Medical University of South Carolina Protocol

Protocol Title: **Double-Blind, Sham-Controlled Crossover Pilot Study of Low Field Magnetic Stimulation (LFMS) on Subjective and Objective Measures of Sleep**

PI Name: Thomas Uhde, MD

1.0 OJECTIVES/SPECIFIC AIMS

Insomnia is a risk factor for the later development of mood and anxiety disorders, alcohol and substance use relapse, peripartum depression, suicide, motor vehicular accidents, poorer outcome in the treatment of a large array of medical diseases, increased economic burden, and lost work and social productivity (Dorheim, Bjorvatn, & Eberhard-Gran, 2014; Morin & Jarrin, 2012; Taylor & Bramoweth, 2010; Woznica, Carney, Kuo, & Moss, 2015). Several classes of medications are used to manage insomnia; however, currently available medications have limitations in terms of durability and side-effects, including the risk of abuse and dependence with hypnotic and benzodiazepine compounds. And, even though non-pharmacological treatments of insomnia, such as sleep restriction, are effective, patients often refuse and/or are unwilling to participate in the requirements of this intervention due to poor tolerance and/or potential cognitive impairments. Thus, poor tolerance and/or acceptability of sleep restriction are limiting factors in the utility of current non-pharmacological treatments of insomnia.

The medical field needs new modalities, which do not involve benzodiazepine or hypnotic medications, for treating insomnia. We propose to study the effects of Low Field Magnetic Stimulation (LFMS) on sleep in patients suffering from insomnia disorder. LFMS has several similarities to repetitive transcranial magnetic stimulation (rTMS), which already has been approved by the FDA as a treatment for depression. However, in contrast to rTMS, LFMS produces a much smaller magnitude of electric field in the brain (approximately 1 V/m) compared to rTMS devices (approximately 100 V/m). Also, LFMS has magnetic field indices (20 Gauss peak field strength, 1 KHz frequency, trapezoidal magnetic field waveforms) that fall within the range of those used in spectroscopic and standard fMRI studies. Thus the FDA has conferred a non-significant risk determination of LFMS for humans. LFMS is unlikely to directly cause neuronal firing or neuronal depolarization and no seizures have been reported with LFMS in any investigational trials to date. Taken together, these observations indicate that LFMS has a very safe adverse-risk profile. Of note, Dr. George and his team at MUSC also have been investigating the effects of low frequency magnetic stimulation (LFMS) on pain threshold in healthy normal controls. Preliminary data in 43 healthy volunteers as well as over 300 depression patients studied to date have found LFMS to be well-tolerated and devoid of any serious adverse effects. The most common self-reports in the MUSC trial have been a mild tingling sensation on the scalp, which typically lasts for a few seconds; note, however, that subjects and investigators are still blind to condition, and thus the tingling may be occurring in sham control sessions as well as active treatment. Thus, neurostimulation with the current LFMS device, provided by Tal Medical and approved by the MUSC IRB (Pro00048321), has been extremely well-tolerated and without any adverse events.

Low field magnetic stimulation (LFMS) is a novel and safe form of brain neurostimulation that has shown rapid antidepressant effects in both humans and animal models of depression (Carlezon et al., 2005; M. L. Rohan et al., 2014; M. Rohan et al., 2004). It is unknown whether LFMS has positive hypnotic effects in humans.

Aim 1: To test whether a 20 minute session of LFMS, compared to sham LFMS, has sleep-promoting effects.
Hypothesis: 20 minutes of active LFMS compared sham LFMS will decrease subjective and objective polysomnographic measures of sleep latency (SL), number of awakenings after sleep onset (#awake), and wake time after sleep onset (WASO) and increase total sleep time (TST).

Aim 2: To determine whether active LFMS compared to sham LFMS improves the overall *quality* of sleep.
Hypothesis: 20 minutes of active LFMS compared to sham LFMS will be associated with a significantly greater improvement in overall quality of sleep (i.e. restorative sleep) as indicated by a change on the MUSC Sleep Quality Scale.

Aim 3: To examine the relationship between measures of state anxiety and change in insomnia severity from pre- to post-treatment in active LFMS compared to sham LFMS.

Hypothesis: Higher baseline levels of state anxiety and greater decreases in state anxiety before and immediately after treatment with active but not sham LFMS will be significantly correlated with improvements on subjective and objective measures of sleep (SL, #awake, WASO, and TST).

Aim 4: To examine the relationship between measures of depression and change in insomnia severity from pre- to post-treatment in active LFMS compared to sham LFMS.***

Hypothesis: Measures of depression or changes in ratings of depression will not be associated with any subjective or objective indices of sleep after either active or sham LFMS.

