Study Title**: Supplementation with Amino Acid Rehabilitative Therapy in TBI (SmARTTBI):**

A Randomized Placebo-Controlled Trial to Improve Sleep

NCT number**: NCT04603443**

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VAPORHCS Research Protocol/Local Protocol Addendum

Title

Supplemental Amino Acid Rehabilitative Therapy in TBI (SmART-TBI)

Specific Aims/Purpose

1. Determine the feasibility and acceptability of BCAA supplementation in Veterans with mTBI.
   a) Feasibility: Recruitment, retention, participation, screen failures, and adherence metrics.
   b) Acceptability: Patient satisfaction with study methods, structured assessment of side effects, and reasons for non-adherence
2. Determine the limited efficacy of BCAA on sleep and related measures in Veterans with mTBI.

Hypotheses:

a) Hypothesis 1 (exploratory): Participants in the BCAA treatment groups will have greater improvement on subjective and objective sleep measures than those in the placebo group.
b) Hypothesis 2 (exploratory): Sleep measures will improve in a BCAA dose dependent manner.
c) Hypothesis 3 (exploratory): Participants in the BCAA treatment groups will have greater improvement on cognition and quality of life measures than those in the placebo group.

Scientific Rationale and Significance

Statement of problem. Exposure to traumatic brain injury (TBI) is very common among US Veterans and military service members and is often comorbid with post-traumatic stress disorder (PTSD).[1–3] One of the principal complicating factors associated with TBI and/or PTSD, is sleep wake disturbances (e.g., excessive daytime sleepiness, insomnia, hypersomnia, circadian rhythm disorders, etc.).[4–6] The prevalence of sleep disturbances following TBI and/or PTSD is ~50-90%,[7,8] and is associated with staggering functional and economic impacts.[9]

Both TBI and PTSD are independently associated with decreased cognitive function and impaired quality of life.[2,10–15] However, impairments in cognition and quality of life are exacerbated in the presence of combined trauma exposure and sleep disturbances.[10,16,17] These long-term physical, cognitive and neurobehavioral impairments associated with trauma-related sleep disturbances very often delay or derail return to the workforce, the community, and family life.[18] Indeed, sleep disturbances exacerbate trauma related symptoms,[19] impact the individual's ability to cope with these symptoms,[20] worsen neuropsychiatric symptoms post-trauma,[21] and inhibit full participation in rehabilitation treatment programs.[22] Thus, in the presence of trauma, sleep disturbances greatly compound the issue by impeding the efficacy of rehabilitative therapies targeted at improving the aforementioned variety of quality of life parameters that are decreased following trauma exposure.[22,23]

Rehabilitative therapies aimed at improving these health outcomes exist, however, they require extensive manpower, suffer from low efficacy and patient acceptability, and largely neglect the involvement of sleep disturbances despite evidence to support sleep disturbances impeding physical and mental rehabilitation following TBI.[22,24,25]

BCAA background. The BCAAs (Leucine, Isoleucine, and Valine) participate directly and indirectly in a variety of important biochemical functions in the brain. These are essential amino acids, meaning they must be consumed directly in the diet and cannot be synthesized endogenously. Dietary BCAA administration has been studied extensively in healthy people and in a variety of disease states over many decades.[26] BCAA therapy has been studied most extensively as it relates to exercise physiology, hepatic pathology, and various neurological and psychiatric disorders. Patients have been treated with BCAAs for variable lengths of time including for more than 2 years.[27] In addition, many athletes consume BCAAs as nutritional supplements for years without adverse ffects.[28] (https://ods.od.nih.gov/factsheets/ExerciseAndAthleticPerformance-HealthProfessional/).
Previous work in rats has determined the safe upper limit of leucine consumption, determined by the point at which leucine oxidation plateaus, is 8.9 g/kg bodyweight (equivalent to ~600 g leucine/day in a 70 kg human).[29,30] Finally, a current randomized controlled clinical trial evaluating BCAA supplementation in acutely concussed adolescents and adults is administering doses between 60 and 15 g/day for a duration of 21 consecutive days (clinicaltrials.gov identifier: NCT01860404).

BCAAs have widespread beneficial effects, such as promoting muscle protein synthesis in peripheral skeletal muscle, as well as promoting neurotransmitter synthesis in the brain. Specifically, BCAAs are the precursors to ~50% of de novo glutamate and GABA (i.e., the principle excitatory and inhibitory neurotransmitters of the CNS, respectively) synthesis in the brain.[26,31,32] This is the primary link between dietary BCAA supplementation and potential changes in brain function. Additionally, a major fraction of dietary BCAAs are not metabolized by the liver and freely pass into the systemic circulation causing plasma concentrations to rise rapidly after ingestion and in proportion to their dose (or content via solid food). BCAAs in the plasma are able to pass through the blood brain barrier by a CNS endothelial cell transporter. This specific transporter also moves a variety of other amino acids across the blood brain barrier relative to amino acid concentration gradients, and thus, in the face of increased plasma BCAA concentration, CNS BCAA concentration rises and the concentration of competing amino acids (e.g., tryptophan, tyrosine, and phenylalanine) decreases. These competing amino acids are precursors to other neurotransmitters (i.e., monoamines and catecholamines). Therefore, BCAA consumption in isolation, rather than in the presence of other amino acids (e.g., in a liquid protein shake or solid food meal) produces changes in overall CNS biochemical composition.

Previous work in humans have explored the therapeutic use of BCAAs in health and disease. BCAAs have been used in athletes to improve physical performance and mental concentration/focus during training and competition.[33] The rationale being that prolonged or intense exercise causes depletion of BCAAs within a) the muscle, negatively impacting muscle bioenergetics and accelerating peripheral fatigue and b) the plasma, resulting in an increase in CNS uptake of tryptophan, synthesis of serotonin, and promotion of central fatigue. BCAAs have been used in patients with phenylketonuria, a genetic metabolic disease that prevents the conversion of phenylalanine to tyrosine and causes elevated levels of plasma phenylalanine. Thus, supplementation with BCAAs, which inhibits the transport of phenylalanine into the brain helps promote normal CNS phenylalanine levels.[27] Dietary BCAA supplementation has also been used in patients with hepatic cirrhosis, demonstrating the safety of additional dietary protein in the face of liver dysfunction. Hepatic cirrhosis causes elevated levels of similar competing amino acids (e.g., tryptophan, tyrosine, and phenylalanine) due to a reduced ability to metabolize these amino acids. Therefore, raising plasma BCAA concentrations has been shown to help normalize CNS neurotransmitter composition.[34,35] Finally, BCAAs have been studied in a variety of psychiatric and neurological disorders, including as a treatment for bipolar disorder (by reducing tyrosine uptake and preventing manic episodes), in schizophrenic patients with impaired motor control (by reducing the relative concentration of CNS phenylalanine concentrations), as a treatment for amyotrophic lateral sclerosis (by restoring a more normal cortical excitation:inhibition ratio), in patients with spinocerebellar degeneration[36] or cancer[37] (both as a means to promote metabolic rate and prevent muscle wasting).

In the context of trauma exposure and BCAA supplementation in humans, there have been no prior studies related to PTSD, and only limited work related to TBI. These TBI related studies have predominantly been in the context of severe TBI (i.e., TBI requiring hospitalization), but nevertheless have reported a reduction in plasma BCAA levels in the acute post-injury period[38,39] and up to 17 months after injury,[40] that BCAA supplementation improves cognitive recovery post-injury,[41,42] and that BCAA supplementation improved cerebral oxygen consumption.[39] In addition to this already published work, there is one on-going clinical trial (clinicaltrials.gov identifier: NCT01860404) exploring the potential for dietary BCAA supplementation to improve cognition post mild sports related TBI in young adults (ages 11-34). This study is also exclusively examining the acute injury phase, with subjects needing to be <72 hours post-injury to be enrolled.

Rationale for BCAAs to effect sleep and cognition. The mechanistic link between trauma exposure and poor sleep and cognition has been proposed to stem from an impairment in cortical network excitability. Alterations in network excitation and inhibition affect orexinergic neuronal activity in the lateral hypothalamus and hippocampal function, thereby impairing sleep-wake regulation and cognitive performance.

