Cover page

Study Official Title: Use of Bioboosti Non-pharmacologic Device for Insomnia Treatment - a pilot study

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PARTNERS HUMAN RESEARCH COMMITTEE PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Milena Pavlova, MD

PROTOCOL TITLE
Use of Bioboosti Non-pharmacologic Device for Insomnia Treatment – a pilot study

FUNDING
Biomobie (Shanghai) Regenerative Medicine Technology Co., Ltd.

VERSION DATE

06/04/2018

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Hypothesis 1: Patients with insomnia have longer, more consolidated sleep after treatment with Bioboosti.

Specific Aim 1: This hypothesis will be tested in a prospective study, using within subject comparisons, whereby sleep measures before treatment are compared to those after treatment.

Hypothesis 2: Sleep improvement will lead to a lesser subjective daytime sleepiness and reduction in migraine frequency/intensity.

Specific Aim 2: This hypothesis will be tested by comparing subjective measures of sleepiness, measured by standard instruments (Epworth sleepiness scale score, ESS, Karolinska sleepiness scale KSS), relative to total sleep time and wake after sleep onset. Migraine frequency and intensity will be recorded using standardized headache diaries.

Exploratory aim: To evaluate the physiological mechanisms, by which Bioboosti may exert its effect on sleep and overall health. This will be accomplished by a measurement of hormones directly affecting sleep and

sympathetic autonomic nervous system (urinary cortisol and catecholamines), immune, as well as autonomic function.

Arm 1

Aim 1: To test the hypothesis that treatment with BioBoosti has sustained efficacy in treating insomnia.

Our primary endpoint would be insomnia symptoms after 1 year of BioBoosti use as compared to initial symptoms (prior to starting treatment). Measurement of insomnia will be done in serial comparisons every 3 months for ISI, TST(Total Sleep Time), WASO(Wake After Sleep Onset), as well a PSQI at year 1. We will use repeated measures ANOVA to compare ISI, TST, WASO, at months 3,6,9, and 12 and a T-test to compare PSQI at baseline to that after 1 year.

Arms 2

Aim 2: To test the hypothesis that patient with Insomnia and comorbid Migraine will have longer, more consolidated sleep with lesser migraine frequency/intensity after treatment with BioBoosti.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Insomnia is a leading health complaint, seen in almost 25% of the population. Insomnia complaints can be associated not only with discomfort for the patient, but also with loss of productivity, poor health, and a higher healthcare utilization. Insufficient or poor quality sleep increases the risk of a variety of disorders, leading to abnormalities of endocrine (Buxton, Pavlova et al 2010) and immune function (Lange et al 2011). Insomnia probably has the some of the same consequences as insufficient sleep from other causes. For example, in a recent study in our group (Buxton, Pavlova et al, 2011), we found that sleep fragmentation, as measured by wake after sleep onset (WASO), predicts diabetes risk in insomnia patients.

Treatment of insomnia is particularly challenging among patients with comorbidities, where insomnia is also more common. For example, insomnia is seen in 40-51% of patients with epilepsy (Vendrame 2013, Lopez et al 2013). Many studies indicate that patients with epilepsy frequently have fragmented sleep, as well as excessive daytime somnolence (Holoway et al 2011, Meyer et al 2011, Manni et al 2010, Krishnan et al 2012). Yet treatment of insomnia in these patients is very challenging, as many of the

frequently used medications may interact with antiepileptic medications, or affect seizure threshold. For example, benzodiazepines, which are among the most commonly used of treatment of insomnia, can be associated with withdrawal seizures, and are particularly risky in these patients. Similar considerations exist for the patients with cardiac disease and dementia. For example, although long term benzodiazepine use can be associated with frequent falls (Berry et al, 2015), impaired memory (Billioti et al, 2015) and even all-cause mortality (Iennum et al, 2015), they are frequently prescribed and needed. From a recent review (Defrancesco, et al, 2015) it can be inferred that every fifth patient with Alzheimer's disease will need benzodiazepine treatment.

Sleep disturbances can serve as a trigger for migraines, and insomnia in particular is a common comorbidity in patients with chronic migraine. Addressing insomnia in patients with chronic migraine can result in reductions in migraine frequency (Smitherman, et al, 2016)

The use of non-pharmacologic treatments of insomnia has gained much attention in recent years. For example, lectures on use of yoga in the treatment received a very high attendance at a recent CME course lead by the principal investigator of this study. This is only one example of the importance and high impact of any such research.