***Note: Patients with clinical depression will be excluded from this investigation.

2.0 BACKGROUND AND SIGNIFICANCE

It is well-known that depressed patients, particularly those with comorbid anxiety, often suffer from co-existing insomnia, which may take the form of one or more of the following characteristics: difficulty falling asleep, multiple awakenings from sleep, early morning awakening, or simply non-restorative sleep. Within a single depressive episode, insomnia (when present) may precede the symptoms of sadness, co-emerge at the same time, or develop after the depressive episode has become fully established. Insomnia also appears to be more prevalent in moderate-to-severe major depression and increasing evidence suggests that depression and insomnia share overlapping biological diatheses.

Many depression rating scales used in clinical trials include individual items on sleep. However, individual items or subscale factors related to disturbed sleep are not typically analyzed separately. Clinical trial evidence generally suggest that changes in depressed mood, anxiety, and insomnia often change in parallel (i.e., when mood improves, sleep improves and vice versa), although the temporal time-course and severity of each symptom cluster may be out of phase. Moreover, there may be different degrees of improvement and/or worsening of mood and sleep over the longitudinal course of illness in people suffering from co-existing depression and insomnia. Taken together, these data and clinical observations suggest that some effective treatments of depression may also be effective in the treatment of insomnia disorder.

The purpose of this study is to determine whether active LFMS improves, *in the presence of high baseline anxiety scores but the absence of clinical depression,* the sleep of patients with insomnia disorder. While the effects of LFMS on insomnia disorder are unknown, several studies have been conducted in patients with major depression where, based upon historical data, one might reasonably conjecture many, if not most, of the participants suffered from some degree of co-existing insomnia.

Low field magnetic stimulation, as a potential treatment of depression, arose from clinical observations in depressed patients who were being studied with functional magnetic resonance imaging at the McLean Hospital in 2001. Bipolar depression patients undergoing an fMRI scan for research purposes unexpectedly reported mood improvement following completion of a single, 20 minute diagnostic scan (M. Rohan et al., 2004). Then, a single-blind pilot study showed that a greater number of depressed patients improved with active LFMS exposure than with sham treatment. Another double-blind, LFMS versus sham cross-over study in patients with unipolar and bipolar depression demonstrated a rapid and large improvement in depression in the active treatment (M. L. Rohan et al., 2014). Notably, HAMD-17 scores describing anxiety levels showed substantial improvement in the depressed population. In our proposed study, we will use the similar type of device used in these aforementioned investigations, which were well-tolerated, and the same device being used here at MUSC.

The MUSC Brain Stimulation Laboratory has been a clinical and research center of excellence with respect to Brain Stimulation techniques for over 20 years now. We have three lab rooms (each 300 square feet) with an extensive array of devices. The Sleep Research Laboratory is on the same floor within 100 feet of the LFMS device. Forty-three healthy control subjects have been studied at MUSC (Pro00048321) using the same device and parameters of administration that are proposed for this study of participants with insomnia disorder.

3.0 INTERVENTION TO BE STUDIED

The LFMS investigational device v1.1 is a table-top device intended for use in a clinic or hospital setting under the supervision of a trained operator. The device has three major components:

1) Coil and Coil Housing. Mounted inside a patient friendly assembly, the magnetic coil delivers a low strength electromagnetic field to the head of the subject. The coil is designed to be used in conjunction with a standard hospital bed, exam table or gurney. The coil housing fits over the head down to the eyebrows leaving the field of vision about 50% unobstructed to avoid claustrophobic feelings.

2) PC with LFMS control software. The device is controlled by a personal computer with a custom software program that produces the desired waveform. The software enables randomization by blinding administration of sham or active treatment based on a unique patient ID and session ID number entered into the device. The software also tracks device function by monitoring in real time the electrical current to the coil and comparing it to the reference waveform.

3) Power system and control electronics. A pair of off-the-shelf amplifiers (AE Techron 7224) are set up in a parallel configuration and run under current control. The control electronics (USB data card – Measurement Computing USB-1608G) take the signal from the computer and convert it to the specified voltage waveform to the amplifiers corresponding to the electrical current waveform.

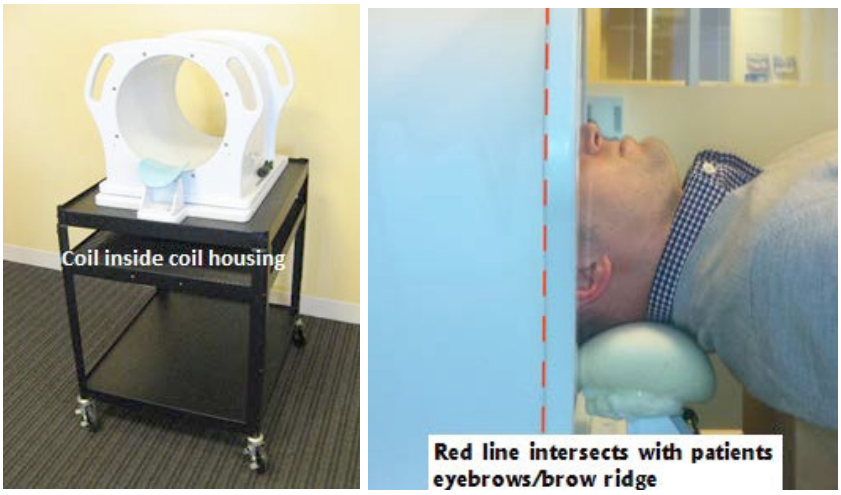

Figure B2: Pictures of LFMS Investigational Device v1.1 showing the device and how a patient is positioned in the device during treatment.

