HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Use of the Frequen-ZZZ Sleep Pad to Increase Restorative Sleep: A Proof-of-Concept Study

Principal Investigator:
Name: Anne-Marie Chang
Department: Biobehavioral Health
Telephone: 814-863-5226
E-mail Address: amchang@psu.edu

Version Date:

Provide version date for this document. This date must be updated each time this document is submitted to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

12/08/2023

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual," under "ClinicalTrials.gov" for more information.

NCT05908344

Human Research Protection Program
Office for Research Protections
101 Technology Center
University Park, PA 16802-7014
Phone: 814-865-1775
Fax: 814-863-8699
Email: irb-orp@psu.edu
https://www.research.psu.edu/irb

Table of Contents

1.0 Objectives

1.1 Study Objectives

We propose to examine the potential effects of the Frequen-ZZZ/Sleepergize sleep pad – a noninvasive, unobtrusive appliance that generates a magnetic gradient, and that is used on the bed – on multiple sleep outcomes in an 8-week randomized crossover study, and to calculate the effect sizes of the intervention to inform power and sample size for future studies.

1.2 Primary Study Endpoints

Primary outcomes include changes in:
-slow-wave sleep (e.g., stage N3 quantity, proportion, & power-spectral features)
-sleep duration
-sleep onset latency
-sleep quality (e.g., frequency and duration of awakenings; sleep stage entropy measures)
-insomnia symptoms (e.g. self-reports on the Insomnia Severity Index [ISI])

1.3 Secondary Study Endpoints

Secondary outcomes include changes in:
-other sleep stages (e.g. N1, N2, REM; quantity, proportion, & power-spectral features)
-spindle characteristics (e.g., count, stage distribution, power-spectral features)
-other subjective outcomes
-inflammatory biomarkers

Exploratory outcomes are changes in pain intensity, pain-related functional interference, and dream content valence.

Additional data to be collected:
These are not considered “Endpoints” because we are not planning an analysis that compares groups based on the following criteria. This information is collected at the Consent visit (#1):

-Demographics: Although this is a small pilot study, demographic questions are relevant to characterize the overall participant sample when reporting data. This information is for the purpose of recognizing potential limitations of our recruited study group (e.g. our ability to extend the results to other groups). These items (“SES Survey” in CATS) were inspired based on the NIH-NIA CROMS system template for clinical trials and standard NIH-funded race/ethnicity questionnaire (“Race and Ethnicity Survey”) with some adjustments (for example: included is an income question to reflect the overall sample’s financial SES for this small sample size study, selected rather than the income amount brackets otherwise typically included in similar surveys for larger studies).

-Health History: This survey includes items considered by the Investigators to be minimally sufficient context for interpreting a particular participant’s sleep data and the potential relatedness of study events to the intervention. Some responses also prompt consenting team members to ask relevant probing questions that assess participant readiness for participation/scheduling. This also includes potentially relevant sleeping behavior covariates for exploration, such as sleeping position.

2.0 Background

2.1 Study Rationale

Studying the relationship between sleep and health is important to understand how we might optimize sleep to the benefit of our overall mental and physical well-being.

Normal healthy sleep is generally categorized as the absence of sleep disturbances and disorders, but it also involves obtaining sufficient duration, good quality, and appropriate timing.[8] Insufficient or poor sleep results in a greater risk for adverse health outcomes and complication, and also has been associated with increased mortality rates and diminished quality of life.[9] Therefore, sleep is associated with overall well-being and is necessary for health maintenance. This pilot intervention is expected to provide evidence for the feasibility and efficacy of a sleep-enhancing intervention that generates and systematically applies magnetic field potentials to a sleeper's environment. The exact mechanism of this intervention is not yet understood.

Insufficient sleep, as well as the negative affect and perceived stress that tend to co-occur with poor sleep, have all been linked with higher levels of peripheral inflammation[12,13]. A preponderance of work investigating links between sleep and inflammation is focused on adverse effects of sleep *disruption*; here, we hope to focus on whether changes can be effected by sleep *improvement*, and specifically by sleep improvement via this unique intervention type (non-invasive, unobtrusive electromagnetic field potential).

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Written informed consent is obtained from the subject.
2. Subject is an English speaker and reader. They are able to understand the procedures related to the study.
3. Subject is 40-65 years of age at enrollment
    a. By self-report at Screening & verified with photo ID at full Consent
4. Subject is not engaged in rotating or nocturnal shift employment
    a. By self-report at Screening
5. Subject is living independently
    a. By self-report and/or according to their status at a community living facility
6. Subject's personal residence is equipped with functional WiFi and subject is willing to permit study device connection to their WiFi
    a. By self-report at Screening
7. Insomnia Severity Index score of ≥8 at enrollment
    a. Based on self-administration at screening
8. Willing to refrain from initiating new, sleep-directed interventions (e.g. medication; behavioral) that are not a part of this study protocol for the duration of study participation
    a. By self-report
9. Willing to refrain from all nicotine use for the duration of participation
    a. By self-report

10. Willing to refrain from pet access to the bed or sleeping space for the duration of participation (by self-report)
11. Regularly sleeping on a non-water bed
    a. By self-report
12. Has and uses own smart phone or tablet device, and is willing to continue to use personal device daily for study purposes
    a. By self-report

