM	Rapid Eye Movement
SOC	Standard of Care
SPSS	Statistical Package for the Social Sciences
TNT	Traumatic Nightmares Treated
TRNS	Trauma-Related Nightmare Survey
UP	Unanticipated Problem
UPR	Unanticipated Problem Report
δ	Delta (gr) – change in measurement (i.e.: PSQI)
σ	Sigma (gr) – variability (i.e.: variance)

15. Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

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17. Appendix A

Excluded Medications	**Use**
Verenicline	Anti-Smoking
Non-dihydropyridines	
verapamil	Calcium channel blockers --affect the heart. Reduce Heart Rate.
Diltiazem	Calcium channel blockers --affect the heart. Reduce Heart Rate.
Beta-Blockers (not ophthalmic)	Reduce blood pressure, slows heart rate.
	Treats: Heart Failure, anxiety, migraines
	May cause: Headache, depression, confusion, dizziness, NIGHTMARES, Hallucinations.
acebutolol (Sectral)	
atenolol (Tenormin)	
betaxolol (Kerlone)	
betaxolol (Betoptic S)	
bisoprolol fumarate (Zebeta)	
carteolol (Cartrol, discontinued)	
carvedilol (Coreg)	
esmolol (Brevibloc)	
labetalol (Trandate [Normodyne - discontinued])	
metoprolol (Lopressor, Toprol XL)	
nadolol (Corgard)	

nebivolol (Bystolic)	
penbutolol (Levatol)	
pindolol (Visken, discontinued)	
propranolol (Hemangeol, Inderal LA, Inderal XL, InnoPran XL)	
sotalol (Betapace, Sorine)	
Timolol (Blocadren, discontinued)	
Alpha Blockers	MUST Taper then be off med for at least 2 weeks before enrolling.