In the context of sleep, previous work by the PI on this protocol (Dr. Lim) and our group has shown that sleep-wake regulation is significantly impaired in a preclinical model of head trauma (i.e., TBI induced via controlled cortical impact and fluid percussion injury in mice).[43,44] Coincident with these sleep impairments we also showed a reduction in orexin neuronal activation[43], a finding that has been replicated in other work in mice[45] and rats.[46] Importantly, dietary BCAA supplementation for 5 days[44] restored normal sleep-wake regulation and orexin neuronal activation.[43] Although the mechanism was unknown, we hypothesized based on the aforementioned rationale, that BCAA supplementation would restore normal cortical excitation that would

translate to increased hypothalamic orexinergic activity. Evidence to support this mechanistic link was published this year in the journal *SLEEP* based on work conducted here at the VA Portland Health Care System.[47] This worked showed that cortical wide glutamatergic inputs were increased following BCAA supplementation in an identical preclinical model of brain trauma.[47] It remains to be determined whether this simple, benign, and rapidly deployable dietary therapy can be translated to Veterans with a history of trauma exposure to improve sleep quality.

In the context of cognitive function, previous work by our group in a similar pre-clinical model of trauma has demonstrated that the hippocampus, a brain structure involved in higher-order cognitive function has reduced BCAA levels and that dietary BCAA supplementation restored hippocampal BCAA levels to pre-trauma levels.[48] Furthermore, the cognitive dysfunction associated with trauma exposure in this preclinical model was restored following dietary BCAA supplementation.[48]

Summary. Therapeutic strategies that are cost effective, minimally burdensome, and effective at improving sleep and cognitive function post TBI are desperately needed. Dietary BCAA supplementation holds significant potential based on the extensive pre-clinical data generated by our group, and has been repeatedly shown to be well tolerated and safe in healthy humans and in a variety of disease states. Furthermore, dietary BCAA supplementation has not been examined in humans (including Veterans) in the chronic phase of recovery from trauma (including TBI).

Research Design and Methods

Individuals will be recruited for participation in this study after determination of eligibility. For full details regarding the informed consent process, eligibility criteria, and specific recruitment strategies, see the *Subject Identification/Recruitment* section. Briefly, a total of n=200 subjects will be targeted for enrollment: n=50 subjects assigned to each of the four treatment groups – the target sample size is powered for feasibility and is based on the rationale below.

Patients meeting inclusion/exclusion criteria will be included in this study, regardless of gender or racial/ethnicity status. For full details see the *Study Population* section.

It is required for participants to allow their data/specimens to be placed in Dr. Lim's Repository #4086 (*Morning Bright Light for Sleep Data Repository*) in order to participate in this study. Our lab's overarching goal is to conduct long-term analysis of outcome measures of TBI and sleep disturbances, including critical questions related to chronic traumatic encephalopathy and other neurodegenerative/dementia-related outcomes. Given that this study will invest considerable resources in enrolling a large cohort of subjects with TBI and sleep disturbances, required banking is the most judicious use of limited resources and will provide a large return on investment for this valuable cohort.

If any data collection activity described in this protocol is collected for a participant under another protocol's consent and is subsequently contributed to Dr. Lim's Sleep & Health Applied Research Efforts repository (OHSU IRB#24823), this protocol may request that data from the repository instead of requesting duplicate data collection activities.

Timeline of Visits

The study timeline will ideally consist of up to 7 visits (with additional visits for supplement pauses as needed), conducted either in person or via video or phone, or any combination thereof. (as described below):

Due to travel burden to subjects and risk of exposure due to infection (e.g. COVID-related or otherwise), research visits, including consent, may be conducted remotely via home visits, or video conferencing visits. In this case, we will record their home address prior to consent (to mail consent docs, questionnaires for televisits, and to come to their home for home visits). Home address will be provided by the interested participant and stored on secure VA masterlist. For video conferencing and for initiating DocuSign services where feasible, we will record the potential participant's email address in order to initiate emailing of DocuSign consent links or to send them the VA Video Connect (VVC) or other VA approved

teleconferencing service links to allow for secure video sharing. This email will be provided by the participant and stored on a secure VA masterlist.

Visit 1: Establish baseline period

Subjects will undergo the following activities:

- *Informed consent and HIPAA authorization.* (may be in person or remote through video chat) Written and verbal informed consent will be obtained. In the event that a participant is unable to come in person, video or telephone consent will be obtained in one of the following ways:
    - *Mailed-* Hard copy of the ICF and HIPAA forms would be mailed to the potential participant and an appointment would be scheduled to review the forms over phone or video. If they agree the participant will sign the form and mail back to the study team. The study team member will then sign and mail back the fully executed signed copies to the participant.
    - *DocuSign-* Where DocuSign is feasible, study staff will initiate the emailing of a DocuSign envelope providing subjects links to the consent and authorization forms ahead of the consent discussion. Subjects will then be guided through downloading the fully executed consent form.
- Questionnaires including the Head Trauma Events Characteristics (HTEC) form may be filled out prior to VA study personnel receiving signed consent forms back in the mail, but the rest of the study activities described below will not occur until the signed consent and authorization has been received.
- If TBI, PTSD, and/or depression is indicated on surveys, individuals without a VA medical record will be asked for permission for study staff to request their medical record to confirm or examine further information regarding these issues.
- Participants capable of becoming pregnant will be asked to provide assurance that they are not pregnant, trying to conceive, or nursing. If a subject responds that pregnancy is possible, they may be given a standard urine pregnancy test if requested.
- *Diagnostic TBI interview.* (May be in person or remote through phone/video chat) Subjects will undergo a structured diagnostic interview adapted from the Head Trauma Events Characteristics (HTEC), administered by the Study Neuropsychologist or appropriately trained research staff with expertise in TBI. The HTEC form was originally proposed in the 2009 VA/DoD Clinical Practice Guideline for Management of Concussion/mild Traumatic Brain Injury (mTBI) in an effort to better triage patients with suspected TBI history.[79] It is used to evaluate TBI symptoms to characterize the initial injury and determine whether the symptoms are temporally related to the event characterized as a concussion/mTBI. Through semi-structured diagnostic interviewing, detailed information is gathered about a patient's injury characteristics so an estimation of injury severity and corresponding prognosis and treatment guidelines can be obtained.
- *Actigraphy watch.* (May be given in person or mailed) Subjects will be given a fully charged and individually configured actigraphy watch (Phillips Respironics Actiwatch 2) to wear for the duration of the study. This actiwatch collects data related to subject's sleep-wake cycle including activity (via a built-in accelerometer) and light exposure (via a built-in luxometer). Actigraphy has been validated against the gold-standard in-lab polysomnography in healthy humans as well as those with chronic insomnia and depression.[49] Watches are user-friendly, requiring no user input to operate. Data will be directly written to the watch and viewable only through data download on study team computers.
- *Bedmat.* (May be given in person or mailed) Subjects will be given an individually configured bedmat (EMFIT Inc.) to place under their mattress for the duration of the study. The bedmat collects data related to time in and out of bed and overall restlessness during sleep via piezo sensors; it also collects approximate heart rate and breathing rate. Data will be directly written to an SD card attached to the bedmat or uploaded via cellular or via WiFi connection to a secure online database from which it will be written to an SD card. Inclusion of Wifi connected bedmats allows data collection in homes with poor cellular connectivity. Bedmats require minimal or no user input to operate and data is viewable only through data download onto study team computers. (See Information Management section of this protocol for further details.)
- *Sleep diary.* (May be given in person, mailed, emailed, or texted) Subjects will be given a daily study diary with instructions on how to complete it so they can record when they go to bed, when they wake up, and at what time they consumed their assigned study treatment each day. Study diaries will be coded with a study ID with no other identifiable information. Sleep diaries will be either on paper or

completed electronically through a REDCap link, which may be emailed or texted using the automated Twilio service.