3.1.1 Does this research involve collecting data from individuals residing outside of the US?

☒ No

☐ Yes – identify the countries where data collection will take place

Not Applicable

3.2 Exclusion Criteria

1. Diagnosed with a sleep disorder
    a. By self-report
2. Has an implanted medical device (e.g., pacemaker, cochlear)
    a. By self-report
3. Diagnosed serious mental/neurologic health disorder or substance use disorder
    a. E.g., autism, psychosis, depression/bipolar, dementia
    b. By self-report
4. Personal health history of epilepsy or traumatic brain injury
    a. By self-report
5. Taking any physician-directed pharmacologic intervention for sleep or actively engaged in a clinically-validated course of therapy (including behavioral therapy for sleep)
    a. By self-report
6. Diagnosed with hydration problems, or taking prescribed diuretic medication(s).
    a. By self-report
7. Pregnant, breast-feeding, or planning to become pregnant during the study participation period
    a. By self-report
8. History of negative reaction to acupuncture.
    a. By self-report
9. Recreational use of illicit substances in the past month
    a. E.g., marijuana, cocaine, amphetamines, depressants, hallucinogens (LSD, PCP, mushrooms), narcotics (heroin/opiates)
    b. By self-report
10. Any nicotine use in the past 3 months
    a. By self-report
11. History of sensitivity to, or considers oneself to be uniquely sensitive to, radiofrequency
    a. E.g., discomfort when in physical proximity to radio-emitting objects, such as cell towers or modems
    b. By self-report
12. Was previously engaged in this research as a randomized participant
13. If a participant does not live within a reasonable commutable distance from the PSU-UP campus (i.e. ~20min) to accommodate off-site study visits, then they must be willing to accept the costs and responsibilities of coming to campus (15-17 visits) in order to participate
    a. By self-report

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects may withdraw their consent to participate in the study at any time for any reason.

Researchers may withdraw subjects from participation at any time at their discretion, regardless of participant desire to proceed. Reasons for researcher-determined withdrawal of subjects may include:

1. Discovery that a participant meets any exclusion criterion
2. Subject is unable or unwilling to adhere to protocol requirements, including reasonable scheduling timeline and/or commitments noted in Inclusion Criteria. Specifically:
    a. Initiating a new, sleep-directed intervention (e.g. medication; behavioral) that is not a part of this study protocol during the course of study participation will warrant withdrawal of subjects by researchers (consistent with Inclusion Criteria). Adherence will be determined by intermittent participant self-report on study surveys.
3. Apparent or suspected safety reasons
4. Inability of the research team to conduct the protocol (e.g., technical or power failure)

3.3.2 Follow-up for withdrawn subjects

Safety data would be necessary with early withdrawal only in the case of an adverse event. Participants who withdraw from the study prior to completion and who were already randomized at the time of their withdrawal will be offered a survey similar to those completing the study to assess both their awareness of their assigned condition order and so that they have the opportunity to request to be contacted with information about their randomized order after the study concludes (please refer to CATS attachment, “End of Study Survey”). Study participants who withdraw early from the study will also be offered the same optional Follow-Up survey that is offered to completed participants.

Study participants who withdraw early from the study may or may not be eligible to participate again at a later time, depending on the reason for, and timing of, early withdrawal.

There are not any known risks to participants related to truncation of the study intervention (sleep pad use) in excess of those present prior to participation.

4.0 Recruitment Methods

4.1 Identification of subjects

Participants may be identified and recruited directly by several means. Flyers (please refer to CATS attachment) in the Penn State University Park and Centre County region at cooperating businesses/organizations/facilities will be the primary recruitment method, targeting participants in the central-Pennsylvania region. Additional potential recruitment methods include: word of mouth, web-based advertisements (including social media, e-flyers, or similar virtual communications’ please refer to CATS attachment “Other Electronic Recruitment”), emails through relevant Penn State University listservs, online participant recruitment platforms (e.g., StudyFinder, ResearchMatch, ActivePALS), news stories about the Investigators’ laboratories and their research, and/or direct contact from a repository

of previous research participants who indicated interest in future research participation (using contact information that they provided at that time, please refer to CATS attachment: Direct Recruitment Email").

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

A link to complete the screening (which includes a Screening Consent Form, please refer to CATS attachments) in REDCap will be included in study promotions where feasible. IRB-approved recruitment materials/messages will include contact information (e.g. phone and email) of study staff, which interested parties may use to communicate with members of our research team and inquire about this study. A study-dedicated PSU email account that is password-protected with 2-factor authentication (sleeppad@psu.edu) will be established for use in such communications.

Social media accounts dedicated to this research may be created for recruitment, and researchers will also have the option to re-post/share/tweet/forward and otherwise promote advertising post(s) from their own personal social media accounts. Advertising post(s) will be consistent with approved electronic recruitment language (please refer to CATS attachment, "Electronic Recruitment Language") and flyers.

Interested individuals are directed to complete electronic screening in REDCap and, if eligible, to provide their contact information for use in scheduling an appointment for completing in-person screening qualification activities and Informed Research Consent at a later time.

