Title (If funded, provide exact title of funded project)

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of a Proprietary Spearmint Extract Blend, on Sleep in Healthy Men and Women

Contact information

Principal Investigator Name: Michael Grandner, PhD, MTR, CBSM, FAASM

Net ID: grandner

UA Email Address: grandner@psychiatry.arizona.edu

College/Division: Medicine

Department/ Unit: Psychiatry

Status ☐ Undergraduate Student ☐ Graduate Student ☐ Resident ☒ Faculty ☐ Staff

Alternate Contact (These individuals will receive copies of all correspondence):

Add Line	Name	UA Net ID	Research Role	Institution	Email Address
Delete Line	Pamela Alfonso Miller, MD	**palfonsomiller**	Alt Contact	UA	palfonsomiller@psychiatry.arizon
Delete Line	Bryan Clines	**bclines**	Alt Contact	UA	bclines@psychiatry.arizona.edu
Delete Line	Manuel Acuna	manuelacuna	Alt Contact	UA	macuna@psychiatry.arizona.edu

* List all additional Research Personnel on the Research Personnel Form and attach with your submission

General Information

What is the expected length of this project? Approximately 18 months

Is this project strictly a review of data or specimens? No recruitment, interaction, or consent? ☐ Yes ☒ No

Is the University of Arizona ceding IRB review to another IRB? ☐ Yes ☒ No

Will the University of Arizona be the coordinating center for a multi-site study? ☐ Yes ☒ No

Will the University of Arizona be the IRB of Record for multiple sites? ☐ Yes ☒ No

Does this project involve medical procedures which the PI is not licensed to conduct? ☒ Yes ☐ No

Explain the procedures requiring a licensed medical personnel:

Although the PI is a licensed Behavioral Sleep Medicine Clinician and is experienced in the use of melatonin in his clinical practice, a study physician was added to oversee participants in the rare occurrence of potential melatonin side effects.

Is this an Investigator-initiated study? ☒ Yes ☐ No

If the research is conducted at one of the Banner University Medical Center sites: Has the Payer Coverage Analysis (PCA) been completed by the University of Arizona Health Sciences Administration? If you are unsure, please contact crc@email.arizona.edu.

Is this project a Clinical Trial? ☒ Yes ☐ No

*A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

☐ ClincialTrials.gov "NCT" number for this trial:

☒ Registration pending

☐ Clinical trial does not require registration

Funding Information

Will the project be supported by any funding? ☒ Yes ☐ No

☐ Federal funding (e.g., NIH, NSF, DoE, DoD)

☐ Foundation Funding

☐ Departmental Funds

☐ Gift Funds

☒ Industry Funded

Provide IRB Payment eDoc: 6657071

Please review HSPP Guidance, Fees for Human Research, for more information.

Name of funding agency: Kemin Foods LC

UAccess Institutional Proposal or Award #: 619774

If you need help locating any of the UAccess numbers, please call Sponsored Projects & Contracting Services at 626-6000.

Location of Research

☐ Banner - University Medical Center

☐ University of Arizona Cancer Center

☒ University of Arizona Campus

*If the location is not your home department, you will need get Site Authorization from that department prior to submission.

University of Arizona Department of Psychiatry, UAHS 7th floor: Study procedures/assessments, data analyses & UAH

☐ Outside the US

☐ Online

☐ Other

Financial Conflict of Interest Disclosure

In order to submit this application, each *Investigator* must complete the University's Conflict of Interest ("COI") requirements.

Investigator is defined in the University's Individual Conflict of Interest in Research Policy, and generally means anyone with responsibility for the design, conduct or reporting of the research.

If you are filling this out on behalf of other investigators, you will need to confirm the answers to this and any following COI questions in this form directly with each Investigator. Each Investigator can log on to the COI Disclosure System to view the current status of their disclosures. For an overview of the COI disclosure process for IRB submissions, see the COI FAQ webpage.

1. Is *each* Investigator on the project up-to-date with COI disclosures? ☒ Yes ☐ No

To be up-to-date, an Investigator must have submitted a disclosure through the COI Disclosure System since the prior June 1.

2. Has *any* Investigator disclosed any outside financial or personal interest though the COI Disclosure System? ☒ Yes ☐ No

Please list each investigator who has disclosed such an interest:

Add Line	Name
Delete Line	Michael Grandner, PhD

For each Investigator listed above, the COI Program will review the application against the disclosed outside interest(s) to determine if a conflict exists. Until that determination is complete this application can not be submitted to the IRB.

2a. Is the application for (1) a non-sponsored project (i.e., you are not receiving external funds to support it) or (2) part of an industry-funded clinical trial? ☒ Yes ☐ No

Each investigator listed above MUST manually add the project to his or her disclosure form. Each Investigator can log on to the COI Disclosure System to add this project to their disclosure form. For instructions on how to do this, please visit the COI FAQ webpage.

2b. For all Investigators listed above, is the COI Review Process complete? ☒ Yes ☐ No

3. Is a drug, device or other investigational product being used or evaluated in this project? ☒ Yes ☐ No

3a. Do any Investigators have an interest in intellectual property rights (*e.g.*, as inventor, owner, licensee, or assignee of a patent or copyright) that are the subject of the research, or have they received (or might they receive) royalties, licensing fees or other income from the sale of the drug or device? ☐ Yes ☒ No

3b. With respect to the drug or device, does the University of Arizona (i) own a patent or other intellectual property rights, or (ii) hold or sponsor an "investigational new drug" (IND) application or "investigational device exemption" (IDE)? ☐ Yes ☒ No

Project Abstract

Background: Provide the scientific or scholarly background for the proposed Human Research. Discuss relevant prior experience or preliminary data (e.g., existing literature). (Limit 10000 Characters including spaces)

Many adults who do not suffer from any sleep disorders still experience inadequate sleep and feel that their sleep is not refreshing. Poor sleep is common in adults and may affect quality of life. Data from 2014 indicates that approximately 35% of the US population is receiving insufficient sleep (Liu et al., 2016). which may be associated, since insufficient sleep may be associated with cardiometabolic disease risk factors including weight gain, obesity, hypertension, diabetes, and inflammation (Grandner et al., 2016), as well as poor daytime functioning and many other outcomes (Grandner, 2017). Cognitive deficits are routinely seen in the laboratory, especially on the Psychomotor Vigilance Task (PVT) (Lim and Dinges, 2010). The National Institutes of Health suggests that adults aim for 7-8 h of sleep per night; however, approximately 28% of adults in the United States reported sleeping 6 h or less based on data from 2008 to 2010 (Schoenborn 2010).

