Enhancing Precision Sleep Medicine in traumatic Brain Injury: Examining the feasibility of Home-Based Measurement of Circadian Timing

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Project Title: Feasibility of Home-Based Measurement of Circadian Timing in Veterans with TBI and Insomnia
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I. Hypotheses and Specific Aims:

The purpose of this study is to evaluate the feasibility of two methods of measuring circadian timing (i.e., dim light melatonin onset, or DLMO) in the home environment of Veterans with traumatic brain injury (TBI) and insomnia: 1) direct measurement of self-collected salivary melatonin; and 2) indirect estimation of DLMO using activity and light-exposure data collected through actigraphy. Additionally, this study will evaluate the degree to which circadian misalignment is associated with functional impairment and sleep disturbance.

Aim 1: Evaluate the feasibility of two methods of home DLMO measurement (i.e., self-collected salivary melatonin and actigraphy data) in Veterans with TBI and insomnia.

- Feasibility for each method will be defined as the ability to measure DLMO for ≥70% of participants.
- Qualitative interviews will provide data on user experience to further examine factors impacting the feasibility of each method.

Aim 2: Explore the associations between circadian misalignment, functional impairment, and sleep disturbance.

- Circadian misalignment will be defined as the difference in timing between saliva- or actigraphy-measured DLMO and attempted sleep initiation (i.e., average sleep diary-reported bedtime).
- Functional impairment will be assessed using the WHO Disability Assessment Schedule 2.0.[1]
- Sleep disturbance will be measured via the sleep disturbance module of the Patient-Reported Outcomes Measurement Information System.[2]

II. Background and Significance:

Insomnia is a pervasive problem among Veterans with traumatic brain injury (TBI). Veterans with TBI frequently experience sleep disturbances following their injury.[3,4] Insomnia, an impairing disorder characterized by difficulty initiating or maintaining sleep, is the most common sleep disturbance reported following TBI.[5] Indeed, Veterans with TBI are 50% more likely to develop future insomnia compared to their non-injured peers.[4]

The development of insomnia following TBI can delay recovery and contribute to functional impairments. Compared to TBI patients with normal sleep, those with insomnia have up to eightfold greater odds of functional impairment in the six months after injury.[6] Post-TBI, United States (U.S.) Veterans who had poor sleep were more likely to report pain was interfering with their lives, have diminished health-related quality of life, and perform worse on neurobehavioral measures.[3,7] A large-sample study found that insomnia was associated with decreased life satisfaction both immediately following TBI and one-year post-injury.[8] Furthermore, insomnia is strongly associated with, and can exacerbate, other TBI sequelae such as depression, chronic pain, and fatigue,[3,9] which can further delay rehabilitation and recovery from TBI.

Mechanisms underlying insomnia in TBI are heterogeneous, indicating that a "one-size-fits-all" approach to treatment is likely inadequate. While the precise mechanisms that

underlie insomnia after TBI remain unknown, the extant research suggests that TBI can impact numerous systems that regulate sleep and wake states. Insomnia can result from damage to specific brain regions involved in sleep initiation (e.g., basal forebrain).[10] Widespread brain damage, such as diffuse axonal injury, can disturb sleep through disruption of neuronal signaling, buildup of cellular waste byproducts, and toxic metabolic cascades.[11] Perturbation of hormonal systems are also associated with insomnia following brain injury.[11] Moreover, physical and psychological sequelae of TBI, such as pain, depression, or posttraumatic stress disorder (PTSD), can contribute to insomnia.[10] Therefore, it is necessary to differentiate Veterans who may benefit from standard evidence-based treatments, such as Cognitive Behavioral Therapy for Insomnia (CBTI), and those who may require enhanced treatments targeting specific underlying mechanisms.