A safe, non-pharmacologic treatment of insomnia is very much needed to help patients with insomnia, especially those with comorbidities. Studies have tested the use of pulsed electromagnetic fields on bone healing (Chalidis et al 2011), wound healing (Cheing et al 2014), peripheral nerve regeneration (Kim et al 2002), neuropathic pain in diabetics (Weintraub et al 2009), and cardiac function after a myocardial infarct (Hao et al 2014). A post-market follow up has shown that the Bioboosti, a device that emits micromagnetic fields, can be effective as an adjuvant therapy for a number of conditions including insomnia (Biomobie 2015). We propose a pilot study to assess the effectiveness of FDA approved Biomobie device (Bioboosti) for the treatment of insomnia.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This is an investigator-initiated study looking at the effects of the Bioboosti device on sleep for patients who have been diagnosed with insomnia and chronic migraine (15 or more headache days per month according to the International Classification of Headache Disorders III-Beta). We will screen

and enroll patients with insomnia and chronic migraine who are ≥18 years old for consistency on sleep data and age range. The study protocol consists of enrollment; baseline sleep and headache assessment, actiwatch use and set up of EEG; removal of the EEG then two weeks of treatment with Bioboosti; a post-treatment sleep assessment followed by a final visit to remove the EEG.
Adult patients ≥18 years old seen in the BWH and FH sleep and headache clinics are eligible for participation in the study. As we are unsure of the effects that the Bioboosti has on the general population, and in turn the various effects of chronic conditions on a person's sleep, we will exclude patients with known untreated moderate or severe sleep apnea, or with major circadian rhythm disorders, as these may confound our analyses. We will also exclude patients who are pregnant or breastfeeding; patients with cardiac pacemaker; any electrical devices; patients with cancer; patients with severe conditions related to heart, brain, kidney and hematopoietic system; patients with severe/unstable angina pectoris, arteria coronaria/peripheral arterial bypass graft, congestive heart failure, renal insufficiency, mechanical intestinal obstruction. Subjects with medication overuse headache defined as using specified abortive medications 9 or more days per month will also be excluded. Abortive medications for the purposes of this study will include opioids, combinations analgesics (barbiturates and/or caffeine contain medications), and triptans.

We anticipate enrolling 20 subjects at Brigham and Women's and Faulkner Hospitals.

We do not anticipate all 20 subjects to participate however, interested enrolled subjects will also be offered to continue the treatment for one year for the evaluation of sustained efficacy of BioBoosti as Insomnia Treatment. We *anticipate* enrolling up to 20 subjects at BWH and Faulkner Hospitals.

The study will also look at the effects of the BioBoosti device on sleep and recurrence of headache for patients who have been diagnosed with both insomnia and migraine. The study protocol remains the same besides the treatment with BioBoosti will be for 4 weeks to allow adequate headache assessment.

We anticipate enrolling 20 additional subjects with insomnia and comorbid migraine at Brigham and Women's and Faulkner Hospitals.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

The BWH and FH sleep clinics will be screened for follow-up patients with insomnia. Study staff will notify the treating physician to inform them of a potential subject. The treating physician will first introduce the study to the potential subject. If the subject gives permission and would like to obtain more information regarding the study, study staff will approach them and provide them with a copy of the consent form to review. Study staff may also contact the subject by phone to explain the study and recruit if it is more convenient for the subject. Study staff and a physician investigator will be available to answer all questions. If the potential subject is interested in participating in the study, the Principal Investigator will consult with the treating physician prior to enrolling the subject. If the subject decides to enroll in the study when approached in the clinic, we will proceed with Visit 1 (Enrollment Visit) that same day. The physician investigator will be available to speak with subjects during the consent process.

For Insomnia

Visit 1

Subjects who are interested in participating will sign the consent form. A screening physical exam will be done, and vital signs (blood pressure, heart rate, pulse rate, respiratory rate) will be measured. Pregnancy test will be done for women of childbearing potential.

Subjects will go home with sleep logs, which are subject records of when they go to sleep and wake up. They will also be given an actiwatch to wear, as an objective measure of sleep and wake periods.

Visit 2

Subjects will be scheduled for a follow up at FH.

Subjective sleep symptoms will be evaluated using validated instruments, including Pittsburgh Sleep Quality Inventory (PSQI), and severity of insomnia - Insomnia Severity Index (ISI), and daytime sleepiness Epworth Sleepiness Scale (ESS), and daily visual analog scale (Karolinska sleepiness scale, KSS).