A number of strategies are recommended to promote sleep quality and quantity, including a series of behavioral recommendations, such as keeping to a routine sleeping schedule, the timing of eating and physical activity in relation to bedtime, avoidance of stimulants, and maintaining a bedroom environment conducive to sleep (National Sleep Foundation 2015). In a previous study (Cook, C., et al., The FASEB Journal, 2015. 29(1 Supplement): p. 900.15.) subjects (40-70 years of age) self-reported significant improvements in "Ease of getting to sleep" and "Alertness and behavior following wakefulness" scores as measured by the Leeds Sleep Evaluation Questionnaire (LSEQ) following 90 days of supplementation with 900 mg of Neumentix (a water-extracted spearmint extract) when administered in the morning. A follow-up cross-over pilot trial (Herrlinger, KA, Society for Neuroscience, 88.27, 2016 and internal trial document TD-16-00116) with a lower dosage of Neumentix or placebo (450 mg) administered 30 minutes before bed for two weeks per treatment was conducted. Subjects (n=6), aged 30-50 years, who reported sleep dissatisfaction by the Sleep Dissatisfaction Questionnaire but did not have sleep apnea were included. Objective sleep parameters, measured by a portable sleep diagnostic device (WatchPat, Caesarea, Israel) , were measured at baseline and at the end of weeks 1 and 2 for each treatment period. Subjects consuming Neumentix had a decrease in time to get to sleep (sleep latency) by 11 minutes compared to placebo at week 1 (p=0.029) and a trend to reduction in sleep latency between groups across the 2 weeks of supplementation (p=0.107). Over the 2-week supplementation, Neumentix significantly increased the time subjects spent in REM sleep by 5% versus placebo (p=0.081) with improvements noted in 5 out of 6 individuals. This modification of sleep architecture is supported by the

simultaneous reduction in the time subjects spent in light sleep by 5% at week 2 (p=0.095) following Neumentix treatment compared to placebo. Neumentix also increased the amount of time subjects were able to sleep while snoring at 40 decibels, typical of an urban ambient sound level, compared to placebo (Week 1 p=0.1047, Week 2 p=0.0676, and across study p=0.0363).

L-theamimne, an amino acid found in green tea, has been proven to have effects on cognitive performance, relaxation and sleep quality (Vuong et al., 2011). L-theanine: Properties, synthesis, and isolation from tea. J. Sci. Food Agric. 91(11):1931–1939.) In a double blind crossover design study(Unno, Keiko et al. 2017), found that reduced caffeine content green tea improved sleep quality and reduced subjective fatigue.

Melatonin is produced by the pineal gland. Its sleep promoting effects are attributed to its action on melatonin receptors present in the suprachiasmatic nucleus of the hypothalamus, nocturnal rise of melatonin secretion is associated with increase in the homeostatic drive to sleep. (Brown, G. M, 1994; Venkataramanujan, et al 2009). Melatonin is a widely available over the counter sleep aid. Melatonin may help promote total sleep time, balance circadian rhythms and regulate the sleep-wake cycle(Pandi-Perumal SR, et al. 2007; Dawson D, 1998; Kräuchi K, et al. 2006)

Using this body of evidence, the current study seeks to simply observe and measure the effects of a new proprietary blend containing spearmint and green tea extract (New blend is yet to be named) in healthy adults. It will be the first randomized, double-blind, placebo controlled trial observing the effects of 30 days of 500 mg of a blend containing Spearmint extract and green tea on sleep when administered 30 minutes before bed in healthy adults. This study will utilize Fit-bit (San Francisco, California) (a tool whose use for evaluation of sleep is growing) for daily evaluation of sleep throughout the study in addition to polysomnography, considered by many researchers to be the gold standard for evaluation of sleep outcomes, at chosen timepoints.

Purpose: Describe the purpose, specific aims, objectives, questions to be answered, hypotheses, and/or primary and secondary study endpoints of the Human Research.

The aims and hypotheses of this study focus on changes to sleep continuity and sleep architecture in participants with no sleep disorders as the study seeks to measure healthy adults. This project has two phases. Phase 1 is a comparison of a currently unnamed proprietary blend containing Spearmint extract and green tea to placebo when administered 30 minutes before bed, on objective measures of sleep. Phase 2 will evaluate the benefits of the proprietary blend + Melatonin over Melatonin alone. Phase 2 will begin once Phase 1 completes its final subject. Participants that take part in Phase 1 become ineligible for phase 2.

For both Phases the Co-primary outcomes will be :
Sleep Diary Outcomes: Sleep Latency (Weekly averages)
Fitbit sleep outcomes: %REM Sleep (Weekly averages) This will be determined via an algorithm specifically validated in these devices using a combination of accelerometer and optical plethysmography signals (Beattie et al., 2017).

The secondary outcomes for both phases will be:
Sleep Diary Outcomes: Total Sleep Time, Sleep Latency, Wake After Sleep Onset, Sleep Efficiency, objective sleep quality (Addressed as: “what was the quality of your sleep?” on a 1-10 visual analogue scale and “How refreshed do you feel upon waking?” also on a 1-10 VAS) (weekly averages)
Fitbit sleep outcomes: Total Sleep Time, Sleep Efficiency, %Light Sleep, %Deep Sleep, %REM Sleep (weekly averages)
Sustained Attention (touchscreen PVT): Attentional lapses, mean reaction time, median reaction time
Other cognitive tasks: Spatial working memory capacity score, Visual Object Learning Task (VOLT) score, Motor Praxis Task (MPT) score, Abstract Matching (AM) score, Line Orientation Task (LOT) score, Digital Symbol Substitution Task (DSST) score, and Balloon analog risk task (BART) score.
Profile of Mood States (POMS): Mood scores (secondary analyses may look at energy level and other variables)

The Center for Epidemiological Studies Depression scale (CESD): Total Score
Perceived Stress Scale (PSS): Total Score
Pittsburgh Sleep Quality Index (PSQI): Total Score (secondary analyses may examine individual items)
The Insomnia Severity Index (ISI): Total Score (secondary analyses may examine individual items)
Vital Signs: Weight, BMI, heart rate, blood pressure
Compliance

In addition, demographic data will be evaluated for any differences present at baseline

Lay Summary: Provide a brief description of the proposed research using terms that someone who is not familiar with the science or your discipline can understand. (Limit 2000 Characters including spaces)

This study seeks to observes the effects of a proprietary spearmint extract and green tea blend on sleep quality and duration in healthy adults. Phase 1 is a comparison of the impact of the proprietary blend compared to placebo when administered 30 minutes before bed, on objective measures of sleep. Phase 2 is to observe the effects of proprietary blend + Melatonin over Melatonin alone. Two Hundred (200) subjects will be recruited and assessed in two phases, following an on-line survey. Phase 1: Placebo Group and Proprietary blend (N=100): includes an on-line screening (Day -14 ± 7), a Baseline visit (Day 0) where participants will be consented (see PSG visit below for exceptions) and asked demographic information, medical and psychiatric history and sleep related questionnaires, and instructed to take the product 30 minutes before bedtime starting on day 3. One follow- up visit (DAY 10 ±3 DAYS), and a final visit (Day 33 ±7 days) will be conducted. At all visits, sleep-related questionnaires, depression and diet questionnaires, psychomotor performance (Psychomotor Vigilance Task) and assessment of neurocognitive function will be conducted. Fitbit devices will be used to objectively characterize sleep during the study period. Sleep diary will prospectively track sleep pattern. PHASE 1 only: A subset of 10 participants (N=5 from each PHASE 1 group) will go through two polysomnography (PSG) studies. PSG NIGHT 1 (DAY -1) and PSG NIGHT 2 (DAY 32). Informed consent for this subset will be obtained at PSG night 1. This will be performed as an exploratory analysis to understand the correlation between the FitBit data and the PSG for powering of a larger second trial.