One distinct, but understudied, causal mechanism implicated in post-TBI insomnia is disruption to the circadian system.[9,11] Circadian rhythms are changes in biochemical, physiological, or behavioral processes that repeat over the course of approximately 24 hours and are responsive to external cues such as light exposure.[12] A mismatch between circadian and desired sleep timing (i.e., "circadian misalignment") can disturb sleep, manifesting as insomnia or circadian rhythm sleep-wake disorders (CRSDs) like delayed or advanced sleep phase disorders.[13,14] Following TBI, circadian misalignment is common, as seen in perturbations of key circadian rhythms involved in sleep regulation (e.g., melatonin production), as well as the manifestation of CSRDs.[15-17] This may be because TBI dysregulates the expression of circadian clock genes, which in turn is correlated with disruption of day/night activity rhythms.[18] Another potential pathway linking TBI to circadian misalignment is the immune system, which communicates bidirectionally with the circadian system and is activated following TBI.[19] Post-TBI inflammation may induce circadian desynchrony—a lack of temporal coordination across tissues, organs, and molecular processes—thus impairing homeostatic control and driving a pathological feedback loop of further inflammation, circadian misalignment, and resulting sequelae.[12,19] Indeed, many impairments that arise from TBI, including sleep-wake disturbances, are also observed in cases of circadian desynchronization, further implicating circadian misalignment in TBI symptomatology.[19]

Accurate detection, and subsequent correction, of circadian misalignment represents a unique, novel, and modifiable treatment target that has the potential to improve the efficacy of circadian-targeted treatments ("chronotherapies") and functional outcomes for Veterans with TBI and insomnia. Failure to detect circadian misalignment underlying insomnia can lead to a choice of an ineffective intervention.[13,17] Treating circadian-driven sleep disturbances requires specialized treatment approaches, such as timed exposure to light and darkness or melatonin supplementation, that aim to modify the timing or signaling strength of the individual's internal biological clock.[13,14] By acting upon this clock, **chronotherapies** can adjust the timing of sleep-wake cycles and consolidate irregular or fragmented sleep.[20,21] However, appropriate and efficacious administration of chronotherapies requires an understanding of the precise timing of the individual's biological clock (i.e., circadian phase), as the potency of these interventions vary across the internal day and night and can range from salubrious to ineffective or even harmful.[22,23] For example, when unguided by circadian phase, standard sleep interventions, like sleep restriction therapy (the main component of CBTI), may fail to address underlying circadian misalignment or may even exacerbate it.[24,25] Additionally, the degree of side effects associated with acute sleep restriction, such as impaired attention, daytime sleepiness, disrupted mood, and dysregulated autonomic function, depend upon the individual's circadian phase prior to the start of the intervention.[26,27] Thus, accurate measurement of circadian misalignment would not only allow providers to identify when an empirically supported chronotherapy (alone or in combination with other sleep interventions) may be indicated, but it could also help providers optimize the delivery of chronotherapies for insomnia and monitor changes to circadian phase, thereby improving treatment response.

Sleep medicine for TBI is hampered by a lack of pragmatic options for measuring circadian phase. Time of dim light melatonin onset (DLMO) is currently considered the "gold standard" for measuring circadian phase and is an important tool for identifying circadian misalignment in insomnia.[13,14] However, laboratory measurement of DLMO is time and cost

prohibitive, as patients must report to the collection facility 6-8 hours before their typical bedtime, remain in supervised dim-light conditions, and give frequent samples (e.g., saliva) until their bedtime or later.[14,28] Such requirements make the routine measurement of DLMO in clinical settings impractical. Indeed, lack of testing for objective markers of circadian phase like DLMO has been recently highlighted as a significant gap in the identification of circadian misalignment when diagnosing and treating sleep disorders.[14] Alternatives to laboratory DLMO that allow healthcare providers to pragmatically and accurately measure circadian phase are needed to advance precision sleep medicine in TBI.