Objective sleep assessment will be performed using ambulatory 72 hour EEG, using sleep montage per standard AASM criteria, and scored by a registered polysomnography technologist using AASM guidelines. If the subject expresses hesitation because of the 72 hour EEG, then a 48 hour EEG will be offered.

Assessment of sympathetic autonomic nervous system function will be done by measuring cortisol and catecholamine levels using standard assays.

Subjects will continue to wear the actiwatch and complete sleep logs daily.

Visit 3

Subjects will return for the EEG to be removed. Subjects will be given a Bioboosti for the treatment phase and instructed on how to use it. The research assistant will be trained in person by a Bioboosti representative. Using the device as part of the training, the research assistant will learn the proper placement of the device on the hands, what the different buttons represent and how to properly charge it. He/she will in turn instruct the participants with this information. Subjects will continue to use the actiwatch.

Treatment phase

There will be two weeks of treatment with Bioboosti. Subjects will be asked to use the device once a day, at approximately one hour prior to initiation of habitual sleep time. They will complete up to 6 therapy cycles. A therapy cycle consists of placing the Bioboosti on the Laogong point, which is located at the center of the palm. The device will remain there for 8 minutes, and this counts as 1 cycle. When the light on the device changes, it indicates that 8 minutes have passed, and a cycle is completed. The subject will then remove the device and replace it on the Laogong point of the other hand. The subject will repeat this up to 6 times, alternating the treatment cycles between one hand to another.

They will complete sleep logs for two weeks, as well as wear the actiwatch.

During this time, subjects should not drive while using the Bioboosti. They will also be advised to maintain a healthy lifestyle, as is done during clinic visits (light diet, regular exercise, smoking cessation, abstinence and sufficient sleep), but these are not terms of exclusion from the study.

Visit 4

Subjects will return after the two weeks of treatment. They will return the completed sleep logs.

Subjective sleep symptoms will be evaluated using validated instruments including, Pittsburgh Sleep Quality Inventory (PSQI), and severity of insomnia - Insomnia Severity Index (ISI), and daytime sleepiness Epworth Sleepiness Scale (ESS), and daily visual analog scale (Karolinska sleepiness scale, KSS).

Objective sleep assessment will be performed using ambulatory 72 hour EEG, using sleep montage per standard AASM criteria, and scored by a registered polysomnography technologist using AASM guidelines. If the subject expresses hesitation because of the 72 hour EEG, then a 48 hour EEG will be offered.

Assessment of urine cortisol and catecholamines will be done as a measure of sympathetic function.

Subjects will continue to wear the actiwatch and complete sleep logs daily.

Visit 5

Subjects will return for the EEG to be removed. They will return the Bioboosti, actiwatch and completed sleep logs.

The Bioboosti devices will be checked on their return to the study staff. If it is determined that the device is not functioning properly, the participant will be asked to redo the study.

Testing of each patient requires about one month as outlined above. With efficient recruitment and minimal attrition rate, 20 participants can complete the study.

Sustained Efficacy Phase

Subjects participating in the study will also be asked if they are interested in the long-term use of BioBoosti device. In that case, they will be consented again to go forward with the long-term use. At the end of this process, they will be given sleep and headache logs.

They will be offered to continue the treatment for one year with regular follow-up. One month prior to each follow-up they will be asked to use the actiwatch to objectively evaluate the sleep patterns. They will either pick up the device or will be offered a home visit for the actiwatch use.

Visit at 3rd,6th, 9th months

- Subjects will complete the Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Inventory (PSQI).
- They will return the completed sleep logs.
- They will be asked to continue filling out new sleep logs for the following visit.
- They will return the Actiwatch.

Visit at 12th month

Subjects will be asked to return the sleep logs and actiwatch and will be asked to complete the Pittsburgh Sleep Quality Inventory (PSQI), and Insomnia Severity Index (ISI), and daytime sleepiness Epworth Sleepiness Scale (ESS).

For Patients with Insomnia and Migraine

We do not anticipate for this longer testing period to increase the risk, as to date, none of the individuals with insomnia have reported any negative effects from the treatment.

Visit 1

Subjects who are interested in participating will sign the consent form. A screening physical exam will be done, and vital signs (blood pressure, heart rate, pulse rate, respiratory rate) will be measured. Pregnancy test will be done for women of childbearing potential.