- *Pain testing.* Cold Pressor Test. (may be in person or mailed) The cold pressor test may be used at VAPORHCS and at visits that are conducted remotely. This test will consist of an ice bath that subject's are instructed to submerge their non-dominant hand into. Threshold and Tolerance will be measured with a stop watch. Threshold will be determined by the amount of time that the subject perceives the temperature as mildly painful. Tolerance will be determined by the amount of time that causes the subject to withdraw their hand. This will be done during a single trial. The upper limit of allowing the hand in the icebath is 5 minutes.
- *Overnight Polysomnography (PSG).* (May be in person at VAPORHCS or the Somnomedics at home sleep test may be given in person or mailed). Subjects will undergo either an attended, Type I polysomnography or unattended, Type II home sleep test using Somnomedics at home sleep testing collected according to American Academy of Sleep Medicine lab guidelines. Subjects may need to undergo more than 1 night of testing depending on data quality, lack of sleep, or other issues.
- *Questionnaires.* (May be completed in person or remotely at home). Subjects will complete baseline questionnaires administered either on paper or electronically. In total, these surveys take ~20-30 minutes to complete and include past medical history as well as self-reported measures on sleep, social habits, quality of life, mental health, pain/sensory sensitivity, and other metrics related to subject's prior trauma exposure history. These may be completed electronically, where an email is generated through RedCap that contains the link to the questionnaires. Participants will need an internet connection or cellular data in order to complete questionnaires electronically.
- *Cognitive testing.* (May be completed in person or remotely through video chat) Subjects will engage in a series of standard neuropsychological tests either administered by trained study personnel or adapted to electronic delivery. Testing will include evaluations of domains related to memory, attention, executive function, language, and processing speed. Instruments that may be used in evaluation may include but not be limited to; the Wide Range Achievement Test- IV (WRAT-IV; Reading subtest), the Hopkins Verbal Learning Test – Revised (HVLT-R), the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Digit Span subtest, Symbol Search subtest, and Letter-Number Sequencing subtest), and Delis-Kaplin Executive Function System (D-KEFS; Trails subtest, Verbal Fluency subtest, and Color-Word subtest). Audio recordings may be made to allow review and confirmation of details recorded by study staff.
- *Blood draw*. (Only completed in person. Not completed if visits are 100% remote) Subjects may provide a blood sample consisting of 2-3 Lavender and 2-3 Tiger top tubes, each 7 ml in volume, such that both plasma and serum samples can be collected. Study personnel will process and aliquot samples, code them with the Subject ID, and store them at -80ºC in a locked freezer. Samples will be coded and labeled with only subjects' study ID.
- *PharmChek Sweatpatch.* (May be given in person or mailed to be completed at home) Biomarkers including markers of neuronal injury and cytokines will be collected using a sweat patch that participant's will be instructed to wear for 12-72 hours. They will be instructed to place it on their abdomen and avoid being fully submerged in water (showering is okay). They will be mailed at room temperature to the VA where they will be stored in a -20 freezer until analysis. They will be coded and labeled with the subject's study ID and the timepoint.
- *Oragene saliva collection.* (May be given in person or mailed to be completed at home) Saliva will be collected using the Oragene saliva collection kit for DNA analysis. Participants will provide about 2 mL of saliva into the Oragene tube that will then be labeled with subject ID and timepoint and stored at -80C in a locked freezer. This may be mailed to the VA using tertiary containment if the visits are completed remotely, or this can be completed at the VA.
- *Reimbursement.* (May be given to subjects or mailed). Subjects will be compensated $120 for completing each night of overnight polysomnography ($10/hr x 12 hrs, maximum of 2 nights as needed for good quality sleep data), $20 for questionnaires, $20 for cognitive testing, and $20 for the biomarkers. Thus, subjects may be eligible to receive a maximum of $300 at the end of this visit.

Subjects will engage in a period of baseline monitoring for a minimum of 2 weeks before being randomized to a treatment group. This baseline period will provide data on subjects' normal sleep-wake cycle (including study diary, actiwatch, and 1-2 nights of overnight PSG). During this time, subjects will consume 20 ounces

of water in the morning and afternoon without BCAAs or placebo to familiarize subjects with the potential increase in water consumption they will experience following this baseline period.

Visit 2: Receive/start study drug
Subjects will undergo the following activities:

- *Randomization.* See Randomization section below for further details.
- *Drug dispensing. (*May be given in person or mailed) Study personnel will arrange dispensation of a maximum of 3 months' worth of BCAA or placebo over the course of the study. Subjects will receive 2 to 4 weeks' worth of study drug at a time and be given a short tutorial during visit 2 on how to empty the contents of each foil pouch into an empty shaker bottle, fill the bottle to the 20 oz indicator line, and thoroughly dissolve the powder into solution before consuming the liquid.
    - Subjects will also be offered flavoring powders to improve palatability as needed, these may include: raspberry lemonade flavor (Crystal Light brand), unsweetened orange, lemon, lime (TrueCitrus brand), or unsweetened lemon, orange, pink lemonade (Kool Aid Brand). If none of these can be used to improve palatability, subjects may be provided with $20 Kroger brand gift cards with which to purchase their choice of flavoring amendment as needed.
- *Recharge and replace actigraphy watch.*
- *Reimbursement*. *(*May be given in person or mailed) Subjects will be compensated $20 for coming to Visit 2.

During the (up to 12-week) experimental period in which subjects consume their assigned treatment, study personnel will make weekly calls to answer questions, troubleshoot palatability issues, and ensure participants are answering the daily sleep diary and taking the study drug as prescribed. The 4 week supplementation periods may be extended to accommodate pauses in supplementation as needed. If subjects report any side effects from taking the study supplement, a brief phone call will be scheduled to record their responses on the Monitoring of Side Effects Scale (MOSES) form and a covid questionnaire may be collected if indicated.

If subjects are not able to tolerate the full 20oz study supplement twice a day, they may switch to adding both packets to the morning 20oz drink, drink half, and refrigerate the rest until they drink the other half in the afternoon. Alternately, they may try to consume the supplement once a day instead for the remaining duration of the study.

Visits 3-4: Assess interim effects of study drug (every 4 weeks)
Subjects will undergo the following activities:

- *Drug Accounting/dispensing. (*May be given in person or mailed) Subjects will retain all used packets for accounting. These will be reviewed with staff for study accounting and then discarded. The next 4-weeks' of taking study drug may commence. (Dispensing may be every 2 weeks or 4 weeks as appropriate)
- *Actigraphy watch*. *(*May be given in person or mailed) Actiwatches will be downloaded and a replacement watch issued for the next 4 weeks.
- *Bedmat.* Bedmat data will be downloaded.
- *Sleep diary*. *(*May be given in person, mailed, emailed, or texted). Subjects' sleep diaries will be reviewed and new sleep diaries may be provided.
- *Questionnaires.* (May be completed in person or remotely. May be mailed, emailed, or completed within Redcap as described for visit 1). Subjects will complete questionnaires with the same surveys as in the baseline period, including measures related to sleep, cognition, mental health, pain/sensory sensitivity, and quality of life. In addition, they will complete a structured assessment of side effects as well as surveys to assess aspects of patient satisfaction with the study protocol, study drug, equipment, and staff.
- *Blood draw.* (Not completed if visits are 100% remote) Subjects may provide a blood sample as described in the baseline period.
- *Sweat patch.* (May be given in person or mailed to be completed at home). Subjects will provide a sweat sample as described in the baseline period.

- *Saliva sample.* (May be given in person or mailed to be completed at home if not collected during baseline). Subjects may provide a saliva sample as described in the baseline period.
- Monitoring of Side Effects Scale (MOSES) conversation to capture any unreported side effects.
- *Reimbursement*. (May be given in person or mailed). Subjects will be compensated $20 for completing the questionnaires and $20 for the biomarkers. Thus, subjects are eligible to receive a maximum of $40 at the end of each of these visits.

Study pause and/or early supplementation stop activities: (as needed per subject or investigator)
These visits may occur more than once per subject and will be reimbursed as described for the visits these duplicate or replace.

Subjects completing *5 days of supplementation or more* who:

- Cease supplementation - will be asked to participate in Visits 5-7 as described below. If further visits are declined, at minimum they will return study equipment, perform drug accounting, be asked to complete a Monitoring of Side Effects Scale (MOSES) conversation, a covid questionnaire if indicated, and participant study satisfaction survey.
- Pause supplementation - will be asked complete Visit 5 activities as described below with the following exceptions as appropriate:
    - Not returning the bedmat/thermometer
    - Potentially returning/receiving new actiwatch as needed
    - Omitting or substituting the Visit 5 questionnaire battery with the supplement pause questionnaire and a covid questionnaire if indicated.

  These individuals will return to supplementation when ready (ie travel completed, illness recovery, side effects subside, etc…) continuing the normal visit schedule from where they left off.

Subjects completing less than a total of 5 days of supplementation who:

- Cease supplementation will be asked to return all study materials, perform drug accounting, and complete a Monitoring of Side Effects Scale (MOSES) and participant study satisfaction survey. No further visits will be required.