Overall, LFMS at the intensity, frequency and number of stimuli proposed in the current protocol is considered a "non-significant risk" by the FDA; it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). Of the 43 subjects who have participated in the aforementioned trial at MUSC, 7 reported mild, transient tingling on the scalp, though it is unknown if these subjects were receiving active or sham treatment. Otherwise, the treatments are well-tolerated and there have been no drop-outs.

4.0 STUDY ENDPOINTS

The main *subjective* outcome measures will be sleep latency (sSL), wake after sleep onset (sWASO), total sleep time (sTST), Ease of Falling Asleep (EFS), and Sleep Quality.

Secondary (exploratory) *subjective* outcome measures will be number of nocturnal awakenings (sNA), ESS, Concentration, and Fatigue.

The main *objective* outcome measures of efficacy will be sleep latency to persistent sleep (i.e., latency to 10 minutes of persistent sleep), sleep efficiency (time in bed/total sleep time), and wake after sleep onset (WASO).

The following traditional polysomnographic indices will be obtained during both active and sham conditions:
% Stage 1, % Stage 2, % Delta Sleep (Stages 3 & 4), and % Rapid Eye Movement (REM) Sleep.

5.0 INCLUSION AND EXCLUSION CRITERIA / STUDY POPULATION

Participants

Participants will be adults, aged 18-65, who meet DSM-5 criteria for insomnia disorder. Participants who meet both DSM-5 insomnia disorder and generalized anxiety disorder will be candidates for participating *if the insomnia is their predominant complaint and the primary reason for seeking treatment.*

Inclusion Criteria (all measures listed are described in detail in section 10.0)

DSM-5 insomnia disorder (per the SCISD)
- Difficulty falling asleep, maintaining sleep, waking up too early, or non-restorative sleep
- Frequency: ≥ 3 times per week
- Duration: ≥ 3 months
- Daytime impairment (subjective) in at least one of the following areas:
  - Excessive Daytime Sleepiness
  - Fatigue
  - Problems attending or concentrating on tasks
  - Transient memory problems
  - Performing tasks in a timely manner (compared to the person's usual level of performance)

Pittsburgh Sleep Quality Index (PSQI) ≥ 6 and one of the following:
- Sleep Efficiency ≤ 85% (per Consensus Sleep Diary)
- Insomnia Severity Index (ISI) score ≥ 15

Sleep latency (subjective) and/or time awake after sleep onset (subjective) >30 minutes.

Not currently depressed (previous major depressive episodes and current antidepressant medication permitted as long as remission and current medication dosage has been stable for ≥ 1 month).

Willing to refrain from alcohol for **twenty-four** hours before presenting to sleep lab for sleep studies

BMI ≥ 18 and ≤ 50 kg/m^2

Exclusion criteria:

Current major depressive episode

Current substance-induced depressive disorder

Self-reported use of benzodiazepines or hypnotic drugs in last two weeks

Self-reported use of marijuana in previous 72 hours

Alcohol Use Disorders Identification Test (AUDIT) score ≥ 10

Fagerstrom Test for Nicotine Dependence (FTND) score ≥ 4

Insomnia limited to early morning awakening (without difficulty initiating or maintaining sleep), Narcolepsy

Seizure Disorder (not including childhood febrile seizures)

Recent treatment with anticonvulsant medications

Obstructive or central sleep apnea

Circadian rhythm sleep-wake disorders

Recurrent isolated sleep paralysis

Current substance-induced insomnia

Chronic pain disorder

Daily Caffeine Consumption ≥ 500 mg/d (Uhde, 1989)

Restless legs syndrome

Periodic Leg Movement Disorder

Benzodiazepines or antipsychotic medications during past 30 days

Presence of drugs of abuse (excluding marijuana, urinalysis)

Pregnancy or plans to become pregnant

History of severe allergic reactions to adhesive tape

History of neurological disorder

Conductive, ferromagnetic or other magnetic-sensitive metals in the head, neck, chest, upper arms, or any area that will be within 18 inches of the treatment coil.

6.0 NUMBER OF SUBJECTS

We will enroll 20 male and female adults (with approximately equal gender distribution).