Novel methods of DLMO measurement have been developed that may enhance the accessibility and practicality of circadian phase assessment; however, their feasibility for Veterans with TBI and insomnia remains unknown. In the past decade, two new approaches for measuring DLMO at home have emerged. The first involves directly testing for DLMO in self-collected saliva samples.[28,29] Although similar to laboratory DLMO measurement, in that Veterans are still required to collect frequent saliva samples under dim light conditions, self-collected saliva allows Veterans to remain in the comfort of their own homes during the collection procedures. This approach could increase uptake of DLMO measurement by clinicians, as it would circumvent the need for a referral to another facility or service. Initial research has shown that obtaining DLMO from self-collected saliva is viable for over 85% of participants, suggesting that patients are able to adhere to collection procedures.[28,29] The second novel approach involves indirectly measuring DLMO from the patient's daily activity levels and light exposure. By employing established mathematical models of the human circadian pacemaker, DLMO can be estimated based on the amount and timing of light exposure throughout the day, as well as the timing of sleep.[30] Excitingly, the data needed for indirect DLMO measurement can be acquired passively via wearable sensor technology, such as a wrist-worn actigraphy device, meaning that circadian phase can be assessed with minimal patient burden. Previous research has achieved high rates of data acquisition using this approach and successfully estimated DLMO with as little as a few days of actigraphy data.[31-33] More important, both home DLMO approaches have been validated against laboratory DLMO in healthy participants[28,33] and participants with disordered sleep,[29,32] suggesting that they can measure circadian phase with enough accuracy to be used in clinical practice.

While these initial findings are promising, additional work is needed before they can be applied to the care of insomnia in Veterans with TBI. Potential barriers inherent to each home DLMO method may limit successful measurement of circadian phase. For example, the requirements of home saliva collection, such as avoiding light exposure and providing samples at prespecified times, may be difficult for Veterans experiencing TBI symptoms like cognitive impairment. Similar difficulties may be encountered when using actigraphy, as Veterans may inadvertently cover the light sensor with clothing or forget to wear the device continuously over the assessment period. Establishing the feasibility of home DLMO methods in Veterans with TBI and insomnia is a vital first step for their implementation in clinical care.

Significance. In summary, there is a crucial need for circadian phase assessment to be made a routine part of insomnia care for Veterans with TBI, yet the primary way of doing so, laboratory DLMO, is rarely used due to its high level of burden. This project will address the above gap by evaluating the feasibility of two pragmatic methods for measuring circadian phase via DLMO in the home environment: direct measurement of DLMO through self-collected saliva and indirect measurement of DLMO via activity and light exposure data. Additionally, this study will be the first direct exploration of the hypothesized relationships between circadian misalignment, functional impairment, and sleep disturbance in Veterans with TBI. Thus, findings from this study may inform the development and testing of tailored sleep interventions for Veterans with TBI, with the goal of enhancing functional outcomes by restoring synchrony between biological timing and psychosocial demands. **For example, accurate and accessible measurement of circadian phase will allow providers to: 1) detect underlying circadian misalignment in insomnia that would otherwise go unnoticed; 2) provide Veterans with TBI with an appropriate evidence-based sleep intervention (i.e., chronotherapy or standard care); and 3) monitor treatment response and adjust accordingly.** Finally, this research has broad implications for a range of populations seeking rehabilitative care, including those with a history of stroke,[34] spinal cord injury,[35] and serious mental illness.[36]

III. Preliminary Studies/Progress Report:

To date, we are not aware of any study examining the feasibility of home DLMO methods in Veterans with TBI. The proposed methods have been validated in both healthy participants[28,33] and participants with disordered,[29,32] suggesting that they can measure circadian phase with enough accuracy to be used in clinical practice.

IV. Research Methods

A. Measure(s):

Ohio State University TBI Identification Method (OSU TBI-ID). Determination of TBI will be made using the OSU TBI-ID[37], a structured clinical interview designed to assess for lifetime history of TBI. Diagnostically, the OSU TBI-ID is consistent with criteria outlined by the American Congress of Rehabilitation Medicine.

Structured Clinical Interview for DSM-5 Sleep Disorders-Revised (SCISD-R). The SCISD-R[38] is a semi-structured interview to assess for common sleep disorders based criteria from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). The SCISD-R fully assesses for sleep-wake disorders that can be diagnosed via interview, like insomnia and CRSDs, and screens for sleep-wake disorders like obstructive sleep apnea that require polysomnographic confirmation.

