Low Field Magnetic Stimulation: Initial Trial in Geriatric Bipolar Depression

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Phase 1 of Protocol (May 22, 2017)

MCLEAN HOSPITAL RESEARCH PROTOCOL

PROTOCOL TITLE AND DATE

Low Field Magnetic Stimulation: Initial Trial in Geriatric Bipolar Depression
May 22, 2017

NAME AND ADDRESS OF PRINCIPAL INVESTIGATOR

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SITES WHERE THE STUDY WILL BE PERFORMED

Recruitment will take place in the geriatric outpatient clinic at McLean Hospital (South Belknap III) and the Seniors Aging Gracefully Everyday (SAGE) Program, also located in South Belknap. Treatments for this study will be performed at the McLean Hospital Imaging Center.

I. BACKGROUND AND SIGNIFICANCE (including preliminary studies).

a. Historical background

The Low Field Magnetic Stimulation (LFMS) procedure is an application of a series of electromagnetic pulses to the brain. The field and timing parameters of the LFMS pulses, such as pulse timing, duration, frequency, and electric and magnetic field distribution and direction are different from other neuro-stimulation methods. LFMS electromagnetic fields are significantly weaker (< 100x) than those used in ECT and rTMS.

LFMS was discovered at McLean Hospital and has thus far been studied as an experimental antidepressant treatment. LFMS is also being studied at Massachusetts General Hospital and 5 other hospitals in an NIH sponsored trial (RAPID) as well as in studies at Cornell-Weill School of Medicine. The mechanism of action for the antidepressant effects of LFMS is hypothesized to be an interaction between the electromagnetic fields and neurons in cortical regions, brought about by low level electrical stimulation applied with particular timing.

b. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research

LFMS is being investigated as a treatment for depression and anxiety at McLean Hospital in a program that includes a range of projects aimed at investigating mechanisms of action, optimizing treatments, and demonstrating effects of this potential new treatment. There have been three previous clinical studies of LFMS [1][2], a series of pre-clinical studies using the forced swim test [3], and mathematical and modeling solutions have been found for the electric fields inside the head during LFMS. These studies are listed below. During this time, there has also been a steady development effort in the laboratory in the measurement and analysis of low frequency electric fields in the air and in MRI systems.

The first clinical study was a human study using an MRS sequence, during which the antidepressant effects of LFMS were serendipitously discovered [1]. In this study, the LFMS electromagnetic fields were delivered by the MRI system. The second clinical study (2004-2006, 2004-P-002631) also used an MRI system to deliver LFMS. This study had low recruitment due to the difficulty and expense of scheduling subjects for time in a clinical MRI system. A recently completed single-visit study (2006-P-001655) used a specially designed ‘LFMS Device” to deliver LFMS. This device delivered the active portion of the MRI sequence using a tabletop sized coil and small amplifier. This device was reviewed by the FDA in 2006 and was declared to be a “non-significant risk” device. The LFMS device is a non-invasive device that does not present a potential for serious risk to the health, safety, or welfare of a subject. LFMS uses magnetic and electric fields that are at lower levels than those in MRI systems. The proposed multi-visit study will use this device.

Results from protocol 2006-P-001655 were published in Biological Psychology [2]. This study looked at the effects of a single LFMS experimental treatment in subjects with bipolar or unipolar depression. We found a significant reduction in depression symptoms in subjects who received active LFMS relative to sham treatment using the Hamilton Depression Rating Scale (HDRS) ($p < 0.009$), Visual Analog Scale (VAS) ($p < 0.006$) and in the secondary hypothesis using the

Positive and Negative Affect Scale (PANAS), positive scale ($p < 0.001$). The success of this study prompted the proposed study on the effects of LFMS in bipolar depression in a geriatric population.

c. Rationale behind the proposed research, and potential benefits to patients and/or society