Subjects will go home with sleep logs, which are subject records of when they go to sleep and wake up. They will also be given an actiwatch to wear, as an objective measure of sleep and wake periods.

The headache diaries are given which are subject records of the frequency and intensity of their migraines. They will complete the logs for one month.

Visit 2

Subjects will be scheduled for a follow up at FH one month after the first Visit.

Subjective sleep symptoms will be evaluated using validated instruments, including Pittsburgh Sleep Quality Inventory (PSQI), and severity of insomnia - Insomnia Severity Index (ISI), and daytime sleepiness Epworth Sleepiness Scale (ESS), and daily visual analog scale (Karolinska sleepiness scale, KSS).

Objective sleep assessment will be performed using ambulatory 72 hour EEG, using sleep montage per standard AASM criteria, and scored by a registered polysomnography technologist using AASM guidelines. If the subject expresses hesitation because of the 72 hour EEG, then a 48 hour EEG will be offered.

Assessment of sympathetic autonomic nervous system function will be done by measuring cortisol and catecholamine levels using standard assays.

Subjects will continue to wear the actiwatch and complete sleep/Headache logs daily.

Visit 3

Subjects will return for the EEG to be removed. Subjects will be given a Bioboosti for the treatment phase and instructed on how to use it. He/she will in turn instruct the participants with this information. Subjects will continue to use the actiwatch.

Treatment phase

There will be one month of treatment with Bioboosti. Subjects will be asked to use the device once a day, at approximately one hour prior to initiation of habitual sleep time. They will complete up to 6 therapy cycles. A therapy cycle consists of placing the Bioboosti on the Laogong point, which is located at the center of the palm. The device will remain there for 8 minutes, and this counts as 1 cycle. When the light on the device changes, it indicates that 8 minutes have passed, and a cycle is completed. The subject will then remove the device and replace it on the Laogong point of the other hand. The subject will repeat this up to 6 times, alternating the treatment cycles between one hand to another.

They will complete sleep/headache logs for one month, as well as wear the actiwatch.

During this time, subjects should not drive while using the Bioboosti. They will also be advised to maintain a healthy lifestyle, as is done during clinic visits (light diet, regular exercise, smoking cessation, abstinence and sufficient sleep), but these are not terms of exclusion from the study.

They will be instructed to use their usual migraine abortive treatments that were utilized during the run-in phase of data collection, and to avoid the introduction of any new therapies during the treatment phase.

Visit 4

Subjects will return after the one month of treatment. They will return the completed sleep logs.

Subjective sleep symptoms will be evaluated using validated instruments including, Pittsburgh Sleep Quality Inventory (PSQI), and severity of insomnia - Insomnia Severity Index (ISI), and daytime sleepiness Epworth

Sleepiness Scale (ESS), and daily visual analog scale (Karolinska sleepiness scale, KSS).

Objective sleep assessment will be performed using ambulatory 72 hour EEG, using sleep montage per standard AASM criteria, and scored by a registered polysomnography technologist using AASM guidelines. If the subject expresses hesitation because of the 72 hour EEG, then a 48 hour EEG will be offered.

Assessment of urine cortisol and catecholamines will be done as a measure of sympathetic function.

Subjects will continue to wear the actiwatch and complete sleep/headache logs daily.

Visit 5
Subjects will return for the EEG to be removed. They will return the Bioboosti.
They will be asked to continue keeping the sleep/headache logs for another month.

The Bioboosti devices will be checked on their return to the study staff. If it is determined that the device is not functioning properly, the participant will be asked to redo the study.

Visit 6
Subjects will return the completed sleep/headache logs. They will return the actiwatch.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

This study does not involve diagnosis. Other than the Bioboosti, the Principal Investigator will not make changes to the patient's medication regimen. Other treatments that are available to treat insomnia include: healthy sleep hygiene, antihistamines and some prescription medicines like Ambien and Lunesta.

As an alternative to standard care, we are proposing to test the Bioboosti device as a possible safe, non-pharmacologic treatment option for insomnia.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks of participation may include fatigue from completing the questionnaires and feelings of unease answering questions. We will make every attempt to schedule and perform the tasks so as to reduce these risks. Subjects may refuse to answer any question that upsets them.

When wearing the ambulatory EEG, subjects may feel soreness or see reddening of the skin from the glue that is used. There is a risk that the cables could become wrapped around the neck, so they should tape the cables to their back when sleeping. A registered polysomnography technologist will administer the ambulatory EEG so as to minimize these risks.
Subjects may feel discomfort when wearing the actiwatch. The strap is adjustable for their comfort.