7.0 SETTING

Participants will be screened through the sleep and anxiety disorders clinic in the IOP on 5 South or in the sleep laboratory in the IOP on 5 North. Those that pass screening will be scheduled an appointment in the IOP on 5

North to the brain stimulation laboratory and sleep laboratory where consenting and the remaining study procedures will be completed.

The MUSC Brain Stimulation Laboratories where the LFMS device will be located on the 5th floor of the IOP, and the Sleep Laboratory is also located on the 5th floor of the IOP within a few feet of the Brain Stimulation Laboratory. The Sleep Research Laboratory employs certified PSG technicians. We currently use a Compumedics E-series Polysomnography system in our sleep research laboratory. The data export program is capable of exporting data in several formats, including European Data Format (EDF).
After the 20 minute treatment (active versus sham) the participants will walk (or use a wheel-chair) to the sleep bedroom. The participant will have an opportunity to use the bathroom. Afterward, a registered sleep technician or trained research assistant will apply the leads for all-night sleep recording. Immediately after the leads have been attached, rating scales will be administered as outlined in the Research Design section.

8.0 RECRUITMENT METHODS

At any particular time we have approximately 75-100 patients who are being followed in our longitudinal course of sleep and anxiety disorders clinic. This program is focused on gathering prospective, longitudinal data in individuals with sleep problems who are being treated as usual by the clinical members of our sleep-anxiety clinic. Participants in this clinic are routinely invited to participate in separate sleep studies (e.g. Sleep Research Data Repository, Clinical Care Registry etc.) if they meet entry criteria. The majority of patients in this long-term, longitudinal treatment program suffer from insomnia disorder and represents one source of potential patients for the proposed LFMS study.

In addition, 4-10 new patients with insomnia complaints are evaluated each week in our intake-evaluation unit. These initial evaluations are performed, under attending supervision, by psychology interns or senior level residents/fellows in the sleep-anxiety clinic.

Potential participants for the proposed LFMS study will be recruited from these two sources. Given the already well-established nature of these programs, we do not anticipate the need for separate advertisement for the LFMS study. Our sleep-anxiety clinic has a reputation in the region as a research-oriented treatment program. Thus, most of the people referred to our sleep-anxiety program (or, on their own seek an evaluation) typically come with a pre-existing expectation and willingness to participate in research studies.

People being evaluated in the intake-evaluation unit with insomnia (over 90% of our referrals) are routinely offered (after education) the choice of either CBT-I treatment or medications. We will add the option of participating in the LFMS study. Thus, most of the candidates for this study will already be well-known to the investigators. If additional subjects are necessary to meet enrollment numbers, we would simply advertise in the local news media and on campus for potential participants suffering from insomnia to contact our intake number at 843.792.9162.

9.0 CONSENT PROCESS

The consent process will take place in the sleep laboratory in the IOP on 5 North. Participants will be given an overview of the study and informed of the requirement to be healthy [neither underweight nor overweight (BMI $\geq$ 18 and $\leq$ 50 kg/m^2)] without any current problems with substance, including alcohol abuse or dependence. Potential subjects will not be eligible for participation if they are nicotine dependent or report greater than 500 mg/d caffeine consumption. Participants will be instructed to avoid drinking any alcoholic beverages within 24-hours of participating in any component of the study. They will be informed during the initial screening interview that in order to participate in the study they cannot be taking any of the following substances, even if prescribed by a physician: benzodiazepines, hypnotic medications (Z drugs), barbiturates, cocaine, amphetamines, opiates, MDMA or PCP. Candidates will be told that immediately after giving informed consent, a urine sample will be tested for the presence of these compounds. If they are found to be positive, they would not be eligible for participation in the study and would not receive any compensation.

10.0 STUDY DESIGN / METHODS

Design (Sham-controlled, within-subject cross-over study; **see Table 1 for a timeline of measures**)

Step 1: Recruitment, Screening & Consent
Step 2: Adaptation Night (Rating Scales--Sham LFMS—Rating Scales--PSG--Rating Scales)
Steps 3-4: Two Consecutive Treatment Nights (Rating Scales--Active or Sham LFMS—Rating Scales--PSG--Rating Scales)
Steps 5-6 Two Consecutive Treatment Nights (Rating Scales--Sham or Active LFMS--Rating Scales--PSG--Rating Scales)

Each of the two treatment conditions (active versus sham) will be conducted on two consecutive nights. There will be no more than 7 days between the adaptation night and the first treatment condition; there will be no less than 6 and no more than 14 nights between each of the two-night treatment conditions. Thus, each participant who completes the full study will spend a total of 5 nights in the sleep laboratory and the time interval from the first adaptation night to completion of the study may range from 11-26 days for any particular individual.