Structured Clinical Interview for DSM-5 (SCID). The SCID[39] is a reliable and valid semi-structured interview used to diagnose psychiatric disorders in clinical and research settings.

Demographic Form. Information on variables like age, race, ethnicity, sex, gender, and history of sleep treatment will be collected.

Current Medications**.** A list of current medications will be obtained via self-report and chart review.

Morningness-Eveningness Questionnaire (MEQ). The MEQ[40] is a 19-item self-report measure that assesses the degree to which a person is active and alert at certain times of the day.

DLMO. DLMO is considered the most reliable measure of central circadian timing in humans.[28] Actigraphy-based DLMO timing, derived from light exposure and sleep/wake states, will be calculated using the Kronauer limit-cycle model of the human circadian pacemaker.[30] Saliva-based DLMO timing will be calculated using the variable threshold method, in which participant-specific thresholds are defined as two standard deviations above the mean of their first three low daytime melatonin samples; DLMO will be calculated as the clock time that salivary melatonin exceeds this threshold.[28]

Actigraphy. Activity and light data will be passively collected via the use of a wearable sensor (Camntech MotionWatch 8) placed on the participant's non-dominant wrist. Activity data will be used to derive sleep/wake windows which, along with light exposure data, will be used to indirectly model DLMO. Actigraphy has been shown to be a viable method of measuring sleep parameters in individuals with TBI.[41]

Consensus Sleep Diary (CSD). The CSD[42] includes up to 20 self-report items designed by insomnia experts and potential users to standardize sleep self-monitoring. The CSD assesses different aspects of sleep during the previous night and has been shown to be valid and usable in individuals with disordered sleep.[43] The CSD will be modified to include actigraphy-related questions (e.g., times the actigraphy device was removed) and responses will be used to enhance actigraphy-derived estimation of sleep/wake windows.[44]

Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance. The PROMIS sleep disturbance[2] is a 27-item self-report measure with excellent psychometric properties that assesses perceptions of sleep quality and sleep disturbance.

WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). The WHODAS 2.0[1] is a reliable and valid assessment for health and disability that spans six domains of functioning, including cognition, mobility, self-care, interactions with others, life activities, and participation in community activities.

Patient Health Questionnaire-9 (PHQ-9). The PHQ-9[45] is a widely used and validated 9-item self-report measure of depressive symptom severity.

PTSD Checklist for DSM-5 (PCL-5). The PCL-5[46] is a validated 20-item self-report measure of symptoms of PTSD according to DSM-5 criteria.

Qualitative Interview. Additional qualitative questions will be asked regarding the Veteran's experience with the study procedures.

Clinical and diagnostic interviews will be conducted in person or remotely during the baseline screening visit. Additionally, demographics and self-report measures will be administered at this time via REDCap, a secure, HIPAA-compliant web-based application designed for data collection for research studies. REDCap will also be used to capture study diary information during the study, and qualitative interviews will be conducted after data collection procedures via telephone or videoconference.

B. Description of Population to be Enrolled: Potential participants will be all willing and eligible U.S. military Veterans aged 18-64 from the following populations: 1) those seeking outpatient services at the Rocky Mountain Regional Veterans Affairs (VA) Medical Center (e.g., over 1,100 patients with TBI and insomnia in the past year alone, 72% of whom did not have sleep apnea); and 2) those in existing clinical and research databases (the Rocky Mountain Mental Illness Research, Education and Clinical Center [RM MIRECC] research database is comprised of 482 individuals with TBI and insomnia, 338 of whom do not have sleep apnea). Recruitment, inclusion, and attrition calculation estimates (Figure 1) are based on rates noted in previous studies.