  Pause supplementation may be asked to complete a Monitoring of Side Effects Scale (MOSES) conversation and a covid questionnaire if indicated. These individuals will return to supplementation when ready (ie travel completed, illness recovery, side effects subside, etc…) continuing the normal visit schedule from where they left off.

Visit 5: Assess final effects of study drug
Subjects will undergo the following activities:

- *Drug Accounting.* (May be reviewed in person or via video visit with staff). Subjects will retain all used packets for accounting. These will be reviewed with staff for study accounting and then discarded.
- *Equipment Return.* (May be returned in person or mailed). Subjects will return their actigraphy watch, bedmat, and sleep.
- *Overnight Polysomnography.* (May be in person at VAPORHCS or the Somnomedics at home sleep test may be given in person or mailed). Subjects will undergo either an attended, Type I polysomnography or unattended, Type II home sleep test collected according to American Academy of Sleep Medicine lab guidelines, identical to the procedure as described in Visit 1.
- *Questionnaires.* (May be completed in person or remotely. May be mailed, emailed, or completed within Redcap as described for visit 1). Subjects will complete the same validated questionnaires as in Visits 3-4 as well as a participant satisfaction survey.
- *Cognitive testing.* (May be completed in person or remotely through video chat). Subjects will engage in the same standard neuropsychological tests as in Visit 1.
- *Pain testing.* (May be completed in person or remotely through video chat). Subjects will repeat the cold pressor test as described in Visit 1.

- *Blood draw.* (Not completed if visits are 100% remote) Subjects may provide a blood sample as described in the baseline period.
- *Sweat patch.* Subjects will provide a sweat sample as described in the baseline period.
- *Saliva sample.* Subjects may provide a saliva sample if not collected during baseline.
- Monitoring of Side Effects Scale (MOSES) conversation to capture any unreported side effects.
- *Reimbursement.*Subjects will be compensated $120 for completing each night of the overnight PSG (up to 2 nights), $20 for completing the questionnaires, $20 for completing cognitive testing, and $20 for the biomarkers. Thus, subjects may be eligible to receive a maximum of $300 at the end of this visit.

Visits 6-7: Assess persistence of effects after cessation of study drug (after 4 and 12 weeks)
Subjects will undergo the following activities:

- *Questionnaires.* (May be completed in person or remotely. May be mailed, emailed, or completed within Redcap as described for visit 1). Subjects will complete the same validated questionnaires as in Visits 3-4.
- *Blood draw.* (Not completed if visits are 100% remote) Subjects may provide a blood sample as described in the baseline period.
- *Sweat patch.* (May be given in person or mailed to be completed at home). Subjects will provide a sweat sample as described in the baseline period.
- *Saliva sample.* (May be given in person or mailed to be completed at home if not collected during baseline). Subjects may provide a saliva sample as described in the baseline period.
- *Reimbursement*. (May be given in person or mailed). Subjects will be compensated $20 for completing the questionnaires and $20 for the biomarkers. Thus, subjects are eligible to receive a maximum of $40 at the end of each of these visits. An additional $20 may be compensated for necessary activities such as mailing costs incurred by subjects.

Drug Dosing, Quality Assurance, and Randomization.
After providing baseline data following Visit 1, subjects will be randomized into 1 of 4 groups:

1. **High dose BCAA group**: 60 grams of BCAA consumed in two doses (30 grams each) mixed into 20 oz of water for up to 12 weeks (168 total drinks).
2. **Medium dose BCAA group**: 40 grams of BCAA consumed in two doses (20 grams each) mixed into 20 oz of water for up to 12 weeks (168 total drinks).
3. **Low dose BCAA group**: 20 grams of BCAA consumed in two doses (10 grams each) mixed into 20 oz of water for up to 12 weeks (168 total drinks).
4. **Placebo group**: 20 grams of rice protein, consumed in two doses (10 grams each) mixed into 20 oz of water for up to 12 weeks (168 total drinks). Rice protein is low in BCAA content but has the same amount of total protein content as the high dose BCAA group. Use of this placebo will control for any potential effects due to consumption of protein in general.

Randomization will occur after inclusion screening and baseline data collection. Subjects will be randomized to a BCAA or placebo arm using a covariate-adaptive design.

BCAA and rice protein powder will be purchased through the company BulkSupplements©, which has FDA approval for Good Manufacturing Process (GMP; registration #17938017996; see Letter of Support). Study drug with or without flavoring will be packaged into opaque, sealed foil pouches and the contents of the pouches will be blinded such that investigators with direct contact with subjects and the subjects themselves will be unaware of treatment assignment until the study is completed or if early unblinding is necessary (e.g., for clinical/patient safety reasons, or *a priori* planned interim analyses). Subjects will be advised not to consume multiple doses in the event they forget a dose. The exact duration given to consume a given dose is not prescribed, although less than 60 minutes and on an empty stomach is recommended with a warning to sip the product to help prevent gastrointestinal upset until individuals have a chance become more accustomed to the supplement. Part of this discussion may include advice to experiment with adding flavorings a little at a time until the drink becomes palatable enough to sip.

We may communicate via RMS Azure encrypted email, secure messaging (e.g., MyHealthE Vet), text message using a google voice number (no PII or PHI), or phone if participants have questions or concerns.

The sleep diary may be completed by daily RedCap surveys that are texted using the Twilio service. Twilio is a cloud based service that automates text messages. Twilio will access RedCap for a participant's phone number, but no other data will be stored. If participants indicate that they are open to receiving them, Twilio or other equivalent service may also be used to generate automated text message reminders by which subjects may confirm their upcoming study visits.

Study Population

Number of Subjects. A target enrollment of n=200 subjects will allow for n=50 subjects per group (e.g., high dose BCAA, medium dose BCAA, low dose BCAA, and placebo). The sample size was chosen to fulfill the primary study aim, which is to examine feasibility, acceptability, and limited efficacy outcomes. In our pilot study using a 3-week duration, approximately 15% of subjects were unable to be included in analyses for various reasons, including missing data. In addition, we anticipate an additional 25% dropout due to the longer duration of the study timeline (2 weeks baseline + 12 weeks intervention + 12 week follow-up). Thus, we expect ~n=30 completers per arm, which will give us a comfortable target to assess feasibility, acceptability, limited efficacy, as well as to conduct exploratory analyses on subpopulations. This large number of subjects will be necessary in this feasibility study in order to accurately estimate parameters for future sample size/power considerations in the larger RCT (randomized controlled trial). Finally, we are confident we can easily achieve the new enrollment target, given our track record of recruitment for other sleep research studies (~5 subjects per month from clinical referrals, ~5 subjects per month from poster flyers, and n=1000+ subjects enrolled in Dr. Lim's VA IRB-approved data repositories available for additional research studies such as this).

Eligibility Criteria. All subjects must:

1. Be Veterans 18-65 years of age (male and female; any race)
2. Be English speaking
3. Be accessible via phone
4. Be non-decisionally impaired
5. Provide assurance that they are not pregnant, trying to conceive, or breastfeeding (if female). As needed, a urine pregnancy test may be provided upon request and all study subjects must agree to using an accepted method of contraception.)
6. Attest to no history of maple syrup urine disease or phenylketonuria
7. Have either a history of self-reported sleep disturbances, either as determined via the Insomnia Severity Index, Promise: sleep disturbance / sleep related impairment, clinical assessment, and/or a history of self-reported cognitive disturbance (e.g., poor memory, concentration, attention)
8. Not have an allergy to: monkfruit, butternut squash, mango, or cocoa powder.
9. Not be a shift worker (e.g. have worked night or rotating shifts more than twice in the past month).
10. Not have a diagnosis of amyotrophic lateral sclerosis.
11. Not be currently supplementing their diet with branched chain amino acids.
12. Not be pursuing new treatment for sleep apnea nor be starting any other sleep intervention (e.g., positive airway pressure therapy for sleep apnea, sedative-hypnotic medication, or cognitive behavioral therapy for insomnia) during the study; if already engaged in another sleep intervention, this must be stable and not undergo further changes during the study.
13. Meet diagnostic criteria for TBI using a validated clinical interview.