Phase 2: Will observe the effects of the Proprietary Blend +Melatonin vs Melatonin alone on objective measures of sleep and will have all the same study visits and procedures as Phase 1 (there is no PSG component in this phase)

Resources: Describe the resources (personnel, facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

Department of Psychiatry:
The Department of Psychiatry has an active research program with staff devoted to research administration, including an upper level director and three research specialists (not including project-specific coordinators). All have experience with IRB/regulatory matters and grants administration. Business office staff is knowledgeable in grants finance and accounting, and work-study students devoted to research are available for data entry and other administrative support.

Computer:
The home department of the PI, the Department of Psychiatry, provides personal computer resources for word processing, email transmission, internet access, and statistical analysis software for all staff, as well as laser printers, fax machines, scanners and photocopy machines. The University of Arizona maintains full computer and data analytic processing components available to all university faculty on a fiber-optic network system, with automatic daily backup available on a secure server. All computers have networked access to multiple HP printers (desk jet, laser, and color) and one HP 5P color scanner. Software includes Microsoft Office, SPSS statistics software, and Endnote and RefWorks. There is full time computer support in the UA College of Medicine for these resources.

Office Space:
The Department of Psychiatry provides Dr. Grandner with office space in the University of Arizona Health Sciences. Additional office and administrative space is available for the project coordinator and study staff in the Department of Psychiatry Research suites.

Room 7330:
Room 7330 is available as a certified laboratory and research space. University of Arizona's office of Radiation, Chemical & Biological Safety classifies the room as a BSL-2 certified laboratory whereby phlebotomy draws can be performed by a trained individual. This space provides 1 private changing room for subjects, 1 locked storage room for research supplies and data, 1 phlebotomy chair, and room for taking vital signs and performing ECG's.
The facility and equipment will be routinely inspected and maintained. Although emergencies are not expected, should one arise, the space is easily accessible by B-UMC security and a B-UMC crash team by phone and by panic button. The room is equipped with an eye wash station, a first-aid kit, a biological spill kit, and standard operating procedures pertaining to relevant emergency scenarios.

UAHS Center for Sleep and Circadian Science:
The UAHS-CSCS research space consists of a free standing sleep and circadian sciences research center with a total of 2,700 square feet, 4-patient bedrooms that can be used as interview or examination rooms during the day, 3 bathrooms, control room for monitoring patients, attached BSL-2 laboratory for processing and storing biological samples, three offices for research coordinators, technicians, trainees, and other research staff with telephone and internet connections. The bedrooms are used for sleep studies at night and during the day are used for performing interviews, informed consenting, neurocognitive testing, research interviews, and other research related activities. In order to facilitate long-term studies of sleep deprivation and translational experiments there is an adjacent changing room. The bedrooms are furnished with Sleep Number beds that adapt to patient's comfort needs and one of the larger bedrooms is furnished with an additional bed to enable the conduct of pediatric polysomnography that would allow the parent to sleep in the same bedroom if research study protocol allows for the same. The offices have wireless and hard-wired connectivity to the secure University of Arizona servers and have a total of seven desktop PCs (Dell computers) in addition to computers for the sleep diagnostic systems.

Population & Recruitment

Maximum number of participants to be enrolled in the study:

Total number of subjects to be enrolled=200. Up to N=350 screened to allow for replacing unreliable participants, mid-study disqualification, washout, study dropout and/or participants lost to follow up.
Breakdown:
Phase 1: Proprietary blend containing Spearmint extract and green tea (500 mg), Placebo (n=50 per group). A subset of this group (n=5 from Proprietary blend group. n=5 from placebo group) will complete two nights in the sleep lab to collect PSG data

Phase 2: Proprietary blend containing Spearmint extract and green tea (500 mg) + Melatonin (1 mg), Melatonin (1 mg)(n=50 per group)

Sample Size/Power Calculations:
In the pilot data, the two groups demonstrated REM sleep change of -2.3% (SD=4.9%) for the control group and 2.4% (SD=4.2%) in the treatment group. In a sample of N=100 individuals, we would have >99% power to detect this difference. In a more conservative estimate, if both SDs remain the same but the change in REM seen in the control group is 0, then we would require N=46 per group for 80% power to detect that difference. With N=50 per group, this should be sufficient.

In the pilot data, the two groups demonstrated sleep latency change of 6.4mins (SD=5.8) in the control group and -5.3mins (SD=8.1min) in the treatment group. In a sample of N=100 individuals, we would have >99% power to detect this difference. Again, in a more conservative scenario where the control group does not change but the other values remain, we would require N=29 per group for 80% power to detect this difference. With N=50 per group, this should be sufficient. Of note, the sleep latency change in the pilot study was calculated using an objective device, whereas sleep diaries will be used in the proposed study. It is likely that these two are highly correlated, though sleep diaries are preferred as the gold standard (see Schutte-Rodin et al., 2008). It is unclear which will demonstrate greater variability, though it is possible that greater changes may be seen with sleep diaries (see Lichstein et al., 2006).

Please check all the categories of participants that will be included in the research:

☐	Children (1-17 yrs old)	☐	Prisoners
☐	Cognitively Impaired Subjects	☐	Refugees
☒	Adults	☐	UA Staff/ Faculty
☐	Native Americans	☐	UA Students
☐	Pregnant Woman/ Neonates (0-2 yrs old)	☐	Other – please explain below

What are the inclusion and exclusion criteria for study participation?

INCLUSION CRITERIA

To be included in the study, patients must:

1. Subject is a male or female, 22-50 years of age, inclusive.
2. Subject is judged by the Investigator to be in general good health on the basis of medical history.
3. Subject is a non-user of nicotine products for 6 months prior to screening.
4. Subject's initial online screen reveals a score >3 on the PSQI.
5. Subject has a BMI of up to 29.99 kg/m2, inclusive, at screening.
6. Subject is willing to maintain habitual diet and activity patterns throughout the study period, other than the study instructions given for caffeine, alcohol, and vigorous physical activity.
7. Subject is willing to consume study product 30 minutes before bed throughout the study period.
8. Subject will consume no more than 14 alcoholic drinks (12oz beer, 5oz wine, 1.5oz distilled spirits) per week while in the study, no more than 4 drinks on a single occasion, and no more than 1 alcoholic drink within 4 hours of bedtime.
9. Subject will consume no more than 4 servings of caffeine substances per day (8oz coffee, 1oz espresso, 12oz caffeinated soda, 8oz energy drink) and no caffeine within 6 hours of bedtime.
10. Subject will refrain from vigorous physical activity (causing sweating) within 2 hours of bedtime.
11. Subject understands the study procedures and signs forms documenting informed consent to participate in the study and authorization for release of relevant protected health information to the study Investigator.

EXCLUSION CRITERIA

1. Subject has a history or presence of clinically important cardiac, renal, hepatic, endocrine, pulmonary, biliary, pancreatic, chronic pain condition(s), or neurologic disorders in the prior 2 years of screening.
2. Subject has a history of diagnosed clinical depression in the prior 2 years of screening. This will be determined by self report at screening (PHQ9 scores indicating likely depression diagnosis (<=2 on items 1 or 2, plus <=2 on at least 5 other symptoms) will be exclusionary) and with the Mini International Neuropsychiatric Inventory assessed at the screening visit.
3. Subject has an active infection or signs/symptoms of an infection. Clinic visits and/or sleep evaluations will be rescheduled to allow subject to be symptom-free of any type of systemic infection for at least 5 days.
4. Subject has uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg) at screening.