4.2.2 Where potential subjects will be recruited.

Potential participants will be recruited electronically (email, ListServs, social media), in the location(s) of posted flyers (local to the PSU-UP campus), by word-of-mouth, and/or directly (e.g., email); none of these recruitment avenues are bound to a particular physical location.

Study volunteers may encounter the individual contact information of study team members inadvertently elsewhere (e.g., on the university profile pages). In instances of potential volunteers or participants contacting study team members outside the designated email account, those individuals will be redirected to use the dedicated study email account for study-related messaging.

4.2.3 When potential subjects will be recruited.

Potential participants will be recruited as soon as feasible after IRB approval. Recruitment will continue until the target sample size (n=10) reaches randomization. Participant dropout prior to study completion will warrant recruitment of replacement participants up to the target.

4.2.4 Describe the eligibility screening process. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility.

☐ Eligibility screening is occurring *before* consent* - describe the process below
☒ Eligibility screening is occurring *after* consent - describe the process below
☐ Eligibility screening is occurring, consent is not being obtained in this research - describe the process below

☐ Not applicable - Eligibility screening is not being done in this research

Consent will occur in 2 phases. Eligibility screening will happen after an electronic Screening Consent Form has been completed by the subject in the REDCap system. Qualification according to Inclusion and Exclusion Criteria will occur as a part of this eligibility screening survey (please refer to "Screening Survey" in CATS attachments). Participants are informed of and agree to scheduling & attending an initial study visit where completion of the Informed Research Consent Form occurs (please refer to "Informed Research Consent" in CATS attachments) and data collection begins. Information from eligibility screening may be used and reported as study data.

In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

*Unless informed consent is waived by the IRB, screening before consent is only permitted when screening activities are limited to the collection of information through oral or written communication OR when identifiable private information or identifiable biospecimens is obtained by accessing records or stored identifiable biospecimens. Screening before consent is not permitted if data will be used for activities other than eligibility screening/recruitment (e.g., data analysis).

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form** *[Complete Sections 5.2 and 5.6; If this is the only box checked, mark Sections 5.3, 5.4 and 5.5 as 'Not applicable']*

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent)** *[Complete Sections 5.2, 5.3 and 5.6; If this is the only box checked, mark Sections 5.4 and 5.5 as 'Not applicable']*

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).** *[Complete section 5.2, 5.4 and 5.6; If this is the only box checked, mark Section 5.5 as 'Not applicable']*

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** *[Complete Section 5.5; If this is the only box checked, mark Sections 5.2, 5.3, 5.4 and 5.6 as 'Not applicable']*

5.2 Obtaining Informed Consent

5.2.1 Consent Process

An individual accessing the REDcap screening survey (for study qualification) is first presented with an electronic version of the Screening Consent form. A check-box option to proceed to the survey, indicating implied consent for the screening procedure, is required in REDCap before advancing to the survey. Screening consent is not associated with a particular location, although the Screening Consent form indicates that survey questions may be sensitive in nature

(therefore it is at the discretion of an individual to proceed if accessing the electronic survey in a public setting).

After completing the electronic screening process, qualifying participants will schedule an in-person Informed Research Consent appointment with an IRB-approved study team member who is designated as "involved in consent" in the CATS IRB system. Participants may review the consent form in advance, and will be encouraged to consult with family, friends, their PCP, or anyone else that they may wish to consult before deciding whether to participate.

Informed Research Consent may be completed in the participant's personal residence, in a private area of a participant's community living facility, or in the laboratory space of the PI on the PSU-UP campus. A qualified study team member will inform the subject of all study requirements before the subject decides whether or not to participate. Participants will be able to review the consent document and address questions or concerns prior to completing the form (either hard-copy or electronically in the REDCap system). Study coordinators, the Principal Investigator, and other study staff will engage in the ongoing process of informing subjects about study conditions and other information that will inform their decision about whether or not to continue participating. Participants will be offered a copy (electronic or physical) of the Informed Research Consent for their records.

The study team member will also sign to indicate having conducted consent with a given subject/ID.

In the event that a study volunteer elects to take more time to consider participation before choosing to proceed with the Informed Research Consent at their appointment, study staff will attempt to maintain contact with the study volunteer until such time as the volunteer decides to either schedule another appointment for Informed Research Consent completion or to withdraw.

5.2.2 Coercion or Undue Influence during Consent

It is stated in the Screening and Informed Research Consent Forms that participation in this research is completely voluntary, that not being involved does not have any negative consequences, and that participants may withdraw from the study or their consent at any time without repercussions to them.

5.3 Waiver of Written Documentation of Consent

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental*

permission form for participants who want written documentation linking them to the research.)

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

For distinct cultural groups describe the alternative mechanism for documenting that informed consent was obtained:

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, or implied consent form)

The HRP-585 Screening Consent template is used to sufficiently inform potential subjects about the research.

5.4 Consent – Other Considerations

5.4.1 Non-English-Speaking Subjects

Non-English speakers will not be enrolled in the study.