All individuals meeting inclusion/exclusion criteria will be included in this study, regardless of gender or racial/ethnicity status. The gender and ethnic makeup of Veterans at VAPORHCS is 8% women and 8% underrepresented minorities, a narrower demographic than the Portland metropolitan area (50% women and 24% minorities). Therefore, we will need to make extra efforts to include women and minorities in this study. Women and underrepresented minorities will be expressly encouraged to participate through targeted flyers (e.g., representative images, posting in Women's Health Clinics, etc.). If needed, individuals from these underrepresented groups will also be specifically identified and preferentially recontacted from our large data repository. Additional efforts to better represent gender and ethnic minority groups will include extension of our recruitment to individuals in the larger community outside of VAPORHCS. Children

will be excluded as Veterans are at least 18 years old by definition. Pregnant and lactating women, and women trying to conceive, will be excluded as the safety of dietary BCAA supplementation to the developing fetus/infant is currently unknown.

Inclusion of Non-Veterans - This study only recruits Veterans.

Subject Identification/Recruitment

Including by word of mouth, volunteers will be recruited and identified for phone screening through several methods:

a. Clinical referrals
    a. Clinical referrals may be from VA, OHSU, or clinics in the broader community. Primary recruitment will be through the VAPORHCS Sleep Disorders Clinic. These Veterans will all have a clinical referral from a clinical provider (usually primary care) for evaluation of a sleep complaint, one of the commonly presenting symptoms in complex TBI. Potential subjects will initially be referred to the study by a clinical provider at the sleep clinic or related outpatient clinic. For interested Veterans, the clinical provider will provide the name and visit date in person or by phone to the research study staff. No PHI will be recorded prior to phone screening. Research study staff will then conduct phone screening and provide the interested Veteran with the VA ICF to review. In relevant cases, contact by research personnel will be documented in CPRS with the referring clinician as a signer or co-signer.
b. Previously established data repositories #3636 and #4086
    a. An alternative approach to participant recruitment would be identification of individuals with complex TBI housed within a large, existing data repository at VAPORHCS (VA MIRB #3636, PI: Lim, n = 670 participants and VA MIRB #4086 PI: Lim n=500), approximately 30% of whom report TBI. These research participants have all provided informed consent for their data to be kept in the data repository, and have given their permission to be re-contacted for future research studies. Existing data on these participants include extensive and detailed history of TBI from the medical chart, severity, and post-concussive symptoms (as assessed by the Rivermead Post-Concussive Questionnaire; RPQ), as well as clinical pain ratings (Likert pain rating scale at multiple time points).
c. Flyers
    a. Flyers will be used to recruit individuals at VAPORHCS, OHSU, and in the community. In the Portland VA, these flyers will be posted in the building 104 elevator, in handout stands in various clinics, and other VA bulletin boards with approved space for research flyers. They will also be given to clinicians at outpatient clinics to give to interested subjects. Interested subjects who contact us will then be screened over the phone with our phone script. If the participant is eligible and interested after the phone screen, we will proceed with obtaining written and verbal informed consent.
d. Craigslist & institutional affiliated websites including but not limited to:
    a. OHSU Brain Institute（https://www.ohsu.edu/brain-institute/research-ohsu-brain-institute),
    b. Uniformed Services University of the Health Sciences' TBI Research Opportunities and Outreach for Participation in Studies (USUHS TROOPS)（https://troops.cnrm.nih.gov)
    c. the VA National Center for Rehabilitative Auditory Research (NCRAR) Research volunteers needed webpage (https://www.ncrar.research.va.gov/Join_Research_Study/Index.asp), and/or other sanctioned venues.

    We will post on these web pages looking for Veteran volunteers. If any of these sites offer email options for contact, they will be disabled. Interested participants will call the number provided and undergo a phone screen. The post's text will direct interested people to our phone number and/or the website www.portlandsleepstudy.com. This website will reroute to a PVARF sponsored website "http://sharp.pvarf.com/" which will list actively recruiting studies. Any version of IRB-approved flyers will be posted under the "Join a research study" page to describe the study and its requirements. Participants can call the number on the flyer or complete a pre-screening RedCap survey that will assess inclusion/exclusion criteria and collect their name, phone number, and email address. A member of the study team would then contact the

participant and further explain the study and screen the potential participant. If the participant is eligible and interested we will schedule a remote or in person meeting. If a remote visit is preferred we will additionally collect a mailing address.

e. Radio Ads
    a. We will run short (15-60 second) audio or visual banner or video ads aired by radio stations, using a combination of audio broadcasting and internet streaming as needed to reach more participants. The ad will direct interested people to our phone number and/or the website www.portlandsleepstudy.com. This website will reroute to a PVARF sponsored website "http://sharp.pvarf.com/" which will list actively recruiting Lim studies. Any version of IRB-approved flyers will be posted under the "Join a research study" page to describe the study and its requirements. Participants can call the number on the flyer or complete an online pre-screening RedCap survey that will include inclusion/exclusion criteria, their name, phone number, and email address. A member of the study team would then contact the participant and further explain and screen the potential participant. If the participant is eligible and interested we will schedule a remote or in person meeting. If a remote visit is preferred, we will additionally collect a mailing address.
f. VINCI (VA Informatics and Computing Infrastructure database)
    a. A letter from the study, with an opt-in option may be mailed to potential participants identified through administrative VINCI-based data pulls and electronic review of aforementioned VA outpatient clinics, informing Veterans of the project. Interested subjects who contact us will then be screened over the phone with our phone script. If the participant is eligible and interested after the phone screen, we will plan to proceed with obtaining written and verbal informed consent.
g. Research Match
    a. ResearchMatch.org will be used as one of the recruitment tools for this research study/protocol. ResearchMatch Volunteers will be contacted through ResearchMatch.org. Included with this submission is a study recruitment message that will be sent to potential study volunteers.
h. OHSU Study Opportunities page
    a. We will post on OHSU Study Opportunities page and ask that those who are interested call the number provided.
i. National recruitment
    a. With the possibility of remote visits, we will be able to reach potential participants from other areas of the country that would normally not elect to travel to Portland. We may recruit individuals from clinician referral from non-local clinics, national repositories, repositories of collaborators, radio ads, VA approved social media, blog features, newsletters, and press releases such as may be found on the US DVA official blog: VAntage Point found at https://blogs.va.gov/VAntage/, out of area craigslist, postings such as within the North West Military newspaper and blog, and project appropriate venues such as https://www.concussionalliance.org/ Such sites may post any version of an IRB approved flyer and/or IRB approved text and images. Interested participants will be told to call study personnel and/or check out our website.

TROOPS Program- additional detail:

Potential participants may be referred to this study through the Center for Neuroscience and Regenerative Medicine (CNRM) Participant Referral Program, TBI Research Opportunities and Outreach for Participation in Studies (TROOPS). TROOPS is designed to expedite and enhance the participant recruitment and referral process through direct self-enrollment via a web-based platform that is accessible from computers, tablets, and smartphones. All information collected will be voluntarily self-reported by the participants upon their enrollment into the CNRM Referral Program, and will be used to determine their eligibility for various CNRM studies and CNRM collaborative studies. Once referred, the respective study's IRB-approved recruitment and consenting processes will be implemented.

Additionally, in accordance with the TROOPS registry protocol and with participant consent, the study team may share contact information (name, email, phone number, enrollment status, enrollment date if

applicable) of enrolled participants who agree to have their information shared with TROOPS study staff who may contact them to discuss the TROOPS registry in further detail. All PII will be shared in a secure fashion using DoD Safe, Secure ShareFile, encrypted email, or via telephone. Only approved study staff and TROOPS staff will have access to the contact information.

If existing participants inquire about participating in future research, we will tell them about this registry by providing the 'TROOPS referral information' text and we will have them sign a 'Banking your Contact Information for Future Research' addendum if they would rather have us forward on their information instead of supplying it themselves.

Informed Consent & HIPAA Authorization

Written and verbal informed consent as well as HIPAA authorization will be obtained in person by trained study personnel either remotely, at subject's homes, or at the VAPORHCS. Prior to obtaining informed consent, subjects will undergo screening to ensure that they meet eligibility criteria. Study personnel will guide subjects step-by-step through the informed consent document and ensure subjects have had all their questions answered before consent is obtained. Subjects will be reminded that participation is entirely voluntary and they are free to withdraw at any point. If a subject withdraws, the PI may still use information included in the research database that was collected prior to withdrawal if that information is deemed necessary to a particular study per IRB standard practice. No significant health risks are associated with participation in this study.