LFMS and Depression. Results from our single-visit protocol (2006-P-001655) are encouraging, and demonstrate an immediate mood improvement from LFMS in depressed subjects. This indicates that LFMS continues to show potential as a treatment for depression. A study is currently underway, assessing the effects of multiple LFMS experimental treatments in subjects suffering from bipolar depression. One step in the development of LFMS is to extend these results to a similar but new population, geriatric bipolar depression (GBD), in addition to the evaluation of the effect of multiple treatments, as well as observation of the duration of the effect after a delay of one week in this population. The proposed protocol involves three treatments on consecutive days with one follow-up visit; this is a crossover study in which the treatments and follow-up are repeated after a one-week washout with the alternate (active, sham).
The mechanisms of depression in a geriatric population may differ from those in a younger population. In particular, brain structures and connectivity have changed, and there is the increased risk of comorbid diagnoses such as dementia that might confound treatment and assessment. In this study we will extend the findings of LFMS in the general population to directly address the treatment of bipolar depression in a geriatric population. The LFMS group at McLean is currently pursuing a multi-treatment, parallel design study in subjects with bipolar disorder (2012-P-002380) using a similar treatment protocol, and the results from this study will be comparable to the results from that study because of this similarity.

Potential benefits to subjects include the possibility of immediate mood improvement following LFMS. The need for immediate mood improving treatments in crisis and acute scenarios is important. The current delay between the start of anti-depressant therapy and the relief of symptoms is weeks, and is not effective in crisis situations. The discovery of a treatment with immediate effect would be an important addition to the treatment of depression. Additionally, current treatments for depression are not satisfactory for all patients, and any additional therapy alleviating symptoms would benefit patients and society. Finally, the response rate of patients to anti-depressant medication is low and the incidence of treatment resistance is high; this means that additional therapies are needed. The lack of demonstrated side effects from LFMS to date will allow widespread use, either as a monotherapy or as an adjunct therapy, without significant risks.

LFMS and Anxiety. In previous studies we found that LFMS affected symptoms of anxiety, in addition to depression. These results lead us to believe that LFMS should be explored for use in anxiety disorders. A detailed examination of the responses to the Hamilton Depression Rating Scale (HDRS) in the recent study shows that the largest effects are in the "psychic anxiety" and "somatic anxiety" items, along with "depressed mood" and "work and interest." A similar examination of the Positive and Negative Affect Schedule (PANAS) results shows that the improvement is in many of the anxiety-related items on the negative scale such as " distressed," "upset," "scared," "irritable" and "jittery" along with changes in many items on the positive scale such as "enthusiasm," "pride" and "inspiration." Based on this pattern of results, we propose that LFMS may offer relief from symptoms of depressed mood, anxiety, and irritability.

II. SPECIFIC AIMS (Research Objectives)

a. Specify objectives and hypotheses to be tested in the research project

Aim 1: To assess the safety and efficacy of regular LFMS in treating symptoms of depression in older adults suffering from bipolar depression.

- Hypothesis 1: We hypothesize that subjects will show long-term improvement over one week in mood following the first LFMS experimental treatment, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).
- Hypothesis 2: We also hypothesize that subjects will demonstrate an acute improvement in depression as measured by the Beck Depression Index (BDI).

Aim 2: To assess the efficacy of regular LFMS in treating symptoms of anxiety in older adults suffering from bipolar depression.

- Hypothesis 3: We hypothesize that subjects will show long-term improvement over one week in anxiety following the first LFMS experimental treatment, as measured by the Hamilton Anxiety Rating Scale (HARS).

- Hypothesis 4: We also hypothesize that subjects will demonstrate an acute improvement in anxiety as measured by the Beck Anxiety Index (BAI).

Aim 3: To assess any cognitive benefits from regular LFMS in older adults suffering from bipolar depression.