Collection of specimen data will be done as in routine care.

Based on previously acquired data from the company, we do not anticipate any significant likelihood of adverse events. The device has been cleared for safety by the FDA. While we don't anticipate any serious adverse events, it is possible that the patients enrolled in the study experience adverse effects of the Bioboosti. To minimize risks to subjects, proper use of the bioboosti will be explained to them once the device is provided. They will be asked to use only the charger that accompanies the Bioboosti; they cannot use it while it is charging, as it will not be able to provide therapy while charging. They will not use the device when engaging in extreme sports, showering or immersing in water. As a possible device for treating insomnia, subjects may experience sleepiness when using it. As a precaution, they should not to drive while using the Bioboosti. Subjects should handle the device with care from trauma so as not to damage it, as well as keeping the device from places that are damp, extremely cold or hot, exposure to direct sunlight, near any strong magnetic field or microwave field.

Risks will be explained and subjects encouraged to ask questions. In addition to the treating physician, we will monitor for any adverse events that might be related to the device. Side effects subjects might experience due to the Bioboosti will be immediately reported to the treating physician, PI, IRB for major adverse effects as well as sponsor. If any significant events occur, these may lead to the need to discontinue the treatment.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of

improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Based on previously acquired data from the company, we do not anticipate any significant likelihood of adverse events. The device has been cleared for safety by the FDA. While we do not anticipate any serious adverse events, it is possible that the patients enrolled in the study experience adverse effects of the Bioboosti.

To minimize risks to subjects, proper use of the Bioboosti will be explained to them once the device is provided, as described above. A manual on how to use the device will accompany it. A follow-up phone call will be conducted 1-2 days after the participant receives the Bioboosti to go over proper use if needed. A registered polysomnography technologist will administer the ambulatory EEG. Collection of specimen data will be done as in routine care. Risks will be explained and subjects encouraged to ask questions.

In addition to the treating physician, we will monitor for any adverse events that might be related to the device. Side effects subjects might experience due to the Bioboosti will be immediately reported to the treating physician, PI, IRB for major adverse effects as well as sponsor. If any significant events occur, these may lead to the need to discontinue the treatment

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

We do not anticipate any serious risks to subjects. Subjects may experience discomfort due to fatigue from completing the questionnaires and feelings of unease answering questions. We will make every attempt to schedule and perform the tasks so as to reduce these risks. Subjects may refuse to answer any question that upsets them.

When wearing the ambulatory EEG, subjects may feel soreness or see reddening of the skin from the glue that is used. There is a risk that the cables could become wrapped around the neck, so the cables should be taped to the back especially when sleeping.

Subjects may feel discomfort when wearing the actiwatch. The strap is adjustable for their comfort.

As subjects will be starting a new treatment as part of their clinical care while in the study, they may experience side effects to the Bioboosti. Based on previously acquired data from the company, we do not anticipate any

significant likelihood of adverse events. The device has been cleared for safety by the FDA. As a possible device for treating insomnia, subjects may experience sleepiness when using it. As a precaution, they should not to drive while using the Bioboosti.

Subjects will be instructed to report any side effects and/or adverse events they experience. Side effects will be immediately reported to the treating physician and PI, and will be addressed accordingly. However, if any significant events occur, these may lead to need to discontinue the treatment. Per regulatory guidelines, adverse events will be reported to the company.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There is no direct benefit to subjects. The Bioboosti is an FDA-approved device for the treatment of insomnia. If successful, though there is not sufficient data, subjects may experience longer, more consolidated sleep after treatment with Bioboosti and this improved sleep will lead to lesser subjective daytime sleepiness. The device may help patients with migraine by lowering the frequency/intensity of headaches, in addition to improving their sleep.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The subjects for this study will be recruited from the sleep clinics at BWH and FH, and will be representative of the population. As we are unsure of the effects that the Bioboosti has on the general population, and in turn the various effects of chronic conditions on a person's sleep, we will exclude patients with known untreated moderate or severe sleep apnea, or with major circadian rhythm disorders, as these may confound our analyses. We will also exclude patients who are pregnant or breastfeeding; patients with cardiac pacemaker; any electrical devices; patients with cancer; patients