If a participant is unable to travel to VAPORHCS but still would like to participate, the consent conversation will be performed remotely via phone or video conferencing in one of the following ways:

- *DocuSign* – Study staff will initiate the sending of a DocuSign envelope to furnish the potential participant with links to the consent and authorization forms for conducting the consent conversation. These will be sent with approved template wording that reminds the volunteer not to sign anything until instructed to do so by the consenter during the scheduled phone or video visit. After the consent discussion the consenter will aid the subject in executing the documents and then in retrieving their copies of the fully executed consent and HIPAA Authorization for their records.

  DocuSign will be used as the study's preferred method for fully remote HIPAA/Consent discussion. Choosing to use DocuSign will improve security and privacy for our research volunteers, will alleviate participants' burden in tracking and shipping these crucial study documents, and will help prevent the delays and errors that mail-in consent methods may encounter.

  The study team has been approved by ORD for use of 350 envelopes (emails). Further details are located within the document 'Standard of Operating Procedure: DocuSign for Research'.

- *Mail-* This option will be used in cases where DocuSign isn't feasible. Study staff will mail potential participants the consent and authorization forms ahead of time, and then go over them during a video conference. If they agree to participate they will be told to sign and date the ICF and HIPAA authorization forms, and mail them back to us using a pre-addressed, pre-paid envelope. Once they are received study personnel will also sign and then mail a copy of the fully executed forms back to the subject.

  Alternatively, they may sign both the consent and authorization forms, take pictures of each page, and send the images back to us via encrypted email (initiated by study team) or by using MyHealthyVet.

  If taking and sending pictures of each page of the consent and authorization forms is too onerous for the subject we will continue the remote aspects of the visit using a waiver of documentation of consent form. The questionnaires and cognitive testing may take place in this case.

By consenting and providing authorization to be in this study, subjects are allowing their data/specimens to be placed in Dr. Lim's Repository #4086 (*Morning Bright Light for Sleep Data Repository*).

Inclusion of those with impaired decision-making capacity:
N/A. The study does not include those with impaired decision-making capacity

Risks and Side Effects:

Delivery of care within VAPORHCS outpatient or community care clinics will not be altered by participation in this study. This study poses minimal risks as detailed below.

Psychological

- Some of the questions in the questionnaires inquiring about subjects' social and medical history might cause psychological distress. Subjects will be reminded that they can choose to not answer any of the questions and opt out of the study at any time.
- Since questions will be asked about mood including thoughts of self-harm and depression, there is a possibility that information about suicidal thoughts or evidence of depression will require an intervention. How this information will be handled is discussed below in *Section 5: Data and Safety Monitoring for Clinical Trials*.

Physical

- The blood draw carries the risk of mild discomfort and bruising, which will be minimized by having these procedures conducted by the VAPORHCS Phlebotomy Lab or trained study personnel. These potential risks will be communicated to subjects during the informed consent process and they will be reminded of them prior to the blood draw.
- Wearing the actigraphy watch may cause mild skin irritation from the wristband. Subjects will be advised to remove the actiwatch if necessary.
- Wearing the sweat patch may cause mild skin irritation from the adhesive. Subjects will be advised to remove the patch if there is any negative reaction.
- Cold pressor pain testing. The cold pressor test has minimal risk for discomfort. There is a possibility that participants may have some temporary redness or sensitivity after the test. If at any point a Veteran expressed more than mild discomfort and/or wants to stop the test, they will be instructed to remove their hand from the ice bath. We will not allow the Veteran to have they hand submerged for more than 5 minutes to prevent any tissue damage.
- Risks associated with polysomnography include mild skin irritation at the site of electrode placement, and the potential for a poorer than usual night's sleep. This is a research grade overnight sleep study and therefore no clinical diagnoses will be made from these results. However, any relevant information will be relayed to the clinician of record for review and referral for clinical assessments if warranted. If the study clinician determines that a PSG appears to indicate that a participant may benefit from follow up with clinical sleep testing then study personnel will inform them. Subjects will also be informed there may be no actual cause for concern upon follow up and that clinical follow up would need to be paid for by them or their insurance.
- Subjects may experience mild gastrointestinal discomfort after consumption of BCAA or placebo. These and other side effects will be systematically assessed using a validated side effects scale and addressed as needed by the Clinician of record.
- There are no harmful or potentially toxic components in either the BCAAs or placebo substances as determined by the manufacturer certificate of analysis (see Appendix).
  BCAAs are not known to affect a fetus but could affect a fetus in ways that we do not yet know about. Female participants must provide reassurance that they are not pregnant in order to enroll in the study, and the participant and male partner will attest to use birth control for the duration of the study. Male participants do not need to attest to use birth control if their female partner is not enrolled, because BCAA is not known to affect the germline, the concern is to the developing fetus.

Other

- Because personal health information will be collected, there exists the risk of an accidental disclosure of confidential and/or private information. The exposure of such information may have

associated psychological, financial, or legal ramifications. Given the safeguards that will be implemented, (see *Section 2: Adequacy of Protection Against Risks),* this risk is very low.

Additional Participant Safeguards:

This study will not include vulnerable populations and/or those with impaired decision-making capacity. If it appears that the subject is experiencing decisional impairment or an inability to understand the study, such as failing to repeating back the basic concepts of the study, that person will not be included permitted to participate.

Inclusion of those with impaired decision-making capacity:

N/A. The study does not include those with impaired decision-making capacity

Suicidality*:*

At some point during the course of this study, a subject could disclose suicidal or homicidal thoughts or feelings to a member of the research personnel. All study personnel, including project coordinators, assessors and interventionists, will be trained in the appropriate clinical response to suicidality/homicidal disclosures according to VA guidelines. All study personnel will be trained to respond in a manner that is clinically and ethically responsible, while respecting the Federal Privacy Act and Confidentiality Statutes and HIPAA guidelines.

In most circumstances, study personnel who learn that a subject is in danger of harming him/herself or others will inform the study clinician who is responsible for the subject's clinical care. It will then be the responsibility of these individuals to intervene in accordance with the policies and procedures of the VA. In the case of suicidal ideation or behavior, a detailed suicide risk assessment on the individual will be completed as soon as possible, and no later than 24 hours from the initial screen.

Below is a more detailed account of our local Suicidality protocol.

1. VA Procedures for referring a Veteran for suicidal ideation or threats

a. Each **medical center employee** is responsible for reporting any person in the medical center or on the premises who demonstrates suicidal behavior. Suicidal behavior will be immediately reported to the charge nurse, physician, primary therapist or other clinician in charge of the area when any person exhibits suicidal behavior. A **Code 5** should be called (see MCM No. 00-14, Behavioral Emergencies) if the behavior appears to pose immediate danger. In remote areas of the premises, it may be more effective to call 911.

b. The first **VA police officer** arriving on the scene is responsible for:
(1) Securing the area;
(2) Ensuring evidence is undisturbed;
(3) Supplying needed protection; and
(4) Summoning local police authorities.

c. **Study personnel** will follow the policies and procedures for suicide prevention and management of suicidal behavior and its aftermath anywhere within the medical center or on the premises. In addition, all study personnel will follow established procedures for reporting Serious Adverse Events, of which suicidal behavior by outpatients is an example, to the local Institutional Review Board (IRB) providing oversight.

2. Procedures for Managing Suicidal Behavior:

a. Outpatient Programs or VA Grounds:
- Subjects on VA premises who are assessed to be at risk of imminent self-harm will not be left unattended during any aspect of the evaluation process.
- Responsibility exists for taking clear, immediate, and appropriate action to prevent suicide when a clinical staff member concludes that an outpatient presents an imminent risk of suicide.
- The VA or local police will be called immediately.
- The clinical staff present during the episode will record this information in the medical record when an outpatient indicates or demonstrates suicidal intent.

b. Remote visits:

- Subjects on the phone or videoconference visits who are assessed to be at risk of imminent self-harm will not be left unattended during any aspect of the evaluation process.
- Subjects expressing active thoughts of suicide with an imminent plan will be connected directly with the National Suicide Prevention Lifeline, 1-800-273-8255, through a warm handoff.
- Contact Principal Investigator, Dr. Miranda M. Lim, M.D., Ph.D. at x57404 or cell phone 971-319-3220 to report the incident to ensure that clinical referral to mental health is met.