Step 1: Recruitment, Screening, Consent, and Sleep Diaries

Recruitment, screening, and consent details described in detail above

After giving informed consent, subjects will participate in a brief interview, complete the following rating scales, receive a brief physical examination, and have a urine drug test. Additionally, participants will be asked to maintain a Consensus Sleep Diary (CSD) throughout the study. The CSD is a well-validated daily sleep log that gathers information about bedtime, arise time, time in bed, total sleep time, wake time after sleep onset, total number of awakenings, and self-rated sleep quality. Participants may also be asked to wear an actiwatch for the duration of the study (described in detail below)

Brief Structured Clinical Interview

Structured Clinical Interview for Sleep Disorders (SCISD) is an interview based on the DSM-5 criteria for sleep-wake disorders. Reliability and validity for each disorder has been analyzed based on 189 participants and is in the process of being submitted for publication. For the present study, the module for insomnia will be administered (5 questions, approximately two to five minutes to administer, minimal training required).

Self-Report Screening Measures

Beck Depression Inventory (BDI) is a well-researched, brief, self-report depression screening instrument. It consists of 21-items that assess different aspects of depression (e.g., anhedonia, excessive guilt, suicidal ideation, vegetative symptoms, and tearfulness).

Pittsburgh Sleep Quality Inventory) (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a 19-item questionnaire that assesses subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use sleep medication, and daytime dysfunction.

Insomnia Severity Index (ISI; Morin, 1993) is a self-rated instrument that determines the severity of insomnia along the following categories: no clinically relevant insomnia, subthreshold insomnia, clinical insomnia (moderate severity), and clinical insomnia (severe).

Epworth Sleepiness Scale (ESS; Johns, 1991) is an 8-item questionnaire that measures self-reported average sleep propensity in daily life.

Spielberger Trait Anxiety Scale (STAI; Spielberger, 1968) is a validated 20-item rating scale that measures the person's tendency to experience anxiety, a measure of trait anxiety.

Sleep Diaries. Sleep diaries will be used for seven days to measure subjective sleep patterns. Participants will be asked to make daily diary entries with an estimate of their sleep the night before (e.g., bedtime, sleep onset).

*Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2002) i*s a well-validated, 10-item screening questionnaire with 3 questions on the amount and frequency of drinking, 3 questions on alcohol dependence, and 4 on problems caused by alcohol.

Fagerstrom Test for Nicotine Dependence (FTND; Diaz et al., 2005) is a well-validated, six-item questionnaire to assess current nicotine dependence.

Positive and Negative Affect Scale (PANAS, Watson et al, 1988) is a well-validated 20 item questionnaire to assess components of affect (distress, alertness, nervousness, hostility, enthusiasm).

Physical Examination

A brief physical and neurological examination will be provided, which will include vital signs, weight, head and neck circumference, head breadth and length, and cardiopulmonary examination.

Urine Testing

Urine will be tested using a CLIA Waived kit, which included adulterant testing.

Step 2: Adaptation Night

Rating Scales:

Baseline Only: Spielberger State Anxiety Scale, Beck Depression Scale, ESS, PANAS
Before & After Sham LFMS: Uhde Sleepiness Scale (USS), Anxiety (100 mm), Depression (100 mm), PANAS
After PSG: ESS, Sleep Latency, WASO, Number Awakenings, MUSC Sleep Quality Scale, Sleep Diary, PANAS
Ease in Falling Asleep (100 mm), Concentration (100 mm), Fatigue (100 mm)

Physiological Measures

Polysomnogram (PSG)

Participants who complete the full study will have five nights of sleep recordings (i.e. polysomnography, PSG). Our standard PSG procedure requires surface electrodes to be placed on the face and scalp. An EEG (electroencephalogram) will be used to measure and record brain wave activity. An EMG (electromyogram) records muscle activity such as face twitches, teeth grinding, and leg movements. Together, these recording provide data to determine the presence of REM versus non-REM stage sleep. An EOG (electro-oculogram) will be used to record eye movements. These movements are important in determining the different sleep stages, particularly REM stage sleep. Elastic belts will be placed around the chest and abdomen to measure patterns of breathing. A bandage-like oximeter probe will be placed on a finger to measure the amount of oxygen in the subject's blood. An EKG (electrocardiogram) will record heart rate and rhythm. A nasal airflow sensor may also be used to record airflow. A snore microphone will be used to record snoring activity, and video recording capture movements, movement artifacts and sleep related movement disorders. Subjects will be video and audio recorded during all PSG testing. All data will be recorded digitally and saved for a future analysis.

The sleep recordings will be amplified using standard clinical polygraphs (E-series Compumedics Amplifier System) in accordance with American Academy of Sleep Medicine requirements. The sleep records subsequently will be scored independently of knowledge of the diagnoses as well as treatment condition (active and sham), according to standardized criteria. After each PSG night, subjects will complete a post-sleep questionnaire upon awakening in the morning and will estimate time to fall asleep, number of nightly awakenings, total sleep time, soundness and quality of sleep, and morning sleepiness. These dependent variables will be assessed with both parametric and nonparametric statistical tests. For example, regression analyses may be used to predict developing and/or the progression of psychopathology and/or medical illnesses.