III. SUBJECT SELECTION

Up to 30 subjects will be enrolled in order to achieve our target of 10 completers of the treatment protocol. Subjects will be referred by clinicians from the Division of Geriatric Psychiatry at McLean Hospital.

a. Inclusion/Exclusion criteria

Inclusion criteria:

1. Subjects will be men or women aged 55 years or older.
2. Subjects will have a diagnosis of Bipolar Disorder Type I or II, current episode depressed as measure by a MADRS $\geq$ 20.
3. Subjects must have failed at least one FDA approved treatment for bipolar depression before enrolling in this study. Failed treatment is defined as 8 weeks of treatment at standard dose (SSRI, SNRI, mood stabilizer, or typical or atypical antipsychotic).
4. Subjects must be maintained on a stable dose of all psychotropic medications for a period of at least two weeks prior to screening.
5. Subjects must be capable of providing informed consent.

Exclusion criteria:

1. Dangerous or active suicidal ideation.
2. Subjects meeting DSM-IV-TR criteria for any Axis I disorder other than Bipolar Disorder or an anxiety disorder (e.g. Major Depressive Disorder, dementia).
3. Subject has an MMSE score $\leq$ 24.
4. Subject is pregnant or plans on becoming pregnant.
5. Subject has recent history (within 7 days of screening) of ECT or TMS treatment.
6. Subject has recent history of substance abuse (cannot meet DSM-IV-TR criteria for substance abuse, no significant drug abuse within last 3 months, no history of dependence in last year, no drug use within last month, other than marijuana use).
7. Subject has any contraindication for MRI (i.e. Presence of a pacemaker, neurostimulator, or metal in head or neck).

For safety purposes, use of the LFMS device follows standard MRI procedures. The LFMS device is assessed by the McLean Hospital Biomedical Engineering department annually to ensure the device operates within safe parameters.

b. Withdrawal Criteria:

Participation in this research study is voluntary. Subjects will be informed that they may withdraw from this study at any time. Subjects also will be informed that study staff may terminate participation at any time if they feel that it is in the best interest of the subject or study.

Objective criteria for removing a subject from the study include: if they become no longer eligible for the study between screening and treatment per inclusion/exclusion criteria (e.g. drug use or pregnancy), if they have dangerous or active suicidal ideation at any time during the study (as determined by C-SSRS and suicide related questions on the MADRS and BDI and the opinion of a study clinician), or if their CGI-I score, determined as part of the Safety Measures, shows a change of $\geq$ 8, or if any intolerable discomfort from the study procedures occurs.

c. Source of subjects and recruitment methods

Study subjects will be recruited via clinician referrals from the Geriatric Psychiatry Mood and Anxiety Disorders Outpatient Clinic (GPMADOC) and the SAGE Program, located in South Belknap. Clinicians associated with these

programs will identify patients from their group that may be potential subjects. Potential subjects may be given an informational flyer about the study by clinical staff. The clinicians and staff members will not discuss aspects of the study with potential subjects so as to prevent the patient from experiencing undue pressure from their provider. We expect that potential subjects may be confused and/or upset if they were contacted by research staff at McLean without prior knowledge. Therefore, involving clinical staff as the first point of contact is essential to bridge patient communication between the two institutions. Clinicians will not be required or pressured to enroll patients in the study and patients' routine clinical care will not be jeopardized in any way if they choose not to participate. Potential subjects will be told that participation is completely voluntary and can be terminated at any time, for any reason by the patient.

A clinical research study staff member will contact interested and viable study candidates to explain the study procedures, answer any questions that the potential subject may have and conduct a pre-screening interview over the phone. Pre-screen interviews will be reviewed with the principal investigator on a weekly basis. Potential subjects who pass the pre-screen interview and are still interested in the study will be scheduled for an informed consent and prescreening visit at McLean Hospital.

Acceptance will rely on approval by one of the study physicians, in addition to satisfying all other criteria.

Subjects will be paid $30.00 for each visit to help cover the cost of travel and meals. Subjects may earn a maximum of $270.00 over the course of the 9 visits.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for patient registration and/or randomization

A clinical study staff member will contact potential subjects to explain the study procedures and answer any questions that potential subjects may have. If potential subjects are interested, treatment visits will be scheduled.

b. Procedures for obtaining informed consent (including timing of consent process)

Informed Consent will be obtained by either a doctoral-level psychologist or by a CITI certified research assistant. If a research assistant obtains Informed Consent then a study psychologist will be available on site as back-up during the consent process, and subjects will be offered the option of speaking with a study psychologist or physician before consenting. The PI will also be available to answer questions if requested by the subject. Any discussion with additional study staff will be recorded in the consent log. Informed Consent will be obtained using an informed consent for approved by the Partners Healthcare IRB.