5. Subject has a known allergy or sensitivity to any ingredients in the study products.
6. Subject is a heavy consumer of caffeinated beverages (>400 mg caffeine/d from caffeine-containing products) within 2 weeks of screening.
7. Subject diagnosed with a psychiatric disorder that would impair their ability to perform the study, such as a psychotic disorder, bipolar disorder, neurodevelopmental disorder, post-traumatic stress disorder, etc. The subject should not currently be experiencing a major depressive episode. Psychiatric history will be assessed at screening then reassessed at the screening visit; In addition, the Mini International Neuropsychiatric Inventory will be conducted at the screening visit.
8. Subject has a history of use of psychotropic medications (including antidepressants, beta-blockers, and tranquilizers), stimulant medications, medical marijuana and/or narcotics within 4 weeks of screening.
9. Subject has used sleep aid medications, supplements, and/or products (over-the-counter or prescription), including antihistamines, within 2 weeks of screening. If use has occurred a wash-out period can be conducted.
10. Subject has a history of unconventional sleep patterns (e.g., night shift), chronic insomnia (defined as insomnia at least 3 d/week over the past month), a diagnosed sleep disorder (e.g., OSA), or a chronic medical condition that may impact energy/fatigue levels, in the judgment of the Investigator.
11. Subject has a history of cancer within 5 years prior to screening except for non-melanoma skin cancer.
12. Subject is a female who is pregnant, planning to be pregnant during the study period, lactating, or is of childbearing potential and is unwilling to commit to use of a medically approved form of contraception throughout the study period.
13. Subject has a current or recent history (past 12 months of screening) or strong potential for drug or alcohol abuse. Alcohol abuse will be defined as > 14 drinks per week (1 drink = 12 oz. beer, 5 oz. wine, or 1.5 oz. hard liquor).
14. Subject has been exposed to any non-registered drug product within 30 d prior to screening.
15. Individual has a condition the Investigator believes would interfere with his or her ability to provide informed consent, comply with the study protocol, might confound the interpretation of the study results, or put the person at undue risk.

Indicate age range, gender, and ethnicity of your research population:

For both phases defined above, patients will include healthy men and women with poor sleep quality (based on a Pittsburgh Sleep Quality Index>5), aged 22-50 years, each with a body mass index (BMI) of 18.50 to 29.99 kg/m2. Adolescents are not targeted since the product is not being marketed to adolescents. Older adults are not targeted because they are more likely to experience sleep/circadian abnormalities that can confound results.

No vulnerable populations will be included in this study.

Please select the methods that will be used to recruit individuals. Provide copies of documents, as applicable.

☐	Email	☒	Social Media
☒	Flyers	☒	Online Advertisements
☐	TV, Radio, Print	☐	SONA System
☐	In Person Presentations	☐	Phone Calls
☐	Face to Face	☐	Screening of the Electronic Medical Record (EMR)
☐	Other – please explain below		

When will recruitment occur? Provide a time frame with dates if applicable.

Spring-Summer 2018

Where will recruitment take place?

Tucson, AZ

Informed Consent

Please indicate the informed consent process(es) and/or document(s) to be used in the study.Check all that apply. Provide copies of documents, as applicable.

☒	Informed Consent (ICF)– written form	☒	Informed Consent – oral script/online/unsigned
☐	Assent (participants under 18) – written form	☐	Assent – oral script/online/unsigned
☐	Parental Permission – written form	☐	Parental Permission – oral script/online/unsigned
☐	Translated Consent/Assent – written form(s)	☐	Translated Consent/ Assent- oral script/online/unsigned
☐	Combined ICF/PHI Authorization- form	☐	Waivers of consent or waiver or alteration of PHI
☐	Exception From Informed Consent (EFIC)	☐	Broad Consent for future research
☐	Debriefing Script	☐	Protected Health Information (PHI) Authorization-written form
☐	Short Consent Form- written from	☐	Other – please explain below

Describe in detail the consent processes checked above:

Informed Consent:
Informed consent procedures will be carried out prior to the subjects' participation in the research study. Subjects will be recruited as detailed above.

For the Screening survey, the consent will be online only. They will be instructed to click "I agree" after reading the consent document and will not be allowed to complete the survey until they consent to participation. For the screening portion of the study, we request a waiver of documentation of informed consent.

Qualifying participants will be given the consent form at Baseline visit (described below). Potential subjects interested in participating will be able to read the consent form in private. This will afford the prospective subject the opportunity to read the consent form without undue coercion. Thus, the individual will have a period in which to determine whether or not they wish to continue. During the subject's initial visit, they will meet with a study clinician, who will describe the study in detail, ascertain eligibility, address any concerns, and obtain written informed consent. They will be informed that information related to this research study that identifies them will be collected and that study staff and study sponsor's monitor may see this information while reviewing the records for this study. Study staff will also stress that declining to participate in the trial will in no way interfere with the subject's usual care or their relationship with the University of Arizona. They will also be informed that their participation is voluntary and that they can withdraw at any point, again without jeopardizing their standard of care. The study clinicians will take every precaution to ensure that the prospective subject understands what is being asked of them prior to signing the consent form. They will also ensure that they are aware of the risks and benefits associated with the trial. A signed copy will be given to the subject upon completion.

Data Collection Procedures

Please select the methods of data collection that will be employed in this study (select all that apply):

☐	Audio/Video recording	☒	Anthropometric measures (e.g., height, weight, waist circumference, etc.)
☐	Benign Interventions	☐	Biological Specimens (urine/feces, tissue, saliva, skin, hair, nails, nasal swab)
☐	Biological Specimens- Blood Draws	☐	Biological Specimens- Clinical discarded of blood or spciemens
☐	Clinical Data Warehouse	☒	Cognitive or behavioral measures, including daily diaries (Note- if surveys will also be administered,please select the appropriate option above.)
☐	CT Scans	☐	Data previously collected for research purposes

☐	Deception	☐	Data collected using other communication/electronic devices (e.g., cell phones, pagers and texting devices)
☐	Interviews- Focus groups	☒	Interviews- In person
☐	MRI/ Ultrasound with contrast	☐	MRI/ Ultrasound without contrast
☐	Participant Observation	☒	Non- invasive instruments(e.g. external sensors applied to the body)
☒	Screening Data	☒	Self health monitoring (e.g., pedometers, food diaries, etc.)
☐	Surveys- Paper	☒	Surveys- Internet (including online and email based data collection)
☐	Surveys- Telephone	☒	Randomization with Control and Experimental Groups
☐	Records- Billing	☐	Records- Educational
☐	Records- Employee	☐	Records- Lab, pathology and/or radiology results
☐	Records- Medical Review	☐	Records- Mental Health
☐	Records- Physician/Clinical	☐	Use of recombinant DNA
☐	Use of Social Networking Sites	☐	Use of Stem Cells
☐	X-rays Scans	☒	Other activities or interventions- Describe below

Does this project involve investigating a Drug, Device or Biologic? ☐ Yes ☒ No

Please provide details of the research procedures and include the study population who will be completing them.