Actigraphy

An actigraph is a small watch-like devise that records body movements and light intensity that may correlate with the quality of sleep and circadian rhythms. Subjects will be asked to wear the actigraph during the study from the time of consent until completion of the last treatment night. Actigraphy data will be combined with PSG and subjective symptoms to provide a multifactorial assessment of sleep.

Steps 3-6: Cross-Over Treatments

Rating scales and polysomnography will be the same as adaptation night.

Table 1. Timeline of Measures

Condition	visitscreening	AdaptationPM	tationPostAM	Interval	PM - Session 1	pn 1AM – post	PM - Session 2	pn 1AM – post	Interval	PM - Session 3	pn 2AM – post	PM - Session 4	pn 2AM – post
Visit day	1	2	3	(0-7 days)	4	5	5	6	(6-14 days)	7	8	8	9
Active LFMS					X		X						
Sham LFMS		X								X		X	
SCISD	X												
AUDIT	X												
FTND	X												
ISI	X												
PSQI	X												
Physical	X												
Urine test	X												
STAI	X	X			X		X			X		X	
BDI	X	X			X		X			X		X	
ESS	X	X	X		X	X	X	X		X	X	X	X
USS		2X			2X		2X			2X		2X	
Anxiety		2X			2X		2X			2X		2X	
Depression		2X			2X		2X			2X		2X	
PSG		X			X		X			X		X	
MSQS			X			X		X			X	X	X
Ease of sleep			X			X		X			X		X
Concentration			X			X		X			X		X
Fatigue			X			X		X			X		X
PANAS	X	2X	X		2X	X	2X	X		2X	X	2X	X
Sleep Diary		X	X	X	X	X	X	X	X	X	X	X	X

11.0 SPECIMEN COLLECTION AND BANKING (if applicable)

Participants will provide a urinalysis at baseline. This will be discarded immediately after testing.

12.0 DATA MANAGEMENT

The value of this new non-pharmacological treatment will be determined in part by its relative efficacy to hypnotics and other psychotropic medications used to treatment insomnia disorder. Sleep promoting agents with significant clinical efficacy as measured by selective behavioral measures (e.g., subjective sleep latency) have been demonstrated in placebo-controlled studies with 20 subjects. We will therefore enroll 20 participants. Given the exploratory nature of this cross-over study, twenty patients with insomnia disorder contains sufficient power to determine whether active LFMS has evidence of a sleep-promoting “signal” compared to the sham treatment condition. Due to this uncertainty, a preliminary analyses will be run once at least first 5 participants have completed the study, so as to estimate the effect size. Recruitment and randomizations will continue while the data is being analyzed and interpreted. Primary subjective and objective endpoints will be analyzed for the interim analysis. If a signal is found in the interim analyses and subsequent final analyses, a larger and more highly powered investigation will be conducted in the future.

The interim analysis will be based on unblinded data. To preserve the integrity of the study blind, a Data Review Group (DRG) will review the data to estimate the effect size and if 20 subjects will afford sufficient power. The DRG will consist of a statistician not directly affiliated with the study, and with individuals who are not involved in recruiting, randomizing, or treating study participants. The results of the interim analysis will be known only to the DRG.

In the formal analysis, order and gender will be balanced across the two treatment conditions (i.e., sham and active LFMS). Efficacy analyses will be performed using the mean values of dependent measures obtained on

the two consecutive treatment nights for each treatment condition. Given that this is an exploratory examination, all primary and secondary dependent measures will be compared using 1-tailed, paired *t*-tests for normally distributed data and the Mann-Whitney U or Wilcoxon's tests for non-normally distributed data. Correlations will be assessed using Pearson's correlation coefficient.

As per standard sleep research methodology, data from the adaptation night will not be incorporated into the formal analyses. However, adaptation data may be used in an exploratory analysis to examine the possible role of adaptation as a predictor of response.

All files will be kept confidential according to HIPAA rules and regulations. In relation to the collected data, the names and all other unique identifiers of the subjects will be coded to ensure confidentiality. A number will be assigned to each subject and this number will be used for registration, data analyses, and exchange of information within the research community.

The list that matches the names with the code numbers will be kept in a locked file in the sleep laboratory (located in the IOP on 5 North). Only investigators associated with this protocol and essential technical staff will have access to this locked file. All unique identifiers will be removed from the data prior to publication/presentation in the research community.

13. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS (if applicable)

This is a small pilot study of a device already determined by the FDA to be NSR. Polysomnography (PSG) is a standard and validated diagnostic test, which is used to evaluate patients with a wide-range of different medical and sleep disorders. PSG are obtained in thousands of people throughout the world each year without significant complications or untoward effects.