Subjects will be given ample time to review study procedures before consenting and will receive a copy of the signed consent document to keep. Consent will be signed under conditions that give free power of choice without intervention or undue duress, persuasion, coercion, or deception. The clinical study staff will sign the consent after confirming the subject understands the conditions of participation. Signed consent forms will be stored in a locked filing cabinet in a locked office.

c. Treatment assignment, and randomization (if applicable)

This is a randomized, double-blind, sham-controlled crossover study. There is no physical sensation associated with the treatment, and all operating sounds are duplicated during sham, so that the operator, rater, and subject are all blinded. An inaccessible log file records the treatment condition, time and date of each system use for confirmation after the study is un-blinded.

Subjects will be distributed equally into two groups. One group will receive active LFMS during the first treatment week and sham LFMS during the second treatment week, and the second group received sham LFMS first and then active LFMS. Treatment assignments will be randomized and balanced within blocks of 10. Randomization is performed automatically on the first treatment visit. The LFMS Device contains a pre-randomized folder of subject treatment links that are assigned to subjects as they arrive for their first treatment. This list was randomized in ten-subject blocks at the start of the study (using a random number generator) and has been untouched and unviewed since then.

V. STUDY PROCEDURES

Study Overview

a. Study visits and parameters to be measured (e.g., laboratory tests, x-rays, and other testing)

This study will consist of a screening visit; three treatment visits (3 days active or sham LFMS) and one follow-up visit for ratings one week after initial treatment. This is followed one week later by 3 visits with the alternate treatment (3 days active or sham LFMS) and a follow up visit for ratings one week later.

Visits & Procedures	*Screening Week 1*	*LFMS experimental treatment Week 2*			*Follow-Up Visit Week 3*	*LFMS experimental treatment Week 4*			*Follow-Up Visit Week 5*
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Visit 8*	*Visit 9*
LFMS		X	X	X		X	X	X	
M.I.N.I International Neuro-Psychiatric Interview (MINI)	X								
Cumulative Illness Rating Scale (CIRS-G)	X								
Mini Mental State Exam (MMSE)	X								
LFMS Demographics Form	X								
LFMS Medical Screening Form	X								
LFMS Medications Form	X								
Drug Test	X								
Montgomery-Asberg Rating Scale (MADRS)	X	X			X	X			X
Hamilton Anxiety Rating Scale (HARS)	X	X			X	X			X
Positive and Negative Affect Schedule-Extended (PANAS-X)	X	X	X	X	X	X	X	X	X
Beck Anxiety Inventory (BAI)		X	X	X		X	X	X	
Beck Depression Inventory (BDI)		X	X	X		X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X

Clinical Global Impressions – Improvement Scale (CGI-I)		X	X	X	X	X	X	X	X
Clinical Global Impressions – Baseline (CGI-B)	X								
Adverse Events Check-in	X	X	X	X	X	X	X	X	X

Safety Procedures

a. Suicidality Procedures

Suicidal ideation (SI) is not uncommon in people suffering from GBD. Suicidality will be assessed throughout the study during the screening visit, treatment visits and follow-up visits. Using the C-SSRS. The GPMADOC suicidality SOP will be prompted by over threshold responses for certain items on mood rating scales or by spontaneous report of suicidal ideation at any time. Specifically,

- The use of the GPMADOC Suicidality SOP will be triggered by spontaneous report of suicidal ideation or by over-threshold responses to specific items on mood ratings.
- The Suicidality SOP instructs the use of the C-SSRS and uses the responses to questions 4 and 5 as a threshold for physician involvement. If the responses to these two questions are "yes" then the study physician will be contacted for in-person assessment or for phone call-back assessment as appropriate. The C-SSRS will be completed while awaiting the physician.
- The following mood rating items and thresholds trigger use of the Suicidality SOP: C-SSRS, "yes" to questions 4 and 5; MINI, "yes" on items B7, B9 or B10; MADRS, 4 or 6 on item 10; BDI, 2 or 3 on item 9.