All potentially eligible, interested individuals:
INITIAL SCREEN (ONLINE) (DAY -14):
This initial screening will occur online, and will consist of the following:
- Online consent to collect screening information
- Contact information
- Demographic information
- Physical Measures: Height, Weight, body mass index (BMI),
- Medical History (including family medical history and prior and current medication/supplement history)
- Psychiatric History
- Ishihara color test to assess for colorblindness (to determine appropriateness of cognitive testing stimuli)
Participants will be informed if they are colorblind and will be advised to contact their personal physician for further guidance. They will also be provided with contact information for the Psychiatry outpatient clinic should they want to discuss any emerging feelings about the new developments with a mental health professional. For all depression questionnaires participants that score high will be provided Department of psychiatry outpatient services information and advised to contact them.
- PSQI: The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. In addition, a total score will be evaluated in addition to the individual items. A score of 5 has been identified as a cutoff for “poor” sleep (Buysse et al., 1989).
- CESD The Center for Epidemiological Studies Depression scale is a well-validated measure of mood symptoms that captures clinically relevant symptoms, as well as sub-clinical complaints. This scale will allow for a fuller characterization of depression symptoms and complaints. A total score is calculated for this tool.
- ISI: The Insomnia Severity Index is a brief insomnia screening tool that is the gold standard for quantifying severity of clinical insomnia symptoms. As with the PSQI, the ISI is included to account for changes in sleep due to treatment. In addition, a total score will be evaluated in addition to the individual items.
- PSS: The perceived Stress Scale is the most widely used psychological instrument for measuring the perception of

stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. A total score is calculated for this tool.
- MAP: The Multivariable Apnea Prediction (MAP) index The Multivariable Apnea Prediction Index is a standardized tool used to estimate the risk of sleep apnea based on existing risk factors, including nighttime respiratory symptoms (loud snoring, snorting or gasping, choking or struggling for breath/perception of breathing cessation), frequency and other factors like age, sex, and body mass index. Any subject with a sleep apnea risk score of 0.5 (Moderate Risk) and over will be disqualified and will be referred to a Banner Health sleep center. A total score is calculated for this tool.
- HRQOL: the CDC Health-Related Quality of Life (HRQOL) examines the subject's perceived physical and mental health over time. These questions ask about recent pain, depression, anxiety, sleeplessness, vitality, and the cause, duration, and severity of a current activity limitation an individual may have in his or her life. A total score is calculated for this tool by subtracting healthy days from unhealthy days in a 30 day period
- POMS: The Profile of Mood States (POMS) is a psychological rating scale used to assess transient, distinct mood states. The POMS measures six different dimensions of mood swings over a period of time. These include: Tension or Anxiety, Anger or Hostility, Vigor or Activity, Fatigue or Inertia, Depression or Dejection, Confusion or Bewilderment. A total score will be evaluated in addition to the individual items.
- PHQ9 : The PATIENT HEALTH QUESTIONNAIRE-9. (PHQ-9) will screen for depression symptoms. It is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression: It incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. Participants with a score >9 will be excluded. A total score is calculated for this tool.
- BRISC: Brief index of sleep control. The BRISC is a reliable and valid screening tool to estimate self-perceived control over sleep across multiple domains. It is brief, simple, and strongly associated with overall self-reported sleep quality, insomnia, daytime sleepiness, and sleep duration. Total BRISC scores are computed as an average of item scores.

- Sleep continuity items: included to account for changes in sleep due to treatment. Individual items will be evaluated

- Karolinska Sleepiness scale: The KSS is a 9-point Likert scale that provides a subjective assessment of an individual's level of drowsiness at the time of the assessment. Is included to account for changes in sleep due to treatment.

The STOP-Bang questionnaire: is a validated screening tool for Obstructive Sleep Apnea (OSA). The higher the STOP-Bang score, the greater is the probability of moderate-to-severe OSA. Participants that screen high on the STOP-Bang at any point of the study will be disqualified and referred to a Banner Health sleep center.

All potentially eligible individuals who pass online screening:
BASELINE VISIT (DAY 0± 3):
Subjects deemed eligible will be scheduled for an initial study visit to further determine eligibility and obtain baseline assessments. Subjects will be schedule to arrive at their convenience and will complete the following measures/procedures:
- Obtaining informed consent for the study
- Measurement of height, weight, body mass index (BMI) using professional equipment
- Readministration and reassessment of medical, psychiatric, and sleep history, inclusion and exclusion criteria, and prior and current medication/supplement use, and vital signs
- Female participants will have a urine pregnancy test administered.
- Re-administration of screening questionnaires to ensure eligibility (PSQI, CESD, ISI, PSS, Sleep Continuity, BrISC, STOP-Bang: See above)

- Administration of the International Neuropsychiatric Inventory (MINI), a standard structured interview for the detection of DSM-IV mental illness.
- Administration of the Profile of Mood States (POMS): a psychological rating scale used to assess transient, distinct mood states. The POMS measures six different dimensions of mood swings over a period of time. These include: Tension or Anxiety, Anger or Hostility, Vigor or Activity, Fatigue or Inertia, Depression or Dejection, Confusion or Bewilderment. A total score will be evaluated in addition to the individual items.
- Administration of the Automated Self-Administered 24-hour (ASA24®) dietary assessment tool, will be used to provide 24-hour dietary intake data in the form of food diaries. Subjects will report guide respondents to report eating occasions and time of consumption. ASA 24® will be completed at home at the subject's convenience online via a link that will be provided to them after the Baseline Visit. Subjects will be provided with a username and password generated by study staff.
- Assessment of baseline sustained attention using PVT-Touch: The Psychomotor Vigilance Task (PVT) is routinely used to assess impairment due to sleep loss and is the gold-standard of assessment of neurobehavioral impairment associated with sleep curtailment. Variables obtained will include mean and median reaction time (RT), and number of lapses (RT greater than 500ms). The PVT is a simple task where after being handed a touch screen device the subject presses the screen as soon as soon as a stimulus appears on the screen (i.e a bullseye). The stimulus will appear randomly every few seconds for 5–10 minutes. The main measurement of this task is not to assess the reaction time, but to see how many times the button is not pressed when the stimulus is on. The purpose of the PVT is to measure sustained attention, and give a numerical measure of sleepiness by counting the number of lapses in attention of the tested subject.
- Administration of Expectancy Questionnaire.
- Assessment of neurocognitive function, using tests of working memory and executive function. These will be administered on a tablet, and will include:

1. Spatial working memory capacity: Working memory refers to the ability to hold information in memory in order to be manipulated. Previous studies have shown that sleep loss impairs working memory. Working memory will be assessed with n-back tasks and Visual and spatial working memory will be assessed with the Visual Object Learning Task (VOLT). The n-back task assesses a person's ability to hold information in memory for a period of time when presented with distracting information. Participants are shown a sequence of six images one at a time and are to identify images that occurred "n" trials ago. "N" will vary for each trial. Example trial: before they start with the trial participants will see a message asking them to tap the screen if the picture on the screen is the same one they saw 2 screens ago (2-Back). For every picture they see they must recall if they had seen it exactly 2 pictures ago. If picture 4 and picture 6 are the same they would tap the screen once they see picture six because it is the 2-Back. They are directed to be as fast as and accurate as possible Average administration time: 1.9 min
For the Visual Object Learning Task (VOLT) Participants first memorize a set of 3-dimensional Euclidean shapes. During recall, participants are to distinguish between the initial shapes mixed with ten distractor shapes. Average administration time: 1.7 min