5.4.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

Subjects who are independent living and indicate both a physical and cognitive capability of self-care will be eligible to participate in the study. Participants will initially self-attest to these criteria on a screening qualification survey and will be further screened by a research team member at full consent. The enrollment population age range in this research is unlikely to present issues related to cognitive decline/MCI.

5.6.2.2 Adults Unable to Consent

Not applicable; those who cannot provide their own informed consent will not be enrolled in the study.

5.6.2.3 Assent of Adults Unable to Consent

Not applicable; those who cannot provide their own informed consent will not be enrolled in the study.

5.4.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Not applicable; subjects must be 40-65 years of age.

5.6.3.2 Assent of subjects who are not yet adults

Not applicable; subjects must be 40-65 years of age.

6.0 Study Design and Procedures

6.1 Study Design

This 8-week, randomized, cross-over, at-home clinical trial of mid-life adults (men and women aged 40-65 years) consists of four segments: Baseline (week 1), active Intervention/Control (weeks 2-4), Washout (week 5), and active Intervention/Control (weeks 6-8).

6.2 Study Procedures

General overview

Participants complete Screening Consent in REDCap and, if eligible based on screening surveys, schedule their consent appointment and study dates.

Participants complete an Informed Research Consent in-person with study staff. Participation in the ~8wk study begins immediately after completion of this consent.

Throughout the entire ~8wk study:
-Ambulatory sleep measurement (via wrist-worn actigraphy, day and night ~24hrs)
-Twice daily self-assessment of sleep, related activities, and device usage (via REDCap sleep diaries [~1min each, totaling ~2min daily]) administered in the morning ("Morning" survey in CATS) and evening ("Bedtime" survey in CATS)
-Weekly REDCap surveys (participants receive survey link at either/both their personal email or phone number [by text message], according to their preference; ~15min each). Participants may choose to receive email or text message reminders, or phone/voicemail reminders, to their personal accounts/devices about surveys
-Responding to questions by staff during each study visit to determine ongoing qualification and possible study events

Overview of 4 study parts (details in below, specific sections):

-"Baseline": Baseline data collection without sleep pad device present/in-use (week ~1) and randomization. Objective sleep monitoring for 2 nights. Blood sample (up to 40cc / up to 3 tablespoons) collected.

-"Phase 1": Active intervention/control with either the sleep pad or an identical-looking/operated 'sham' pad present/in-use nightly (weeks ~2-4). Objective sleep monitoring for 2 nights. Blood sample (up to 40cc / up to 3 tablespoons) collected.

-“Washout”: Break from presence/use of the sleep pad device (week ~5)

-“Phase 2”: Active intervention/control with either the sleep pad or an identical-looking/operated ‘sham’ pad present/in-use nightly (weeks ~6-8). Objective sleep monitoring for 2 nights. Blood sample (up to 40cc / up to 3 tablespoons) collected.

All participants will complete all parts of the study (i.e. both intervention and control) but the order in which they experience these conditions will be randomized at the end of Baseline week after verifying compliance with study procedures and eligibility to continue.

All visits may take place in either a participant’s personal residence or privately at the PSU-UP campus, excepting for participants whose distance from campus is too great for staff commute (i.e., more than about 20min one-way). In those cases, participants must come to the PSU-UP campus for study visits.

Specific study procedures

Polysomnography (PSG): A cluster of measures acquired by bioelectrically-sensitive sensors that include EEG (neurocortical field potentials), EOG (ocular muscle), EMG (chin), and EKG (cardiac activity). Surface (non-invasive) electrodes will be applied to specific locations on the subject's face, head, and chest using temporary adhesives that are designed for clinical use on humans. Our sleep monitoring system permits ambulatory collection via a portable amplifier worn/carried as participants go about their regular activities, with the exception of bathing.

Actigraphy: Activity-sensitive wrist-worn ambulatory device that is non-invasive. Records signals pertaining to motion activity and light exposure. An “on-wrist detection” feature permits compliance verification on devices to determine valid recordings.

Surveys:

Insomnia Severity Index (ISI) - The ISI assesses perceived severity of insomnia. The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = 0.67), the Dysfunctional Beliefs and Attitudes about Sleep (r = 0.55), and sleep diaries (range from 0.32-0.91).[10, 11]

PROMIS Pain Intensity and Interference (PI&I) – The PI&I assesses retrospective average weekly pain both in terms of severity and functionality. Intensity: A weekly self-report quantifying pain on a visual analog scale. Interference: A weekly self-report on a visual analog scale of whether and how much pain interfered with typical daily experiences. Responses to these exploratory surveys are expected to change (improve) as a function of sleep (improvement).[14]

6.2.1 Visit 1 - Informed Research Consent and Baseline Start

Informed Research Consent and study initiation (including and initial intake survey [please refer to CATS attachments “Race/Ethnicity Survey,” “Socioeconomic Survey,” and “Health History Survey”] and collection of payment information (consistent with PSU tax reporting requirements) will take about 1hr to complete. Upon completion:

-Participants receive instruction regarding, and begin data collection with, ambulatory activity (actigraphy) monitor
-Participants are equipped with abbreviated Polysomnography (PSG) monitoring equipment and recording is initiated

Above procedures after Consent take about 1 hour to complete.