The data acquired during the PSG testing could uncover a previously unknown problem or medical condition. In this case, participants will be informed of the findings and, if necessary, given a referral the appropriate medical professionals at MUSC. Additionally, one question on one measure (BDI-II) inquires about feelings of self-harm/suicide. This question will be examined individually every time the measure is completed. One of the clinicians on our team (Uhde, Milanak) will be present or on call at all times to assist with further assesment and referral if appropriate. If pt requires immediate referral he or she will be excused from the remainder of the study.

We do not anticipate any major safety issues and will thus keep the data blinded for the entirety of the study. If there are major SAE's and/or unanticipated problems, we will work closely with the IRB to consider pausing or stopping the study.

14.0 WITHDRAWAL OF SUBJECTS

Patients can withdraw from the study at any time. However, they will not receive payment for time points they do not complete.

15.0 RISKS TO SUBJECTS

Potential risks related to:

Low Frequency Magnetic Stimulation (LFMS): Overall, LFMS at the intensity, frequency and number of stimuli proposed in the current protocol is considered a "non-significant risk" by the FDA; it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). Nonetheless, we list the conceivable "potential" risks associated with LFMS below:

Mood Worsening- Although possible, there is no evidence to date in over 300 patients that LFMS causes depression or worsens mood. Patients with current major depression disorder are excluded from participation in this study. If a worsening of mood were to develop, Dr. Uhde would provide medical care or refer to a member of the department's mental health team.

Pain-Most evidence suggests that rTMS provides temporary relief from pain, a temporary decrease in sensitivity to pain, or no effect at all. No data are not available for LFMS. Taken together, other than mild tingling of the scalp, there is little evidence that LFMS would induce pain.

Brain Tissue Damage- LFMS is thought to be safe.It is derived from MRI, the treatment which is routinely used to assess brain damage..

Safety in case of pregnancy-This protocol will exclude pregnant women. The risks of using LFMS with pregnant women are currently unknown. Known pregnancy, detection of HCG in urine, or active plans on becoming pregnant is an exclusion criterion for participation in this study.

Unknown Risks-LFMS is an experimental procedure that has not been approved by the FDA as a treatment for insomnia disorder and it may have unknown side effects.

Polysomnography:

Tape Irritation-There is minimal risk associated with the discomfort of having standard clinical EEG paste electrodes applied to the scalp. Rarely, an individual will have a mild irritation to the tape applied over electrodes. People who report past severe allergic reactions or pain to adhesive tape will be excluded from the study.

Anxiety-Some people may find sleeping in an unfamiliar setting uncomfortable. Participation in the adaptation night PSG usually alleviates such anxiety. Participants will be thoroughly educated in advance about the sleep laboratory environment and arrangements. Participants will be invited to visit the laboratory prior to the adaptation PSG if they would find this helpful.

Excessive Daytime Drowsiness-Participants who appear unable to safely operate equipment due to excessive drowsiness after the sleep night electroencephalography will be asked to refrain from driving. They may stay in the lounge area of the sleep laboratory or further rest in the sleep bed until they have recovered from the procedure. They may also be sent home by taxi or picked up by a friend.

Unknown Medical Problems-Although sleep studies are being performed for research purposes, an unknown medical problem or condition might be identified or suggested from PSG findings. This would usually be found on the adaptation night. It is also possible, however, that an existing medical condition or sleep disorder unrelated to insomnia disorder might not be revealed through this research. Another potential risk is that some medical conditions may not be possible to diagnose with a certainty, even when the problem is a sleep disorder. For example, we would be unable to calculate with certainty the severity index of an individual found to have probable obstructive sleep apnea on the PSG. If the participant is found to have (or is suspected to have) sleep apnea, another sleep disorder or medical condition, the subject will be given information regarding appropriate clinical testing and evaluation.

Actigraphy: In rare instances, the Actiwatch worn by participants causes minor skin irritation. All participants will be informed of this risk and reminded they should remove the watch and clean and dry the area each day.

Psychological Testing:

Breach of Confidentiality-The Department of Psychiatry and Behavioral Neurosciences is extremely concerned about all issues related to confidentiality and is experienced in procedures of maintaining it effectively. In relation to this specific study, all data will be identified only by a code number rather than a name. Whenever data are reported, no individual subject will be identified.

Anxiety-A small number of participants may be uncomfortable or anxious when completing rating forms, questionnaires, or answering personal questions about their mental health. All subjects will be informed that they may choose not to answer any questions in which they are uncomfortable answering.

Laboratory testing:

Social Anxiety-Very rarely, participants are uncomfortable providing urine samples for testing. In the event that a person is too shy and/or suspected of having a substance misuse problem, they will be informed that they may choose not to participate in the study, as urinalysis is required.