2. Motor Praxis Task (MPT) : assesses sensory motor speed. Participants are to quickly touch ever-shrinking boxes. Each time a new box appears in a different location on the screen. Average administration time: ~30 seconds

3. Abstract Matching (AM): Assesses abstraction. Participants select pairs of shapes that fit with another shape. Average administration time: 2.4 min

4. Line Orientation Task (LOT) : Assesses spatial orientation. Participants are shown two lines at different angles, and are to rotate one line incrementally until it is parallel to the other. Average administration time: 2.1 min

5. Digital Symbol Substitution Task (DSST) : Assesses complex scanning and visual tracking. Participants touch the number paired to the symbol that matches the current target symbol. Average administration time: 1.6 min

6. Balloon analog risk task (BART): Assesses Risk-decision making. The BART involves a virtual balloon that can be inflated with the press of a button. The goal of the task is to inflate the balloon as much as possible without popping it. However, the bigger the balloon is, the more likely the next button press will pop it. Previous studies have shown that sleep deprivation impacts functioning on the BART. Average administration time: 2.3 min

Subjects will be provided a Fitbit Charge 2 fitness tracker, this device will be used to objectively characterize sleep during the study period. Fitbit sleep outcomes will include: Total Sleep Time, Sleep Efficiency, %Light Sleep, %Deep Sleep, %REM Sleep (weekly averages). Fitbit will be worn device 24/7, unless it is charging or if the participant is swimming or doing some other activity that involves prolonged contact with water.
Subjects will then be instructed on study procedures including completion of a daily study diary, this diary will be used to prospectively track sleep pattern. The diary will record standard information, including time to bed, sleep latency, awakenings, Wake After Sleep Onset (WASO), time awake, time out of bed, naps, exercise, and other sleep-related information. Subjects will also be instructed to keep a consistent diet and lifestyle routine throughout the study. Sleep Diary Outcomes will include: Total Sleep Time, Sleep Latency, Wake After Sleep Onset, Sleep Efficiency (weekly averages).

Participants will then be randomized to one of the study conditions and will be provided instructions to take the product 30 minutes before bedtime starting on Day 3. This will provide 3 NIGHTS of pre-supplementation data for all study groups. A randomization schedule will be created using the excel rand() function indicating the order of randomization. Each participant will be assigned a randomization code according to the order of the randomization list generated. Enrolled participants will be randomized to the different treatment arms at day 0. A copy of this randomization code will be provided to the study sponsor. Recruitment will be achieved in an ordered, blocked design. For the first study (study blend vs placebo), recruitment will occur in blocks of 20, such that for each 20 subjects, 10 will be randomly assigned to each group. The same approach will be used for the second study (Spearmint extract and green tea blend+ melatonin vs melatonin alone).

Study Product
All products to be administered 30 minutes before bed for 30 nights (all will be mixed with excipient to be equivalent weight, capsule size, in an opaque capsule-to ensure blinding):
Phase 1:
Placebo
Spearmint extract and green tea blend (500 mg)
Phase 1 is a comparison of a proprietary Spearmint extract and green tea blend to placebo when administered 30 minutes before bed, on objective measures of sleep. Phase 2 will evaluate the benefits of the Spearmint extract and green tea blend + Melatonin over Melatonin alone.

Phase 2
Melatonin (1 mg)
Spearmint extract and green tea blend (500 mg) + Melatonin (1 mg)
Phase 2 will evaluate the benefits of Spearmint extract and green tea blend + Melatonin over Melatonin alone when administered 30 minutes before bed, on objective measures of sleep.

All subjects:
STUDY VISIT 2 (DAY ±3 DAYS):
- During this study visit subjects will scheduled to arrive at their convenience and will complete the same measures as day 0 (the ASA24® will be completed ± 3 days prior to study visit at subject's convenience); however, in addition study diaries will be collected and fitbit data will be evaluated for completion. Subjects will be reminded of procedures including completion of a daily study diary and to keep a consistent diet (including medications, vitamin and supplements and lifestyle routine throughout the study).

All subjects:
FINAL VISIT (DAY 33) ±3 DAYS:
- During this final study visit, the procedure will be identical to STUDY VISIT 2, re-administering all baseline assessments (the ASA24® will be completed ± 3 days prior to study visit at subject's convenience).
- Unused investigational product will be brought to this visit in the original packaging, including remnants, and calculate compliance by counting the returned unused investigational product.

Subset of 5 subjects from each of the two Phase One groups:
Exploratory analysis: Polysomnography
POLYSOMNOGRAPHY (PHASE 1 ONLY)
PSG NIGHT 1 (Day -1):
• A subset of N=5 individuals from the Phase 1 groups (N=10 total) will stay overnight for 2 nights in the Center for Sleep and Circadian Science. Of the N=50 in each group, N=5 will be randomly selected to be offered this study condition. If that individual declines, an individual will be chosen at random from the remaining that were not chosen in order to achieve N=5 per group. Random number generation will be accomplished using the Excel RAND() function. The protocol for these visits will include:
• Subjects will be escorted to the lab, where Informed consent will be obtained and they will be oriented by study staff
• They will be hooked up to equipment for an overnight polysomnography study. If the patient does present with an identified sleep disorder that would exclude them from further study (e.g., sleep apnea), they will be withdrawn from the study, they will be provided their study results and the contact information for the University Medical Center Tucson's Center for Sleep Disorders so they can pursue/receive further clinical evaluation. These screenings will be conducted according to the CSCS's research standards. The recording montage consists of 14 electrophysiological signals. The basic montage includes 2 EOGs referenced to a single mastoid [LOC & ROC], 6 EEGs referenced to linked mastoids [F3,F4, C3, C4, O1, O2,], 1 bipolar mentalis, an EKG, 2 bipolar tibial EMGs (to screen for Periodic Limb Movement Disorder), a nasal/oral airflow thermocouple, 2 respiratory effort sensors, and an oximeter measure of blood oxygen saturation (to screen for sleep apnea). All 14 signals will be recorded with SD32 amplifiers and use Sandman v10 acquisition software to transmit data directly to the control room where the PSG can be monitored online and simultaneously recorded to PCs located in the control room. PSG data will be scored according to Rectch and Kales standards (epoch by epoch state determinations) and the sleep continuity and sleep architecture variables will be calculated to lab standards. Additionally, AI/AHI and PLMI indices will be calculated according to AASM criteria. Subjects with an AI (vs. AHI) and a PLMI of >10 (or who exhibit evidence of other sleep disorders) will be ineligible to continue the study and will be referred to a clinic. The specific time to bed will be scheduled based upon the subject's habitual time to bed (as determined by the sleep diary).

PSG NIGHT 2 (DAY 32) ±3 DAYS:
- The subset of N=10 that completed polysomnography assessment at the start of the study will again complete that assessment at the end of the study in an identical protocol

- Outcomes evaluated will include: total sleep time, sleep latency, wake time after sleep onset, sleep efficiency, % Stage N1, % Stage N2, % Stage N3, % Stage REM, Arousal Index, Fragmentation Index.

This will be performed as an exploratory analysis to understand the correlation between the FitBit data and the PSG for powering of a larger second trial.

Please state the estimated time commitment for subject participation.

33 Days, ±3 days

Benefits, Costs, Compensation & Risks

Describe the anticipated benefits of this study to society, academic knowledge or both.

It is possible that the study supplement could improve sleep quality. An indirect benefit includes contribution to advancing science.