-Participants may return home (if applicable) and are continuously monitored throughout the subsequent remaining day and overnight with PSG

6.2.2 Visit 2 (Baseline)

Study team members visit the participant the following morning to remove PSG.

Above procedures take about 30min 'active' engagement to complete.

6.2.3 Visit 3 (Baseline)

After at least one overnight without PSG, another participant visit occurs.

-Actigraphy device is exchanged (for later compliance evaluation).
-Participant is re-equipped with abbreviated PSG and recording is initiated
-Participants return home (if applicable) and are continuously monitored throughout the subsequent remaining day and overnight with PSG

Above procedures take about 1hr 'active' engagement to complete.

6.2.4 Visit 4 (Baseline)

Study team members visit the participant the following morning to remove PSG.

-Participants whose actigraphy data evidence compliance and with at least one successful overnight PSG monitoring proceed in the study. Participants whose activity data suggest noncompliance or who experience technical failure of either actigraphy or PSG during the first study week may have the option (at researcher discretion) to repeat their first week of study activities up to this point without additional compensation.

Above procedures take about 30min 'active' engagement to complete.

6.2.5 Visit 5 (Baseline)

Participant has a fasted (~8hrs immediately preceding the appointment, no food and limited water intake) blood draw conducted by qualified Clinical Research Center (CRC; Noll Laboratory) staff.

-Participant completes weekly REDCap surveys

Above procedures take about 30min 'active' engagement to complete.

6.2.6 Visit 6 (Baseline)

Qualifying participants are randomized to an order of study conditions upon completion of this visit.

-Participant receives the Frequen-ZZZ sleep pad device or sham device (consistent with their randomization order; participant will not be informed of their assignment) and is trained on its setup/use

Above procedures take about 30min ‘active’ engagement to complete.

6.2.7 Visit 7 - Phase I Start: Intervention or Control

Near the end of the 3rd study week, participants have an in-person study visit to be equipped with abbreviated PSG monitoring. Overnight recording is initiated.

Above procedures take about 1 hour ‘active’ engagement to complete.

-Participant returns home (if applicable) and is continuously monitored throughout the subsequent remaining day and overnight with PSG

6.2.8 Visit 8 (Phase I)

Study team members visit the participant the following morning to remove PSG.

Above procedures take about 30min ‘active’ engagement to complete.

6.2.9 Visit 9 (Phase I)

Near the end of the 4th study week, participant is re-equipped with abbreviated PSG. Overnight recording is initiated.

Above procedures take about 1hr ‘active’ engagement to complete.

-Participant returns home (if applicable) and is continuously monitored throughout the subsequent remaining day and overnight with PSG

6.2.10 Visit 10 (Phase I)

Study team members visit the participant the following morning to remove PSG.

Above procedures take about 30min ‘active’ engagement to complete.

6.2.11 Visit 11 (Phase I)

Participant has a fasted blood draw conducted by qualified Clinical Research Center (CRC; Noll Laboratory) staff. This visit (11) may be combined with the previous visit (10) if a participant elects for the blood draw to occur in their personal residence.

-Participant returns the bedside controller.
-Participants keep the bed pad portion of the sleep pad system for re-use later in the study.

Above procedures take about 30min ‘active’ engagement to complete.

6.2.12 Washout and Visit 12

The ~5th study week will consist of a "washout" during which no participants use the functional features of sleep pad system. However, throughout this week, participants do continue 24hr actigraphy monitoring, continue to complete daily sleep diary and device usage survey entries (~2min combined), and continue to complete the weekly REDCap survey all noted in the general summary above.

Note that an optional pause of study activities at the conclusion of the Washout week will be available. Participants are not required to continue passive (actigraphy) monitoring or surveys during any pause period (>1wk). Maximum duration of appropriate pause will be determined by Co-Investigators, but is not anticipated to exceed 10wks.

Total anticipated Washout active study time commitment is 30min.

At the beginning of study week 6, a participant receives again for use the bedside controller, either by delivery (in-person or by mail) or pickup from PSU-UP campus. Because receipt may occur in person, this is considered the "12th visit" although not necessarily requiring a "visit".

6.2.13 Visit 13 – Phase 2 Start: Intervention or Control

Near the end of the 7th study week, participants have an in-person study visit to be equipped with abbreviated PSG monitoring. Overnight recording is initiated.

Above procedures take about 1 hour 'active' engagement to complete.

-Participant returns home (if applicable) and is continuously monitored throughout the subsequent remaining day and overnight with PSG

6.2.14 Visit 14 (Phase 2)

Study team members visit the participant the following morning to remove PSG.

Above procedures take about 30min 'active' engagement to complete.

6.2.15 Visit 15 (Phase 2)

Near the end of the 8th study week, participant is re-equipped with abbreviated PSG. Overnight recording is initiated.

Above procedures take about 1hr 'active' engagement to complete.

-Participants returns home (if applicable) and is continuously monitored throughout the subsequent remaining day and overnight with PSG.

6.2.16 Visit 16 (Phase 2)

Study team members visit the participant the following morning to remove PSG.

-Participant returns sleep pad system (including pad and controller).

Above procedures take about 30min 'active' engagement to complete.