16.0 POTENTIAL BENEFITS TO SUBJECTS OR OTHERS

Potential Benefits of the Proposed Research to the Subjects and Others

It is important to determine if this new form of brain stimulation, which in preliminary investigations has rapid antidepressant effects (within 20 minutes), will also have positive sleep-promoting effects in people with insomnia disorder. A non-invasive, non-addicting, and non-benzodiazepine treatment for insomnia would potentially have

widespread health promoting value insofar as insomnia and insomnia disorder are risk factors for developing or worsening a wide range of sleep, psychiatric and medical disorders.

Importance of the Knowledge to be Gained

See above.
Data obtained in this study will provide useful information regarding the indications for investigating LFMS in a larger cohort of patients suffering from insomnia disorder or co-existing insomnia in medical diseases in which benzodiazepine or hypnotic drugs are contraindicated.

Payment

Participants will be paid by gift cards: $10.00 for the screening visit, $35.00 for the first adaptation night, $35.00 for the first night of $_{a\text{-}s}$LFMS-PSG, $40.00 for each of the next two nights of $_{a\text{-}s}$LFMS-PSG and $75.00 for the final $_{a\text{-}s}$LFMS night and next morning follow-up interview. The total compensation for participating in this study is $235.00. This will be paid with gift cards in two payments. The first payment will be provided following completion of the screening appointment and first three nights in the sleep laboratory. The second payment will be provided at the end of the last visit.

18. DRUGS OR DEVICES

The LFMS machine used in this study is a large piece of equipment that is permanently housed securely in the MUSC Brain Stimulation Laboratories on the 5th floor of the IOP. Only key study personnel and their guests (i.e., participants) have access to it.

REFERENCES/LITERATURE CITATIONS

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2002). The alcohol use disorders identification test. *Guidelines for Use in Primary Care. 2nd Ed. New York (USA): World Health Organization-WHO*.

Buysse, D. J., Reynolds, C. F. 3Rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. *Psychiatry Res*. http://doi.org/10.1016/0165-1781(89)90047-4

Carlezon, W. a., Rohan, M. L., Mague, S. D., Meloni, E. G., Parsegian, A., Cayetano, K., … Renshaw, P. F. (2005). Antidepressant-like effects of cranial stimulation within a low-energy magnetic field in rats. *Biological Psychiatry*, *57*(6), 571–576. http://doi.org/10.1016/j.biopsych.2004.12.011

Diaz, F. J., Jané, M., Saltó, E., Pardell, H., Salleras, L., Pinet, C., & de Leon, J. (2005). A brief measure of high nicotine dependence for busy clinicians and large epidemiological surveys. *Australian and New Zealand Journal of Psychiatry*, *39*(3), 161–168. http://doi.org/10.1111/j.1440-1614.2005.01538.x

Dorheim, S. K., Bjorvatn, B., & Eberhard-Gran, M. (2014). Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study. *PLoS ONE*, *9*(4). http://doi.org/10.1371/journal.pone.0094674

Johns, M. W. (1991). A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *SLEEP*, *14*(6), 540–545.

Morin, C. M. (1993). *Insomnia: Psychological Assessment and Management*. New York: Guilford Press.

Morin, C. M., & Jarrin, D. C. (2012). Epidemiology of Insomnia: Prevalence, Course, Risk Factors, and Health Burden. *Clinics in Sleep Medicine*, *8*(3), 281–297. http://doi.org/10.1016/j.jsmc.2013.05.002

Rohan, M. L., Yamamoto, R. T., Ravichandran, C. T., Cayetano, K. R., Morales, O. G., Olson, D. P., … Cohen, B. M. (2014). Rapid Mood-Elevating Effects of Low Field Magnetic Stimulation in Depression. *Biological Psychiatry*, *76*(3), 186–193. http://doi.org/10.1016/j.biopsych.2013.10.024

Rohan, M., Parow, A., Stoll, A. L., Demopulos, C., Friedman, S., Ph, D., … Renshaw, P. F. (2004). Low-Field Magnetic Stimulation in Bipolar Depression Using an MRI-Based Stimulator. *Psychiatry: Interpersonal and Biological Processes*, *161*, 93–98.

Spielberger, C. D. (1968). *Spielberger state-trait inventory*. *California: Mind Garden*.

Taylor, D. J., & Bramoweth, A. D. (2010). Patterns and Consequences of Inadequate Sleep in College Students: Substance Use and Motor Vehicle Accidents. *Journal of Adolescent Health*, *46*(6), 610–612. http://doi.org/10.1016/j.jadohealth.2009.12.010

Woznica, A. a., Carney, C. E., Kuo, J. R., & Moss, T. G. (2015). The insomnia and suicide link: Toward an enhanced understanding of this relationship. *Sleep Medicine Reviews*, *22*, 37–46. http://doi.org/10.1016/j.smrv.2014.10.004