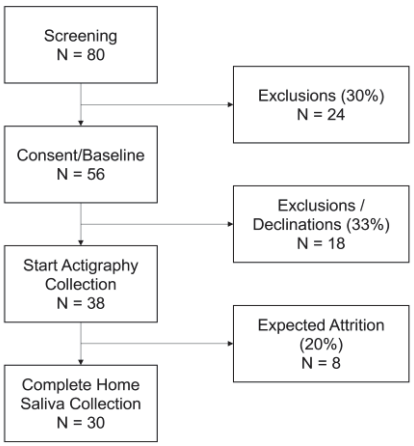

Figure 1. Anticipated Participant Flow

While the above Veterans will constitute the primary study population, caregivers of enrolled Veterans will be invited to complete a collateral interview regarding the Veterans' experiences with the study procedures. Because Veterans may not have a caregiver, and because caregivers will not be recruited independent of Veterans, they will be an optional secondary study population. Caregivers will not be asked to undergo any study procedures other than a brief collateral interview. All data collected will be pertain to the Veterans' experiences.

Inclusion criteria. 1) Age between 18 and 64; 2) History of TBI via the OSU TBI-ID;[37] 3) current insomnia via the SCISD-R,[38] and 4) access to (i.e., internet access) and ability to use Research Electronic Data Capture (REDCap) survey system.

Exclusion criteria. 1) History of alcohol or substance abuse in the past 12 months via the SCID;[39]; 2) history of psychotic or bipolar disorder via SCID; 3) current use of beta-blockers or melatonin supplements/agonists (including over-the-counter or herbal products). Due to their

potential to affect sleep, antidepressants (if taken) will be required to have a current stable dose without changes in the previous month; 4) current participation in a sleep-targeted psychotherapy; 5) transmeridian travel (i.e., change in at least 2 time zones) in past month; 6) shift work (i.e., at least 6 hours between 10 pm and 8 am) in past 6 months; 7) pregnancy/lactation; 8) untreated obstructive sleep apnea (possible or definite) via SCISD-R; 9) lack of access to a home freezer; 10) blindness; and 11) inability to independently provide informed consent. Note: determination of sleep apnea will be based only on self-report (per SCISD-R) and participants with potential or previously diagnosed sleep apnea will be excluded if not receiving treatment. Determination of treated sleep apnea will also be based on self-report (i.e., treatment ≥4 hours per night) and, when available, confirmation via medical records (e.g., documented CPAP adherence).

C. Study Design and Research Methods (Figure 2):

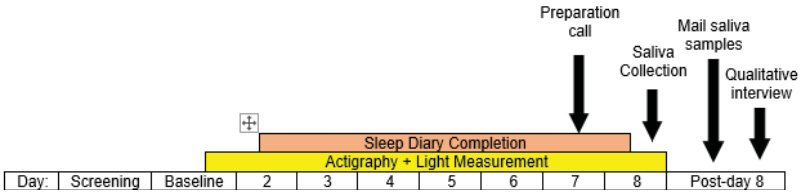

Figure 2. Schematic of study procedures.

Recruitment. Multiple means will be used to inform potential participants (i.e., Veterans with TBI and insomnia receiving care in the Veterans Health Administration) about this research project. This includes letters, flyers, advertisements, presentations, a website, and/or involving professionals treating Veterans. The RM MIRECC recruitment team will assist in recruitment by identifying individuals via existing medical records (e.g., VA Corporate Data Warehouse) using diagnostic codes of interest (e.g., TBI, insomnia). The VA CDW may also be used to obtain names, addresses, and phone numbers of Veterans who may be eligible to participate in the study in order to send information describing the study and inviting participation by mail. We may also send mailings to Veterans who participated in research with the RM MIRECC and consented to be contacted for future research (COMIRB#: 10-0554; i.e., the MIRECC Repository). An initial invitation (see Recruitment Letter) may be sent by U.S. mail from the PI to participate in the study and may include a flyer. Once the letter has been sent, the study team may follow-up via a maximum of three additional letters, emails, or telephone calls.