6.2.17 Visit 17 (Phase 2)

Participant has a fasted blood draw conducted by qualified Clinical Research Center (CRC; Noll Laboratory) staff. This visit (17) may be combined with the previous visit (16) if a participant elects for the blood draw to occur in their personal residence.

Upon completion, participants receive a ~1min survey to assess both their awareness of their assigned condition order and so that they have the opportunity to request to be contacted with information about their randomized order after the study concludes (please refer to CATS attachment, "End of Study Survey"). Participants also receive an optional ~1min survey via email that is administered through REDCap shortly after ending participation (please refer to CATS attachment, "Follow-Up Survey").

Above procedures take about 30min 'active' engagement to complete.

6.3 Duration of Participation

Screening Consent activities are expected to take about 30min to complete (including initial remote electronic survey and in-person activities at the first study visit). One session expected (secondary screening), with another session optional (if not qualifying on abbreviated MoCA).

Consent activities are expected to take about 1hr to complete. One session is expected, with additional optional session(s) if a participant decides they want more time to consider during a session.

Overall study timeline after Consent concludes is approximately 8wks. During those 8wks, active study engagement by a participant is expected to take about 15hrs, with an expected 17 in-person sessions. That time is spread out across study parts in about the following distribution:

Baseline (week ~1): ~4.5hrs with 6 sessions (visits 1-6 above) including surveys
Part 1 (weeks ~2-4): ~5hrs (weighted towards weeks 3 & 4) with 5 sessions (visits 7-11 above) including surveys
Washout (week ~5): ~30min with 1 session (visit 12 above) including surveys
Part 2 (weeks ~6-8): ~5hrs (weighted towards weeks 7 & 8) with 5 sessions (visits 13-17 above) including surveys

6.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

6.4.1 Description

The test article in this study is an investigational device. The pad portion is designed to be placed onto a bed beneath a fitted sheet in a specific orientation relative to a pillow and slept upon. The pad is powered with an attached bedside device, applies a safe range of magnetic waves. The stimulation is hypothesized to improve sleep duration and quality.

The Sleep Pad system has undergone preliminary review by the FDA (please refer to CATS attachment, "FDA Review Meeting Minutes") and received enthusiasm for empirical evaluation in this particular protocol as an intervention. According to published FDA device categorization guidelines (please refer to CATS attachment, "FDA Risk Categorization Guidelines," particularly pg.3 after title pg.) and in light of electromagnetic safety data (please refer to CATS

attachments, “Electromagnetic Field Safety Testing” and “FCC Compliance Test Statement”), this study’s PI considers the Sleep Pad system to be Not of Significant Risk (NSR). The device should not be used with powered covers (e.g. heating pads) nor on water beds, although there are not known risks to doing so. Other radiofrequency signals in the sleeper’s environment may overpower/wash-out the low level magnetic field generated by the pad, so it is recommended to turn off or remove any modem/router located in the bedroom and to put cellular devices into airplane or Do Not Disturb mode during Sleep Pad system use for optimal effect, although there are not known risks to having such devices in use with the Sleep Pad.

6.4.2 Treatment Regimen

Treatment dosing is under participant control, by physical proximity/orientation to the pad portion of the Sleep Pad system, and by a manually operated power button on the bedside controller portion of the Sleep Pad system. Dosing is scheduled to occur throughout the participant’s typical nocturnal sleep period, nightly during the Intervention (either phase I or phase II, depending upon randomization) of the research. The range will be preset to the minimum setting by researchers, and participants will be instructed to not change the settings. Participants verify their “dose” settings by attesting to not having changed settings implemented by researchers in nightly REDCap surveys.

6.4.3 Method for Assigning Subject to Treatment Groups

All participants in this study will experience all study conditions (i.e. a sham (Control) and an active (Intervention) Sleep Pad bedside controller), in a randomized crossover design. The random assignment to intervention order (Sham Sleep Pad System vs. Activated Sleep Pad System at Part 1; reverse at Part 2) will be completed in REDCap, with replacement for early withdrawal, and intention to assign 50% of participants to each study condition order. Participant recruitment will not be stratified, but randomization to a study condition order will be gender-stratified to ensure balanced assignment of males and females (assigned at birth) between condition orders.

Dr. Orfeu M. Buxton is the designated team member who will implement and hold the blind related to these randomization procedures; he does not interact directly with participants. Once randomized, an appropriate Sleep Pad controller ID is designated for use and shared with blinded study team members. The linking list of controller IDs and their settings (activated vs deactivated) is confidentially maintained by the Sponsor and Dr. Buxton unless specific study events require lifting the blind.

6.4.4 Subject Compliance Monitoring

Participants will complete nightly REDCap surveys self-attesting adherence to the protocol during Control/Intervention (Phases 1 & 2) that are shared with the research team as data to confirm Sleep Pad use.

6.4.5 Blinding of the Test Article

This study is a double-blind trial, in which bedside controllers for Sleep Pad systems are coded and either “activated” or “deactivated” (sham) by the manufacturer prior to receipt (in two sets) for use in the research. A “deactivated” bedside controller retains all functionality (and evidence of functionality) of an “activated” bedside controller, excepting the stimulation. The blind is

maintained by a designated study team member who will have access to the list linking device code IDs to their relative active/sham group, and who does not have interaction with study participants. This blind will be lifted if relevant for safety reasons in cases of serious adverse event on a participant case-by-case basis, and on the whole for other researchers after completion of the entire trial for data analysis.