Procedures for Physical Transport of Suicidal Outpatients to a More Secure Facility or Location:

a. Division Outpatient Clinics:
   - Contact VA Police to escort outpatients who present an imminent risk of suicide to the closest Emergency Department for evaluation by Psychiatry. If subjects are at the Portland VA, On Call Psych provider will be contacted @ x55424 or x55425. (Non-credentialed staff my not assess suicidality other than by patient report or that of a reliable person who heard the Vet make suicidal threats).
   - Enter a note into CPRS documenting the event.
   - Contact Principal Investigator, Dr. Miranda M. Lim, M.D., Ph.D. at x57404 or cell phone 971-319-3220 to report the incident for study participant documentation.

Procedures for Reporting Suicidal Behavior:

a. Study personnel will report suicidal behavior or other Serious Adverse Event (SAE) by outpatients to the local IRB by following established guidelines. In cases of an adverse event, we will use the sponsor's adverse event form.

Benefits:

Participants in the study may benefit from dietary BCAA supplementation by improved sleep and/or quality of life. Results from this study are expected to validate this promising sleep-based intervention for individuals with TBI and provide an important treatment option for individuals with TBI who experience sleep-wake disturbances. Subjects will also receive modest monetary compensation for their time, as described in *Subject Compensation*. Finally, participants in our other studies have expressed that they appreciate the opportunity to contribute to research that might benefit others in the future. The risks to participants are minimal and are reasonable in relation to the anticipated potential benefits from the study as well as future benefits of this knowledge.

Protected Health Information:

The following protected health information (PHI) will be collected in this study: history regarding diagnosis of a sleep disorder; medical history will be confirmed or examined in chart if TBI, PTSD, and/or depression is indicated on surveys. In addition, PHI that are part of the 18 HIPAA identifiers will be collected on the cover page only, including patients full name, mailing addresses, email addresses, date of birth, date of visits, last 4 of social security number, and phone number. This information will be entered into a secure REDCap database housed on the OHSU server and a VA master list stored on the VAPORHCS limited-access Research drive or VA OneDrive. After being entered electronically, the cover page will be kept in a locked file cabinet in a locked office in prox card-restricted space (Dr. Lim's VA research space). Follow-up survey questionnaires on symptoms related to sleep, mood, trauma, and social history will be collected on paper copies with a participant ID number and no identifiable data. The original questionnaires will be stored in a locked file cabinet, in a locked office in Dr. Lim's VA research space. These data will also be entered into a HIPAA-secure REDCap database housed at OHSU. Original hardcopy consent and authorization forms will be stored in a locked drawer and office (Dr. Lim's VA research space).

Prior to consent, first and last name and email address will be provided to DocuSign in order to initiate the electronic consent process. The consent to be used will also be relayed to DocuSign and, for this study, the consent will list the subject's status as a veteran who may have had a history of head injury or traumatic brain injury. Please see "Letter_DocuSign Memo for PO" provided with this protocol for details regarding the National VA's decision to deem DocuSign secure and appropriate for e-consent. Screening phone scripts have been

developed which include discussion of this transfer of information and ask potential participants permission for transfer. Mail or in person consent is offered as an alternative within these scripts.

Collaborative Research

This is a multi-site study involving subject recruitment from both OHSU and VAPORHCS. Recruitment will take place at VAPOHCS clinics, OHSU via flyers, and in the community. Craigslist, Research Match, and OHSU study opportunities recruitment will only take place at OHSU. The study visit will take place at VAPORHCS. Analysis of biospecimens may take place at the VA, OHSU, or through outside collaborators. The PI, Miranda Lim, is a VA Staff Physician and Research Investigator at VAPORHCS and also a credentialed neurologist at OHSU. She can be contacted by phone at 503-220-8262 x57404, or e-mail at lmir@ohsu.edu.

Resources Available*:*

The Principal Investigator, Miranda Lim, M.D., Ph.D., is a clinical provider in the Sleep Disorders Clinic at VAPORHCS and a credentialed neurologist at OHSU in the Department of Neurology. There is office and lab space available at the VAPORHCS Sleep Disorders Clinic (building 100-6C), and provided by Research Service (building 101, rooms 432A, 432, 430, 404A, 404C, 533, and 534) with locked file drawers in rooms accessed only via prox card. Testing will occur either at the VAPORHCS at the aforementioned rooms available to the study team or via video or telephone visits. Blood draws will take place either in the VAPORHCS Phlebotomy lab, in VAPORHCS clinical space, or at a location outside of VAPORHCS per subject preference, such as the subject's home.

Subject Compensation/Payment:

Subjects will receive compensation in gift cards, clincards, check, or other cash equivalent. Each subject in each group (BCAA and rice protein) will receive the same compensation for completion of study tasks. In addition to monetary compensation, subjects will be allowed to keep their shaker bottle used to mix each drink (monetary value: ~$10).

- Visit 1: $120 for completing the overnight polysomnography ($10/hr x 12 hrs, up to 2 nights), $20 for questionnaires, $20 for cognitive testing, and $20 for the biomarkers. Total of $180 at the end of this visit, or $300 if a second night of PSG is needed.
- Visit 2: $20 for coming to Visit 2.
- Visit 3: $20 for completing the questionnaires and $20 for the biomarkers. Total of $40.
- Visit 4: $20 for completing the questionnaires and $20 for the biomarkers. Total of $40.
- Visit 5: $120 for completing each night of overnight polysomnography ($10/hr x 12 hrs, up to 2 nights), $20 for questionnaires, $20 for cognitive testing, and $20 for the biomarkers. Total of $180 at the end of this visit, or $300 if a second night of PSG is needed.
- Visit 6: $20 for completing the questionnaires and $20 for the biomarkers. Total of $40.
- Visit 7: $20 for completing the questionnaires and $20 for the biomarkers. Total of $40.

Total compensation: $540 and a shaker bottle, or up to $780 if two additional nights of PSG are needed.

Recruitment materials will not mention the possibility of additional $120 payments for repeat PSGs. Repeat PSGs will only be requested when a visit's PSG does not provide good data, this additional payment is not expected for the majority of participants. Payment for supplement pause activities would be the same as for visit 5 activities, but will also not be mentioned in recruitment materials as to not be coercive since this payment is not expected for the majority of participants either.

Privacy and Confidentiality:

All hard copies of study documents will be stored in a locked file cabinet located within prox card access-only space, identified with a study ID and not the participant's name (See PHI section above).

The study personnel providing informed consent may be a health care provider in the VAPORHCS Sleep Disorders Clinic, but patients who receive a sleep study with VAPORHCS do not need to participate in this study. The VAPORHCS Sleep Disorders Clinic has a high volume of patients, and so there is no need for coercion or undue influence to participate in this study.

To protect privacy and confidentiality, the electronic master list of study subjects and their study identification number will be stored on the VAPORHCS limited-access Research drive or on the VA OneDrive and protected by password access to the VA computer system. Only IRB-approved study personnel will have access to this file. Electronic study data from the questionnaires will be stored in a HIPAA-secure REDCap database on the OHSU server. The study team will assure that only unique study codes are used to store any coded de-identified study data that will be stored within OHSU approved secure storage solutions: DropBox, and Microsoft Teams OneDrive.

Certificate of Confidentiality

N/A. The study does not include a Certificate of Confidentiality.

Information and/or Specimen Management

Sources of data in this study include validated questionnaires, adherence metrics, wrist actigraphy, bedmats, overnight polysomnography, and standardized neuropsychological assessments.

Questionnaires and Adherence Metrics

Questionnaires will consist of subjective sleep, subjective cognition, quality of life, assessment of side effects, and patient satisfaction surveys. There will also be questionnaires about drug and alcohol use and frequency of use. They will be administered either on paper or via the REDCap survey function, and stored in accordance with local VA IRB policies. Data will be entered into a secure, web-based REDCap database and verified for accuracy. Adherence metrics will be evaluated using a combination of drug accounting, self-reported diaries, and serial BCAA levels in the serum.