We note that the CGI is used for withdrawal criteria, but this scale is not used for suicidality assessment, but rather to ensure safe continuation of the study.

b. Medication or Therapy Changes

At the phone screen and on site screening, potential subjects are informed that we do not ask them to discontinue their medications or treatments. However, we ask that they do not make changes to their medications or therapy prior to or during the experimental study period. Stable medication is not a confound. Subjects are also told that if their clinician believes it is in their best interest to make this change, they should do so. They will be asked to inform us if this is the case. We will not ask the subject to withdraw from the study, but their data will be excluded from analyses. If a subject withdraws from the study due to a change in medication, pregnancy or any other reason not related to the actual LFMS procedures and would like to return to the study in the future, they will be allowed to re-enroll. However, they must go through a 2 month washout period. The subject will be partially rescreened to confirm mood state and inclusion/exclusion criteria prior to their first treatment visit.

c. Study visits and parameters to be measured (e.g., laboratory tests, x-rays, and other testing)

Measures

Screening measures

- M.I.N.I International Neuro-Psychiatric Interview (MINI)
- Cumulative Illness Rating Scale – Geriatrics (CIRS-G)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Mini Mental State Exam (MMSE)
- Hamilton Anxiety Rating Scale (HARS)
- Positive and Negative Affect Schedule-Extended (PANAS-X)

- LFMS Medical Screening Form
- LFMS Medications Form
- Clinical Global Impressions – Baseline (CGI-B)

Safety Measures
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Clinical Global Impressions – Improvement Scale (CGI-I)

Long-term measures
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HARS)

Short-term measures
- Positive and Negative Affect Schedule-Expanded Form (PANAS-X)
- Beck Anxiety Inventory (BAI)
- Beck Depression Inventory (BDI)

Screening (Visit 1) Procedures

A study staff member will obtain informed consent (see consent procedures above IV.b.). If informed consent is obtained, then the screening procedures will proceed.

During the screening visit, a trained clinical study staff member will interview and assess the subject using the Screening Measures, during which a detailed medical history will be obtained and current medications noted. Suicidality risk is assessed as part of the Safety Measures; a positive response to items 4 or 5 of the C-SSRS will prompt the use of the Suicidality SOP.

A urine drug screen and, if female, a pregnancy test will be performed. Subjects will be accepted for the treatment trial based on the interview and review of results by a study physician.

The screening visit, including the rating scales and physical exam, will take approximately 2 hours and will be done up to one week before the baseline visit. If subjects meet study criteria after the screening visit, treatment visits will be scheduled.

LFMS (Visits 2-4 and 6-8) Procedures

Contingent on a successful screening visit, subjects will come in on three consecutive days (± 1 day per treatment visit), visits 2-4, to receive either active LFMS or the sham treatment. Each treatment visit will take about 1-1.5 hours to complete. Women of childbearing potential will be required to complete a urine pregnancy screen immediately before beginning each LFMS procedure. The subject will receive the alternate treatment at visits 6-8.

The Safety Measures will be administered. As part of these, the C-SSRS will be used as a suicidality risk assessment and any positive response to items 4 or 5 will prompt the use of the Suicidality SOP (see 'Suicidality Procedures' above). The second part of the Safety Measures is the CGI-I, which will be used to ensure safe continuation of the study; a score of 6 or more will prompt a consultation with the study physician and potential withdrawal from the study (see "Withdrawal Criteria" above). Medication and/or treatment changes will be asked about and noted. Changes in treatment will not prompt withdrawal but will indicate that data will be excluded from analysis (see "Medication and Therapy Change Procedures" above). A brief progress note will be recorded. LFMS procedures will begin immediately after these mood ratings have been administered.

Randomization occurs automatically when the subject number is entered on the LFMS Device during the first treatment visit.