6.4.6 Receiving, Storage, Dispensing and Return

6.4.6.1 Receipt of Test Article

The pad portion of the Sleep Pad system is interchangeable, so a participant will receive and use only one throughout their study. Participants receive two different bedside pad controllers during the course of the study, one at a time; once each for Phase 1 and Phase 2 (Control/Intervention). The bedside controller device code corresponding to a given participant ID and Phase will be documented for later data analysis. Participants receive in-person instruction regarding Sleep Pad system setup upon receipt, and also print and/or electronic instructional materials.

6.4.6.2 Storage

The pad portion of the Sleep Pad system is interchangeable between bedside controllers and can only be “used” (i.e. apply magnetic field) when equipped with a corresponding “activated” bedside controller . Bedside controllers will be stored in the laboratory space and code-labeled according to their internal settings (i.e. one set with codes corresponding to “activated” and one set with codes corresponding to “deactivated,” but to which all Investigators except one are blinded). Pad portions of the Sleep Pad system will be stored separately from bedside controllers until being provided to a study participant. Participants maintain the “pad” portion of the Sleep Pad system throughout the study. Participants will be instructed that only research participants in the study should use the device as directed, and that no individual should attempt to use the device inconsistent with directions. a person in physical proximity to the pad is not expected to have any “exposure” to its signal unless it is used as directed.

6.4.6.3 Preparation and Dispensing

Participants will be randomly assigned to their crossover order (i.e. to their order of using an “activated” or a “deactivated” bedside controller). Activation or deactivation and coded device ID(s) are applied to the bedside controller portion of the Sleep Pad system by the manufacturer, prior to receipt by researchers. Researchers receive coded controllers. A list linking device IDs to their settings, and thereby the blind, is maintained by a designated study team member. “Administration” of the Sleep Pad system occurs when a participant lays upon the pad portion of a system that includes an activated bedside controller, which they have turned on manually, consistent with contact/orientation instructions (as designated in setup instructions).

6.4.6.4 Return or Destruction of the Test Article

The Sleep Pad systems (bedside controller devices [used or unused] and pad portions) will be returned (i.e. shipped) to the Sponsor/manufacturer at the conclusion of the study.

6.4.6.5 Prior and Concomitant Therapy

Participants must be willing to refrain from initiating new, sleep-directed interventions (e.g. medication; behavioral) that are not a part of this study protocol for the duration of study participation. Taking any physician-directed pharmacologic intervention for sleep or being actively engaged in a clinically-validated course of therapy (including behavioral therapy for sleep) is an exclusion criterion.

7.0 Number of Subjects and Statistical Plan

7.1 Number of Subjects

We expect to evaluate up to 35 participants in screening qualification, aiming to initially identify up to 20 eligible individuals according to the screening procedures. Screening evaluations will pause at that time by pausing both the REDCap survey availability and by our otherwise manual control of release of the screening survey REDCap link until it is determined by Investigators that additional recruitment is necessary (e.g. to replace participant drop-outs or if failure to identify 20 eligible individuals occurs). Should recruitment need to be re-opened beyond 35 participants an IRB Protocol modification would occur, expecting to regulate future screening qualification in specific intervals to reduce risk of unnecessary screening of individuals. We aim to complete 10 subjects in this study.

7.2 Sample Size Determination

This pilot study is being used to determine feasibility and effect sizes, therefore no information is available upon which to estimate a minimum necessary sample size. This study will inform the sample size of future studies and proposals.

7.3 Statistical or Analytic Methods

Primary and secondary outcomes will be compared between sleep pad conditions, within participants, as a change score relative to their own Baseline.

8.0 Risks

PSG and ambulatory (actigraphy) monitoring devices are typical clinical outpatient procedures that pose mild risks that include but are not limited to: the attachment and removal of monitoring electrodes may cause mild, temporary discomfort; participants may have difficulty sleeping while the monitoring equipment is attached; participants may experience mild frustration maneuvering around equipped devices; location where sensors are worn or applied may experience temporary skin irritation. It is possible that wearing monitoring equipment may be bothersome enough to interfere with sleep quality (although that is not an intended purpose of any monitor/intervention in this research), which could make subjects feel irritable or more tired during the day time.

To minimize these risks, we thoroughly clean devices between subjects, spread out overnights involving PSG, and can adjust the application site of some sensors as-needed based on reported subject comfort/reactivity.

Participants may feel uncomfortable answering some survey questions. Participants may elect to not answer any survey question that they do not want to, but not answering may affect their study eligibility to initiate or continue in the study, or to be included in research data analyses.

Blood draws often cause mild pain, swelling or bleeding. Fasting before blood draws may be uncomfortable. There may be some bruising (blood under the surface of the skin), which can be minimized by pressing on the site after the needle is removed. There is also a small chance of infection, dizziness, or fainting. These risks will be minimized, and most likely eliminated, by having trained CRC staff perform the blood draw on a seated or reclined participant using sterile supplies. If dizziness or fainting occurs, the symptoms will be alleviated by closely monitoring the participant, directing them to lie flat with their feet raised, and by offering a snack and/or beverage. Participants demonstrating these symptoms may be asked to stay at the blood draw location (i.e. PSU CRC) or to permit study staff to stay at the blood draw location (i.e. in their personal residence) until staff have confirmed that the participant is well enough.