Screening. A waiver of consent and a HIPAA Waiver of Authorization has been obtained for recruitment and to allow members of the research team to view selected medical charts for screening purposes of patients who contact the PI or study coordinator and express interest in the study. A research team member will explain the procedures to interested participants (via phone or video conference) and complete the screening checklist (see Initial Screening and Verbal Consent Form). A review of medical records may also be done to screen for additional criteria that would exclude participation (e.g., certain medical conditions or prescriptions listed in exclusion criteria, documented sleep apnea treatment) if records are available. If applicable, primary caregivers will be invited to attend screening and subsequent sessions. Those who pass screening will be scheduled for eligibility evaluation and Consent/Baseline, either in person or remotely via Microsoft Teams.

Eligibility, Consent, and Baseline Assessment. For enrollment, informed consent will be obtained from interested participants who pass the initial screening (and caregivers, if applicable, to obtain collateral data). If the baseline visit is being conducted remotely via Microsoft Teams, REDCap will be used to collect the consent signature. A signed and dated copy of the Combined Consent/HIPAA will be made available to the participants, either immediately if the baseline session was in person or via mail if the baseline session was remote. Eligibility criteria will be established via administration of the OSU TBI-ID,[37] SCISD-R,[38] and SCID.[39] Following confirmation of eligibility, a member of the research team will administer other measures via the REDCap survey system. Actigraphy and home saliva collection dates

will be scheduled. At this time, a Preparation call will also be scheduled to take place the day before saliva collection.

Practice Training Session. Following baseline assessment (during the same visit), a practice session will take place, so the participant can learn to use the actigraphy device and the home saliva collection kit (Salimetrics, CA, USA), both of which will be given to the participant at the end of the session along with instructional handouts and a nightlight to be used during collection. At the end of the practice session, a brief skills check (e.g., simulating saliva collection procedures) will be conducted to address any remaining difficulties in understanding the study tasks. Furthermore, the practice session will be piloted with the first four study participants and adjustments to the protocol will be made as needed. A step-by-step video on how to complete saliva collection, produced by Salimetrics and available on their website (https://biologyofsleep.com/pdvideo/) will be provided to participants. Based on study findings, teaching resources will be made public for use by other clinicians and researchers. Participants will be provided with locations of return FedEx facilities (for returning saliva samples) closest to their home. Time to complete Baseline procedures and the practice session is estimated to take 2-4 hours. Participants will be compensated ($30) upon completion of baseline assessment. Those who do not wish to continue following eligibility assessment or those deemed ineligible by the investigators will be paid at a prorated level.

Collection of Actigraphy and Sleep Diaries. For the week prior to their home salivary melatonin collection, as well as the day of home saliva collection (i.e., approximately 8 days), participants will be asked to wear an actigraphy device continuously on their non-dominant wrist. They will be instructed to leave the device uncovered, such as by clothing, to allow the light sensor to function properly. Participants will also be asked to complete a daily sleep diary (5 minutes). They will receive a REDCap email link each morning for electronic data submission. A research team member will provide instructions on how to enter sleep diary data. During the week of sleep diary collection, participants will receive follow-up reminders (either by phone or email) if diary responses are not entered during the day. The RM MIRECC has extensive experience using daily electronic study diaries and achieves completion rates over 90% with current procedures, which is accounted for in the expected rate of attrition for the study. Participants will not be required to change their daily routines in any other way. Participants will be compensated ($25) upon completion of this collection window.

Home Saliva Collection.

Pre-collection/Preparation Appointment. The day before saliva collection, participants will be called to remind them of the process. The research team member will go over each step, ensure participants have the correct collection times recorded, and answer any questions. The saliva kit contains all necessary materials for the storage and shipping of specimens (e.g., 7 pre-labeled cryovials). Along with the saliva kit, participants will be provided with a nightlight to facilitate collection, as well as a handout to guide them through the collection process based on the Salimetrics DLMO Profile Saliva Collection protocol. Participants will be asked to avoid alcohol and caffeine for 24 hours prior to saliva collection and to avoid pitted fruit and bananas during the day of collection. The provided handout will also include self-reported checks for methods adherence (e.g., avoiding food, caffeine), which will supplement the objective light adherence check (see next section).