with severe conditions related to heart, brain, kidney and hematopoietic system; patients with severe/unstable angina pectoris, arteria coronaria/peripheral arterial bypass graft, congestive heart failure, renal insufficiency, mechanical intestinal obstruction.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Questionnaires are validated in English. We will not be strictly excluding nonEnglish speakers, however given the small number of subjects and the large number of information that will be communicated verbally and standardized questionnaires, we anticipate that this would be easier for English speakers to participate in the study.
Patients who do not speak English will not be excluded from this study. We will provide potential non-english speaking subjects with the IRB approved short form consent form in their native language. Given that we do not anticipate enrolling more than a significant number of non-English speaking subjects, we will not have the IRB-approved long-form consent translated. A hospital medical interpreter will be scheduled to be present during the consent process and entire screening visit.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/NonEnglish_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

The BWH and FH sleep/hedache clinics will be screened for patients who are diagnosed with insomnia and patients with both insomnia and migraine. Study staff will notify the treating physician to inform them of a potential subject. The treating physician will first introduce the study to the potential subject. If the subject gives permission and would like to obtain more information regarding the study, study staff will approach them and provide them with a copy of the consent form to review. Study staff may also contact the subject by phone to explain the study and recruit if it is more convenient for the subject. Study staff and a physician investigator will be

available to answer all questions. The physician investigator will be available to speak with subjects during the consent process.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will be paid $400.00 if they complete the study. They will receive $100 after the first EEG and the remaining $300 at the end of the study. If subjects do not complete the study, they will not be paid for their participation. Damage to the devices or unreturned devices is equivalent to incompletion of the study. We will also cover the cost of parking up to $40.00 for the subject's study visits.

Sustained Efficacy Phase: Subjects will be paid $350.00 for their participation. They will receive $50.00 after the first 3 follow- up and the remaining $200.00 at the end of the study and cover the cost of the parking for up to $5.00 each visit. Damage to the devices or unreturned devices is equivalent to incompletion of the study.

For guidance, refer to the following Partners policies: Recruitment of Research Subjects https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects https://partnershealthcarepublic.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

The BWH and FH sleep clinics will be screened for patients who have been diagnosed with insomnia and patients with both insomnia and migraine. Study staff will notify the treating physician to inform them of a potential

subject. The treating physician will first introduce the study to the potential subject. If the subject gives permission and would like to obtain more information regarding the study, study staff will approach them and provide them with a copy of the consent form to review. Study staff may also contact the subject by phone to explain the study and recruit if it is more convenient for the subject. Study staff and a physician investigator will be available to answer all questions. If the potential subject is interested in participating in the study, the Principal Investigator will consult with the treating physician prior to enrolling the subject. The subject will be encouraged to ask questions. If the subject is still unsure if he/she wants to participate, he/she will be encouraged to take the consent form home to consider it further. In that case a second visit will be scheduled, the consent form reviewed again, and, if signed, study procedures performed. If the subject decides to sign informed consent at the time the study is introduced, we will proceed with Visit One (Enrollment Visit) that same day. The physician investigator will be available to speak with subjects during the consent process.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decisionmaking capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The Principal Investigator, Dr. Milena Pavlova, will be responsible for overseeing the safety of the subjects in this study. After the first subject is

enrolled, she will meet with the study coordinator weekly to review the adverse event data collected at each study visit. She will also review any complaints about the research at this time. The Principal Investigator and study coordinator will review all data collected to ensure that all subjects complete questions and logs accurately.

If a subject decides to forgo continuation of the study, the research team will ensure their withdrawal in the safest manner possible.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Adverse events will be reported to the Principal Investigator weekly. Any serious adverse events will be reported within 24 hours.

Adverse events that are serious, unexpected, and related or possibly related to the research study will be reported to the IRB within 5 working days/ 7 calendar days after the investigator becomes aware of the event.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Principal Investigator, Dr. Milena Pavlova, will ultimately be responsible for data integrity and quality assurance. The study coordinator will be responsible for accurate collection of the data. Data will be reviewed throughout the period of collection to ensure that subjects provide accurate information. She will review all collected data weekly.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Identifiable information such as subject name will be kept in one file while data collected from the log entries will be kept in separate file. An arbitrary code number will be issued to each subject so as to locate data information without exposing specific identifiable subject information. Study info will be kept and stored on password protected shared drives and only accessible on Partners workstations.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Not applicable.

Urine that will be collected for the study will be analyzed by the Center for Clinical Investigation.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Not applicable

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Not applicable