Use of the Frequen-ZZZ Sleep Pad may cause perceived warmth (although the pad does not emit heat) that may affect sleep. If sleep is successfully deepened by Sleep Pad system use, a device user may experience temporary drowsiness, dizziness, or disorientation upon awakening from deeper sleep (called sleep “inertia”). There is a risk of fall resulting from these sensations. To mitigate this risk, participants will be encouraged to complete their Morning Survey on their phone prior to getting out of bed in the morning, to encourage time for these possible sensations to pass. Participants will also be encouraged to take care if getting out of bed after awakening during the night. Participants are instructed on the optional procedure to pause the Sleep Pad controller during nocturnal awakenings, and this procedure is included in their Quick Reference Guide; this also should facilitate time/care taken upon awakening from Sleep Pad use.

Although it is rare, improper use of the Frequen-ZZZ sleep pad may lead to mild negative side effects, including headaches for short periods of time, restlessness, nausea, and/or perspiration. Participants will be instructed on proper use of the sleep pad at consent, will be reminded of proper use in-person prior to each Intervention/Control study phase, and will be provided with an instructional sheet to take along with them for reference at home. The Sleep Pad has undergone testing by F2 Labs and complies with FCC standards for human exposure to electromagnetic/radio-frequency emissions and some additional emissions regulations (please refer to CATS attachments, “FCC Compliance Test Statement” and “Electromagnetic Field Safety Testing”). The Sleep Pad has not be evaluated under certain conditions, and so should not be used together with other powered equipment (i.e. heated blankets or similar). The Sleep Pad should not be used on a water bed.

There is a risk of loss of confidentiality if participant information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of participant electronic data created by participants or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

9.0 Adverse Event Reporting

9.1 Adverse Event Definitions

For device studies, incorporate the following definitions into the below responses, as written:

Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Recording of Adverse Events

•

The study procedures involve frequent contact between study staff and participants. Research subjects will be routinely questioned about adverse events at such study visits, and relevant responses will be documented by study staff. Relevant events will be advanced to the PI consistent with an Event Reporting SOP on which staff are trained. The PI determines whether advanced events meet criteria for immediate reporting to IRB and maintain documentation of all events for annual IRB reporting.

All adverse events (serious or non-serious) and abnormal findings observed or reported to study team believed to be associated with the study drug(s) or device(s) by the PI will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigators. Resolution will be documented.

An abnormal finding will be classified as an adverse event if one or more of the following criteria are met:

•The finding is accompanied by clinical symptoms
•The finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
•The finding leads to discontinuation of subject participation in the clinical research study
•The finding is considered an adverse event by the Investigators.

An unanticipated adverse device effect will also constitute an “abnormal finding”, defined as:
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

9.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator’s final determination of causality is “unknown and of questionable relationship to the study drug(s) or device(s)”, the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator’s final determination of causality is

"unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

9.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

9.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

9.6 Unblinding Procedures

Unblinding of Investigators prior to the conclusion of data collection is not expected other than for safety-related reasons in association with a study adverse event. A team member who does not have a role interacting with study participants is designated to maintain the blind for this purpose. Unblinding would occur only in cases of "serious" adverse reaction by a participant, in an effort to thoroughly report the circumstances of such adverse reaction to the IRB, Sponsor, and likely also to the FDA if evaluation for a new risk categorization of the investigational device is determined necessary by the IRB.

9.7 Stopping Rules

Not Applicable: This pilot study involves a small sample size and does not have a defined primary safety endpoint. It is considered Minimal Risk by Investigators.

Unanticipated serious adverse events that are clearly related to the study intervention would warrant considering discontinuation of the study, and such decisions would be conducted in collaboration with the PSU CATS IRB. Study pause or interruption appearing unrelated to the study intervention may occur based on participant needs or unexpected events; these would not warrant study stoppage and Investigators will work with affected participants on a case-by-case basis to determine appropriateness of re-enrolling (if pre-randomization) or continuing again in the study.

10.0 Study Monitoring, Auditing and Inspecting

10.1 Study Monitoring Plan

10.1.1 Quality Assurance and Quality Control

The Principal Investigator, experienced in conducting HSR clinical trials with Good Clinical Practice, will take responsibility for overseeing the study and ensuring that it is in compliance with regulatory specifications of the FDA and/or IRB.

The Sponsor will also be involved in the monitoring of study data. The Sponsor will review any reports from Investigators of probably- and possibly- device-related study events, and will report events determined to be promptly reportable consistent with the FDA's timeline.

10.1.2 Safety Monitoring

The PI (Chang) will conduct and monitor the study consistent with Good Clinical Practice guidelines, including a standardized Progress Note entry format that prompts advancing of certain event types to the PI for consideration and maintenance of an Events Log for documenting decisions, outcomes, and annual IRB reporting.