Collection Day. At 5.5 hours prior to their typical self-reported bedtime, participants will be asked to reduce all sources of light as much as possible. Participants will be asked to remain in dim light (e.g., 40-watt lightbulb exposure or lower, closed blinds) and to reduce all electronic screen brightness as much as possible during the saliva collection process, as light exposure can inhibit melatonin production.[28] The nightlight will be provided to assist in dimming the home. As an adherence check, light exposure during saliva collection will continue to be measured using the already provided actigraphy device. Participants will also be asked to refrain from napping, eating major meals, or brushing teeth during the collection period but will

be allowed to consume light snacks. Saliva collection will then begin 5 hours prior to the participant's typical bedtime. Collection will take place each hour until 7 samples have been obtained (5 hours prior to bedtime until 1 hour after typical bedtime). For the 10 minutes prior to each collection, participants will be asked to refrain from eating any food or drinks other than water and to rinse their mouths with water. At the collection time, participants will be asked to provide passive drool (i.e., unstimulated, uncannulated) using the labeled cryovial and record the collection time. They will be asked to store each saliva sample in the fridge or freezer when actively collecting saliva and then store all saliva samples in the freezer once collection is finished, until they are ready to drop the samples off at a FedEx shipping location for overnight shipping using the prepared shipping label. At this point, participants will also return the actigraphy device either in person or via a prepared shipping label. Return of the provided nightlights will not be required. DLMO timing will be determined by Salimetrics laboratory services. Participants will be compensated ($30) for saliva collection.

Qualitative Interview. A brief qualitative interview will be administered to participants (and caregivers, when applicable), including those who discontinue the study early (if possible). This will provide data regarding user experience with the DLMO methods, including potential facilitators and barriers. The interview will take approximately 15-30 minutes and will be audio-recorded via Microsoft Teams. Participants will be compensated ($15) for interview completion. Caregivers that provide collateral information will also be compensated $15 for their time.

D. Description, Risks and Justification of Procedures and Data Collection Tools: One potential risk includes a loss of confidentiality and/or privacy. Minimizing risks to data security will be achieved by employing safeguards built into the framework of the VA Office of Research and Development (R&D). Electronic data will be stored on a local ECHCS server, the national VINCI servers within the VA firewall, or within the REDCap database at the University of Colorado Denver's (UCD's) Colorado Clinical and Translational Sciences Institute (CCTSI), a secure web-based application designed for data collection in research. Data collected for this study placed on the CCTSI REDCap Database will not be accessed or used for any other study or purposes, and will only be accessed by VA-credentialed personnel. The CCTSI REDCap Database is a highly secure, nationally-utilized data management system, and it is housed within the highly-secure environment at the University of Colorado Denver. Files will be user-restricted and/or password protected so that only members of the research team can access the data. All staff will be required to maintain up-to-date training on data security and patient privacy practices. All physical and electronic sources containing study data will be stored separately from patient identifiers and linked using a separate participant identification crosswalk. Hardcopy data will be stored in locked filing cabinets.

To mitigate risk of inadvertent PHI or PII disclosure during DLMO testing by the off-site service laboratory, participants will be fully informed of the procedures and potential risks associated with the collection and testing of saliva samples. When sent to the service laboratory, no identifying information will be included with the saliva samples, which will be labeled only with a de-identified study code. Neither FedEx nor Salimetrics will have access to identifiable information. Also, samples will only be used to measure DLMO. Upon receipt of the samples, the Salimetrics laboratory will process them for DLMO and then dispose of the samples using a biohazardous waste disposal partner. The Salimetrics laboratory will then send the study team a letter confirming the disposal of the samples along with related details.

Another risk is that participants may experience emotional distress when discussing mental and behavioral health history. The nature of this distress is not anticipated to be greater than that encountered in everyday life and during typical clinical care. We will mitigate risk by informing participants that they can elect not to answer any question and that they may discontinue participation in the study at any time. A licensed clinician be available during business hours, including in-person and remote study visits, to provide support for emergent

clinical situations.

Participants may feel some physical discomfort when wearing the wrist-based actigraphy device due to rubbing/chafing, although this is expected to be unlikely and, if present, of minimal severity. We do not anticipate additional risks regarding use of the actigraphy device as it provides passive and non-invasive measurements.