Describe any benefits that individuals may reasonably expect from participation.

It is possible that the study supplement could improve sleep quality.

Describe any costs, monetary and non-monetary, that subjects may incur.

There are no costs to subjects except for their time.

Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.

Subjects will be paid up to 400 dollars for completion of the study (100 for Baseline Visit, 100/Study Visit 1, 200 for Fin Visit).

Please describe all physical, psychological, social, legal, and/or economic risk you feel are associated with participation in this research. NOTE: Risks not directly related to the research need not be included in this section.

Risks associated with the study supplement (spearmint extract+ Green tea blend):
All components of the study supplement are naturally derived, and there are no noticeable side effects associated with the use of this supplement. At higher doses than those used in this study, risks associated may be gastrointestinal disturbances or stomach discomfort.

Risks associated with melatonin may be headache dizziness, nausea, drowsiness, other less common side effects might include short-lasting feelings of depression, mild tremor, mild anxiety, abdominal cramps, irritability, reduced alertness, confusion or disorientation.

Risks associated with questionnaires, interviews, and physical measurements:
It is possible that answering questions in an interview format or in a questionnaire format can arouse uncomfortable feelings or even some level of distress. Although this is very rare, it is possible. It is hoped that the courtesy, professionalism, and experience of these staff members allays any concerns regarding issues arising from the assessments.
Polysomnography is a noninvasive, painless test. Complications are rare. The most common side effect is skin irritation caused by the adhesive used to attach test sensors to participant's skin. Physical discomfort from wearing the sensors and sleeping in a new place and restlessness can also occur.

Though there are risks to confidentiality, these will be minimized as much as possible by proper data management.

Regarding the Fitbit, some irritation to the wrist may occur due to prolonged wearing of the device.

Discuss what steps have been taken to minimize risk to subjects/data.

Study/Clinic staff will be present and/or available at all times to oversee pertinent study activities and provide or arrange for any necessary care. Adverse events will be reported to the IRB per its reporting requirements. A Responsible Physician will be available in case of any emergent events, and will assess serious adverse events to monitor for subject safety.

All study staff will be trained to handle all study activities within their purview and work with the Regulatory Coordinator to assure proper oversight and reporting.

Unblinding will not occur except in the case of emergency situations. In the event that a serious adverse event occurs for which the identity of the investigational product administered is necessary to manage the participant’s condition, the treatment received by the participant will be unblinded and the investigational product identified. Concealment of the allocation of treatment will be employed through the use of opaque sealed envelopes, each labeled with a

randomization number. Each envelope will contain information regarding the treatment associated with each randomization number. These envelopes will be readily available for the investigator to open in the event that it becomes necessary to know which product a participant is taking for the sake of the participant's health care.

Source documents will be reviewed by the sponsor's monitors at regular intervals, in part to ensure that AE's/SAE's are being monitored and reported as required, and that study product is being stored correctly.

Describe the provisions for medical care and available compensation in the event of research related injury. If the Human Research has a clinical trial agreement, this language should reflect what is stated in the agreement.

Study/Clinic staff will be present and/or available at all times to oversee pertinent study activities and provide or arrange for any necessary care. A Responsible Physician will be available in case of any emergent events, and will assess serious adverse events to monitor for subject safety.

Compensation for injury that is a direct result of this research is available from the sponsor.

Privacy and Confidentiality

Will the research team be accessing medical records, educational records or employee records during the research? ☐ Yes ☒ No

Where will the data be stored?

☒	REDCap	☐	Clinical Data Warehouse
☐	Box@UA Health	☐	Box@UA
☒	Password Protected Drive	☐	Encrypted Drive
☐	External Drive (USB, Flash drive)	☒	Department Drive
☐	Cloud Server	☐	UA Records Management & Archives
☒	Departmental Office	☐	Other – please explain below

For each of the storage location checked above, discuss the type of data to be stored (including if the data is identifiable), who may have access to the data, and how long the data will be kept.

*NOTE: You are responsible for following University policy and guidelines for proper transmission and storage of Confidential or Regulated Data, including PHI.

All data will be coded to a master list, which will be kept separately from study data, will be in a locked office, and will only authorized staff will be given access to it. Consent forms will also be kept in a locked cabinet in a locked office only accessible to qualified staff in the PI's research suite.

Paper and computer records will be kept in a secure location and only be accessible to personnel involved in the study. All records will be kept in locked file cabinets. Subject paper files will not contain any identifiable information (e.g., shipping information, screening questionnaire, informed consent). This will be kept in a separate, also locked, location. All computer files will also not include identifiable information. Emails to and from volunteers may be kept in archives, but may only be sent to and from secure email addresses. The only exception is that in some cases, some computer files may include subject ID number and initials (e.g., home sleep study data files). All computers and file cabinets will be behind closed, locked doors. Whenever feasible, identifiers will be removed from study-related information.

REDCap is a secure, web-based application designed to support data capture and storage for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap has been designed to allow for compliance with such standards as HIPAA, 21 CFR Part 11, FISMA (low, moderate, high), and international standards. Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields. The University of Arizona is an institutional member with a Bioinformatics

Manager in the CaTS Research Center responsible for development and maintenance. This application will be used in the development of electronic forms for data collection to be used by study staff in screening and seeing subjects for study visits.

Participants consent to having their data stored indefinitely. After primary study completion data will be de-identified and master list containing identifiable subject information will be destroyed.

Will you be transmitting/receiving any subject data to/from an outside group? ☒ Yes ☐ No

Describe the data to be transmitted/received, name of outside party institution and how the data will be transmitted/received (e.g., secure file transfer, encrypted email).
*NOTE: If you will be transmitting or receiving any PHI or a Limited Data Set as a part of your project, Please go to the following link to review the Data Use Agreement (DUA) from the HIPAA Privacy Program.

A brief monthly report will be submitted to the sponsor (template to be provided by sponsor) and discussed during the end of the month conference call. This report outlines subjects screened, randomized and status within the study, protocol Deviations, and any adverse events that have occurred.

Source documents will be reviewed byt study monitors at previously agreed upon dates to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The participant files will be reviewed to confirm that:
i) Informed consent was obtained and documented
ii) Enrolled participants fulfilled all inclusion criteria and did not meet any exclusion criteria;
iii) AE/SAE reporting has been performed as applicable
iv) Study visits have been conducted as per protocol and information has been recorded in the appropriate place in the source document
v) The study product is being stored correctly and an accurate record of its dispensation to the study participants is being maintained (accountability)
Incorrect, inappropriate, or illegible entries in the participant files will be returned to the Investigator or designee for correction. No data disclosing the identity of participants will leave the study center. The Investigator and any designees will maintain confidentiality of all participant records.
The Investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections and will allow direct access to source data and documents for these purposes.

Discuss how, when and why subjects/data may be removed from the study. If abrupt withdrawal is necessary, discuss how subjects will be withdrawn so that they are not put at increased risk. Discuss what happens if a subject is withdrawn from one part of the study but asked to continue with other parts, such as ongoing follow-up.

If it becomes evident that the participant is unable or unwilling to comply with study procedures, research study staff may withdraw that individual from the study.