Actigraphy

Objective sleep will be measured using wrist actigraphy (Actiwatch2, Phillips Respironics Actiwatch) measured on the non-dominant wrist. Activity levels will be monitored continuously for the 14-week duration of the study (2 weeks of baseline + 12 weeks on study drug). Wrist actigraphy includes an accelerometer, which produces voltage that reflects the amount of motion of the device. Within the sensor, the degree and force of all movements are calculated into activity counts and recorded to the device. Activity levels will be exported via a proprietary USB-connected dock, and analyzed using Philips Actiware software. Data from the Actiwatch2 has been validated against the gold standard in-lab polysomnography in several populations including those with chronic insomnia and depression.[87,88] Raw activity counts will be analyzed for sleep patterns using several exploratory outcomes: Relative Amplitude, Interdaily stability, Sleep Efficiency, Sleep Latency, Wake after Sleep Onset, Bedtime/Waketime variance, Total Sleep Time, Intradaily Variability, and a Sleep Fragmentation Index.[89,90] Actiwatches will be downloaded at 4-week intervals while on study drug. Data will be concatenated and aggregated to the day level for calculation of sleep outcomes before being further summarized for each assessment period (i.e., baseline, 4 weeks, 8 weeks, and 12 weeks). Napping will be assessed using a combination of self-report from the sleep diary and actigraphy data. Actigraphy data will be stored on a coded database on OHSU servers.

Bedmat

Objective times in/out of bed will also be measured using a bedmat placed underneath the mattress, above the boxsprings. The bedmat is approximately 4 inches wide and 2 feet long. Subjects will not be able to sense the bedmat while in bed. Data is collected using piezo-based sensors and will be written directly to an SD card connected to the device. Newer models of the bedmat will collect data within the EMFIT QS password secured online database (https://qs.emfit.com/#/login) via a cellular or wifi connection. For WiFi connection, subjects will not download an app or access the online database and will therefore not be able to provide any identifiers to the EMFIT company. Subjects will connect the device directly to their home WiFi themselves and so the study will not need to collect their home WiFi information. The data collected in this database will not include GPS location, ip address, or any other HIPAA identifiers. Research subjects will not interact with the database in any way. The data will be identified only by the bedmat's device number

and the bedmat's google email address, neither of which will be specific to the subjects, research study, or even OHSU or the VA. The data will be burned directly to the SD card from the database by study staff using personally owned equipment not connected to the OHSU or VA computing infrastructure. Data formats may include screenshots, csv files, or other **non-**macro enabled file formats.

Times in/out of bed will be aggregated to the day level for calculation of time in bed before being further summarized for each assessment period (i.e., baseline, 4 weeks, 8 weeks, and 12 weeks). Similar handling would be pursued for any other experimental measures collected from the mats like heart and respiration rate and overall restlessness. Only study staff will be able to link data collected under each device number to unique subject study identifiers and the bedmat data will be stored on a coded database on OHSU servers.

Polysomnography

Subjects will undergo baseline and post-treatment overnight polysomnography (PSG). As needed to capture data that might otherwise be lost, PSG might also be requested by the investigators for continuing subjects who must pause (for any reason) in taking their supplement after at least 5 days of adherence. This will take place either as a Type I attended study in the VAPORHCS sleep laboratory or as a Type II home sleep test per American Academy of Sleep Medicine (AASM) guidelines: 6-channel sleep EEG montage from both hemispheres as well as electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), nasal airflow, breathing effort, and oxygen saturation. Following the conclusion of the study, standard sleep staging analysis will be manually performed by trained assistants for each 30-second epoch duration according to the standard clinical criteria originally developed by Rechtschaffen and Kales, updated by AASM, and validated by a board certified physician.[91,92] Subjects' sleep staging will be exported into a format that is accessible by our custom scripted sleep analysis program. Exploratory outcomes will be the following: Percentages of Wake, REM, NREM sleep, Sleep Efficiency, Sleep Latency, Number of Stage Transitions, Wake after Sleep Onset. Quantitative EEG may be further explored using spectral power analysis as we have previously described.[23,93,94]

Neuropsychological testing

Objective cognitive outcomes will include neuropsychological assessment items on the NIH FITBIR Common Data Elements Outcomes list. Tests will be purchased from official testing bureaus and administered according to the appropriate testing manuals by a licensed neuropsychologist and/or a trained research assistant directly under the supervision of a trained neuropsychologist. Results will be scored according to approved manuals, and adjusted using normative data.

Research records will be held according to the VA records retention schedule.

Disclosure/Sharing:

N/A. The study does not include disclosure/sharing outside the IRB-approved VAPORHCS study personnel.

Transfer of Data Ownership

N/A. The study does not include transfer of data ownership.

Web Application(s), Mobile Device(s) and/or Mobile Application(s):

N/A. The study does not include web application(s), mobile device(s) and/or mobile application(s).

Data will be entered into an OHSU RedCap database.

Data and Safety Monitoring Plan (DSMP)

Dr. Lim will be responsible for monitoring the safety of the study and complying with the reporting requirements. Dr. Lim is also the Responsible Clinician for this study. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the local site IRB. Serious adverse events will be reported to the local IRB, and the project officer within 48 hours of the time project staff become aware of the incident. The PI will provide a summary of the safe conduct of the study to

project officers on an annual basis as part of the progress report. This report will parallel the written report required by the IRB as part of the annual IRB renewal process. The review of data and procedures may result in early termination of the study, amendment to the protocol, or changes to the data collection plan or study forms. Should the protocol or data collection plans or study forms be amended as a result of data review, the IRB will be notified and the amendment approved prior to study amendment implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research (e.g., other potential risks) that may affect their wish to continue participation in the study.

Data and safety monitoring for this study will be provided by the VA Clinical Science Research & Development (CSR&D) centralized Data Monitoring Committee (DMC). The DMC is provided by CSR&D to ensure independent oversight of the safety and integrity of the project. The DMC is an independent multidisciplinary group, whose members have collectively – through research, education, training, experience, and expertise – the requisite knowledge pertinent to the subject areas to be reviewed. Membership details are available on the CSRD website. The DMC will provide an ongoing independent evaluation of this study focused on safety and feasibility, including participant accrual and retention, adverse events monitoring, and data analyses. Meetings will be held two times per year at which time recommendations will be made to the Director of CSR&D for endorsement. These recommendations will range from approval to continue (unconditionally or with conditions to be addressed) to probation or possibly termination, if there are problems with enrollment or safety concerns.

It is unlikely that study outcomes will adversely affect the health or well-being of research participants in this experimental study. Participants are under usual care for all treatment they receive for their sleep complaint, in addition to the proposed study arms. If depression or risk of suicide are evident due to questionnaire data collected, then the participant will be referred for follow-up. If a participant indicates thoughts of self-harm, then steps will be taken to protect and support the participant as described above in the sections on Suicidality and on Risks and Side Effects.

Step-by-Step Guidance on Conducting the Study

- Recruit subjects from the VAPORHCS Sleep Disorders Clinic, other out-patient clinics, and other approved methods.
- Visit 1
    a. Obtain written and verbal informed consent and HIPAA authorization from subjects
    b. Verify reproductive status with female subjects/ provide pregnancy test if requested
    c. Collect baseline questionnaires
    d. Provide subject with an actigraphy watch and bedmat
    e. Conduct cognitive testing and pain testing
    f. Conduct overnight PSG
    g. Obtain pre-study blood draw, saliva, and/or sweat collection
    h. Provide study diary
    i. Compensate up to $180, or $300 if a second night of PSG is needed
- Allow subjects time to complete their baseline period without consuming BCAA or placebo
- Visit 2
    a. Randomize subject to a group
    b. Provide 4-week supply of BCAA or placebo
    c. Provide a shaker bottle
    d. Provide a new actigraphy watch
    e. Compensate $20
- Visit 3 ***-and-*** Visit 4
    a. Collect mid point questionnaire data
    b. Collect mid point blood draw, saliva (if needed), and/or sweat collection
    c. Collect old and provide new sleep diary and actigraphy watch
    d. Receive previous used/unused drug packets for study accounting.
    e. Compensate $40
    f. Provide subjects with another 4-week supply of BCAA or placebo
        f1. Weekly calls to answer questions and ensure protocol compliance
- Visit 5

a. Collect post-study questionnaires
b. Collect actigraphy watch and bedmat
c. Conduct cognitive testing and pain testing
d. Collect study diary
e. Collect post-study blood draw, saliva (if needed), and/or sweat collection
f. Conduct overnight PSG
g. Receive previous used/unused drug packets for study accounting.
h. Compensate up to $180, or $300 if a second night of PSG is needed

- Visit 6 ***-and-*** Visit 7
  a. Collect follow-up questionnaire data
  b. Collect follow up blood draw, saliva (if needed), and/or sweat collection
  c. Compensate $40

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