Finally, during the self-collection of saliva samples, participants may feel some discomfort or tiredness as a result of staying up one hour past their typical bedtime. However, given that the change to their typical bedtime is relatively minor, the likelihood and severity of discomfort from this are expected to be low.

E. Potential Scientific Problems:

One potential challenge is that participants may find it difficult to follow all the different instructions regarding the data collection process, particularly those for the self-collected saliva. To mitigate this, we will be providing thorough guidance through multiple modalities, including an in-person or remote practice session, a preparation phone call, a step-by-step video, and user-friendly handouts and checklists. We will also be checking adherence to methods using a self-report checklist and the actigraphy-based light meter. Furthermore, one of the two primary Aims of this study is to determine if these two methods of DLMO measurement are feasible. If participants find data collection too complicated even with the provided aids, and the qualitative interviews do not identify addressable barriers, then that will be valuable data indicating that alternative methods of pragmatic measurement of either DLMO or other circadian functions will need to be explored.

We may also encounter challenges in recruitment due to the comorbidity- or medication-related exclusion criteria. We hope to prospectively address this by limiting the number of exclusion criteria, such as excluded medications, and making use of the RM MIRECC's established recruitment team.

F. Data Analysis Plan:

Sample Size. To evaluate the feasibility of the DLMO measurement methods and explore the potential clinical utility of circadian misalignment indices, complete data from 30 study participants will be targeted, which is consistent with previously published research on sample sizes in feasibility studies.[47] This will require enrollment of 38 participants to account for the possibility of up to 20% attrition (see Figure 1). To examine feasibility across TBI severity, we will target 15 completers each of mild and moderate-to-severe subgroups. Qualitative interview data will be collected for a subgroup of up to 30 participants (and up to 30 of corresponding caregivers).

Aim 1. Each home DLMO measurement method will be evaluated separately and considered feasible if ≥70% participants provide adequate data for measurement of DLMO. For the self-collected salivary DLMO method, adequate data will entail: 1) collection and return of at least 5 saliva samples; 2) <5 minutes discrepancy between the reported and pre-specified collection times for the two saliva samples ultimately used to establish DLMO; and 3) ≤50 lux of light exposure within 30 minutes of the two saliva samples ultimately used to establish DLMO. For the actigraphy DLMO method, adequate data will entail wearing the actigraphy device for at least 2 continuous days, with no interval of missing data (e.g., from covering the light sensor) during that time greater than 2 consecutive hours. In addition to total sample feasibility, we will also examine feasibility separately for mild and moderate-to-severe TBI groups and evaluate the number of participants who received support from a caregiver to complete the study. Thematic analysis of interviews will provide additional information on facilitators and barriers of each method of DLMO measurement.

Aim 2. Linear regressions will be conducted to explore the association between circadian misalignment (independent variable) and either functional impairment or sleep disturbance (dependent variables). Functional impairment will be assessed using the WHODAS 2.0 summary score.[1] Sleep disturbance will be assessed using the PROMIS sleep disturbance total score.[2] Circadian misalignment will be defined as the difference in time between DLMO and the average sleep diary-based bedtime. Values for circadian misalignment will be calculated for each home DLMO method and evaluated in four separate statistical models. Covariates for all models will include age, gender, depressive symptom severity, and PTSD symptom severity.

G. Summarize Knowledge to be Gained:

Finding that home DLMO measurement is feasible for Veterans with TBI and sleep disturbances will aid the development of a novel assessment and treatment pathway. Alternatively, it is possible that this study will find that one or both methods of home DLMO measurement are not feasible for this patient population. In that case, the results from the qualitative interview will help determine if any addressable barriers exist in the measurement protocols that may enhance feasibility. If neither home DLMO method is feasible, or if indices of circadian misalignment are not associated with sleep or functioning, other methods for measuring DLMO and circadian functioning will need to be explored for use in the treatment of Veterans with TBI.

H. References:

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