Subjects can voluntarily withdraw from the study at any time by speaking with the PI or study team. The study staff will then ensure the subject withdraws from the study safely and will provide any necessary follow-up care. Subjects will be informed that declining to participate in the sleep research project will in no way interfere with their usual care or relationship with the University of Arizona. They will also be informed that their participation is voluntary and that they can withdraw at any point, again without jeopardizing their standard of care.

The Responsible Physician may remove a subject from the study for any serious adverse event if he/she determines it is in the interest of the subject's safety.

In order to protect subjects, study resources, and the integrity of study data, the Principal Investigator reserves the right to remove any subject at his discretion from the study. This will be communicated to prospective subjects during the consent process.

Describe steps, if any, to protect the privacy of the subjects throughout their participation in the Human Research (e.g. during the recruitment process, consent process, and/or research procedures).

Protection of subject privacy:
Potential subjects interested in participating will be able to read the online disclosure form in private.
Data will only be identified by a unique study ID number assigned to each subject. Once enrolled in the study, this will be the only means of participant identification. No data disclosing the identity of participants will leave the study center. Subjects will be seen in a private room. Publication of all results will maintain participant anonymity.

Protection of data confidentiality:
All subject data will be identified only by code number. Code numbers will be used in all documents for review, evaluation and analyses. Paper research documents will be maintained under double-locked conditions (a locked cabinet within a locked room) and made available only to authorized staff working directly on this project. The master list linking subject identification to their data will be stored in a password-protected file on University servers and/or in the locked paper file described above.

Use of Data/Specimens

In which of the following formats will the data be stored? ☐ Identifiable ☒ Coded ☐ De-Identifed

Who will maintain the code and where will it be stored?

Dr. Grander and the SHRP team will maintain the code and it will be stored in UAHS suite 7326 until study completion at which time it will be destroyed.

What security controls (e.g. administrative, physical, technical) are in place to make sure data/ specimens are secure?

See above

Will data/ specimens be kept for future research, including unspecified future research, genetics and/or whole genome sequencing? ☒ Yes ☐ No

Include a separate section in the informed consent that reflects the future use and storage. See HSPP Guidance, Storing research data and/or specimens for future use.

Will subjects receive results for any future research? ☐ Yes ☒ No

Will the data /specimens be stored in a repository? ☐ Yes ☒ No

Will the data/specimens be shared with collaborating entities? ☒ Yes ☐ No

Will the data/specimens be sold to pharmaceutical companies? ☒ Yes ☐ No

Explain where the data/specimens will be going:

Final report will be submitted with the following format within 4 weeks of study completion.
Title Page
Study Site
Sponsor

Abstract
Include Keywords

Background

Methods
Subjects
Study Design
Patient Populations

Inclusion/Exclusion
Outcome Measure Assessments (for each tes.)
Study Product
Statistical analyses
Results
Subject Demographics and Baseline Comparability
Description of intention-to-treat (ITT) and per protocol (PP)
Outcome Measures for Each Population (ITT, PP)
Safety and Tolerability
Adverse Event Breakdown
Compliance
Discussion
Relevance to Existing Literature (does data agree with or contradict existing literature)
Include Study Limitations
Include Clinical Relevance

Conclusion
References

Provide a brief lay discussion of the plan to monitor for subject safety, if applicable. Describe how the data will be evaluated, include a timeline of when the review(s) will occur, who will review the information, and what information will be reviewed. If there will not be a way to monitor for subject safety, please explain.

Study/Clinic staff will be present and/or available at all times to oversee pertinent study activities and provide or arrange for any necessary care. Adverse events will be reported to the IRB per IRB policies.
All study staff will be trained to handle all study activities within their purview and work with the regulatory coordinator to assure proper oversight and reporting.

An adverse event (AE) is any untoward medical occurrence in a clinical investigation participant who has been administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not it is considered related to that product. Pre-existing conditions which worsen during a study are to be reported as AEs.

During the study, participants should record any adverse effects in their diary. At each visit the participant will be asked "Have you experienced any difficulties or problems since I saw you last"? Any adverse events (AEs) will be documented and in the study record and will be classified according to the description, duration, intensity, frequency, and outcome. The qualified investigator will assess any AEs and decide causality.

Intensity of AEs will be graded on a three-point scale (mild, moderate, severe) and reported in detail in the study record.
Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

The causality relationship of investigational product to the adverse event will be assessed by the qualified investigator as either:
Most probable: There is a reasonable relationship between the investigational product and AEs. The event responds to withdrawal of investigational product (dechallenge) and recurs with rechallenge when clinically feasible.
Probable: There is a reasonable relationship between the investigational product and AEs. The event responds to dechallenge.

Possible: There is a reasonable relationship between the investigational product and AEs. Dechallenge information is lacking or unclear.
Unlikely: There is a temporal relationship to the investigational product administration but there is no reasonable causal relationship between the investigational product and the AEs.
Not related: No temporal relationship to the investigational product administration or there is a reasonable causal relationship between non-investigational product, concurrent disease or circumstance and the AEs.
20)21) Serious Adverse Event
A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that results in any of the following outcomes:
1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability or incapacity
5. A congenital anomaly/birth defect in the offspring of a participant who received the study treatment
Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

You have now completed this form. Next steps:

1) Please save a copy of this document for your records.

2) Email the form to the appropriate individuals for their approval.

3) Once it is ready email the application and attach all additional documents to vpr-irb@email.arizona.edu. Please review HSPP Guidance for any additional documents that are needed.

Principal Investigator

I certify that the information I provide in this application is correct and complete.

☒ Attestation of Principal Investigator

Michael Grandner, PhD, MTR, CBSM, FAASM	Mar 15, 2018
Typed name of Principal Investigator	Date

Scientific/Scholarly Review (See HSPP Guidance on requirements for Scientific/Scholarly Assessment)

☐ Nationally based, federal funding organization (NIH, NSF) subject to full peer review
☐ Nationally based, non-federal funding organization (March of Dimes, Amer Academy of Pediatrics) subject to peer review
☒ Locally constituted peer review (signature required)

Mar 7, 2018

Signature Scientific/ Scholarly Review

Date

Francisco Moreno, M.D., Professor of Psychiatry, College of Medicine Tucson

Print Name and Title

NOTE: Actual signature is not require. The HSPP Office will accept either email confirmation or an actual signature. This means that all signatures might not be on the same document. Attach email confirmations with your submission.

Department/Center/Section Review

I have reviewed this application and determined that all departmental requirements are met and that the investigator has adequate resources to conduct the Human Research.

Mar 6, 2018

Signature of Department/ Center/ Section Review

Date

Ole Thienhaus, M.D. Professor and Department Head, Psychiatry

Print Name and Title

NOTE: Actual signature is not required. The HSPP Office will accept either email confirmation or an actual signature. This means that all signatures might not be on the same document. Attach email confirmations with your submission.

Responsible Physician (projects involving medical procedures which the PI is not licenced to conduct)

I am a physician licensed by the State of Arizona. I will be responsible for ensuring that all procedures that are part of this project and that require the attendance of a licensed physician will have a suitable physician present during the procedures. If at any time this is not possible, I will inform the IRB before any procedures are conducted.

May 16, 2019

Signature of Department/ Center/ Section Review

Date

Salma Imran Patel, MD, MPH

Print Name and Title

NOTE: Actual signature is not required. The HSPP Office will accept either email confirmation or an actual signature. This means that all signatures might not be on the same document. Attach email confirmations with your submission.