At the first visit, subjects will complete the Long Term Measures before LFMS.

At all visits, subjects will complete the Short Term Measures immediately before LFMS.

For LFMS procedures, the subject will lie down on the patient table with his/her head positioned inside the device cylinder, and the operator will start the LFMS device. The device has been designed so that the cylinder does not extend below the eyes in order to reduce claustrophobia. Subjects will be instructed to remain silent during the treatment, except in cases of discomfort, desire to discontinue treatment, or similar situations related to subject safety and study

participation. Subjects will be given one 20 minute exposure to either the LFMS or sham electromagnetic field treatment. Subjects will be told they may receive either the active treatment or a sham, inactive treatment.

After treatment, the Short-Term Measures will be completed again to obtain post-treatment scores. Subjects will also be asked about possible side effects or sensations. After the treatment and mood ratings, subjects may leave immediately or rest in the Imaging Center waiting area until they are ready to leave or return to the GPMADOC and the SAGE Program, located in South Belknap.

Follow-up Visits (Visits 5 and 9)

The week following each set of 3 treatments (visits 5 and 9), subjects will meet with the study staff for a non-treatment follow-up visit. This visit will last up to 1 hour. During this visit, the Safety measures will be administered. As part of these, the C-SSRS will be used as a suicidality risk assessment and any positive response to items 4 or 5 will prompt the use of the Suicidality SOP (see 'Suicidality Procedures' above). Medication and/or treatment changes will be asked about and noted. Changes in treatment will not prompt withdrawal but will indicate that data will be excluded from analysis (see "Medication and Therapy Change Procedures" above).

The Long-term measures will be completed, as well as the PANAS-X. Subjects will be asked if they have experienced any change in their mood or noticed any effects. In addition, subjects will be asked whether they think they received active or sham LFMS.

d. Drugs to be used (dose, method, schedule of administration, dose modifications, toxicities), include Toxicity Grading Scale (if applicable)

N/A

e. Devices to be used

The LFMS Device is an electromagnetic coil situated on a cylinder with an inside diameter of 13.2 inches. It produces weak electromagnetic fields at a frequency of about 1000Hz; the magnetic fields are less than 30 Gauss and the electric fields are up to 1.43 V/m. A fully detailed description of the electromagnetic field distribution and waveform has been presented in the IDE submission to the FDA (and determined to be a non-significant risk device).

f. Procedures/surgical interventions, etc.

N/A

g. Data to be collected and when the data is to be collected

During the treatment visits, research data will be obtained through mood rating scales before and after the LFMS procedures, and through self-report from the subjects. Research data will also be obtained from subjects through mood rating scales at the follow-up visits, one week after the start of each set of experimental LFMS procedures.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g., data collection sheets).

The primary long-term measures will be the change in MADRS and HARS scores at one week compared to baseline across the two treatment weeks. This analysis will be a repeated measures ANOVA with a baseline covariate. The primary short-term analyses using the BDI and BAI scores, which provide additional insight into the details of mood change, will be performed in the same way. Exploratory analyses of the daily change in mood as measured by the PANAS-X will be performed.

b. Study endpoints

The main endpoint of this study is that participants will well tolerate 3 daily active treatments. A secondary endpoint is the expectation that participants will experience a persistent increase in positive mood at one week after the start of treatment. Change in mood over the first treatment is an additional measure that will ensure comparability of the study to previous studies.

c. Statistical methods and Power analysis

This is an exploratory study being performed to characterize the effects of LFMS over daily treatments and at one week in a target population. As the endpoints are safety and tolerance by the participants, no power analysis has been performed. We expect to be able to make the first estimate of an effect size based on the results of this study.

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

a. Complications of surgical and non-surgical procedures, etc.

Risks Related to Confidentiality and Privacy

There is a risk that a breach of privacy or confidentiality could occur. But, all study staff are trained in how to preserve confidentiality and privacy. Risks will be minimized by storing subject data and personal information on a password protected computer or in a locked filing cabinet in a locked office, accessible only to study staff.

Psychosocial (non-medical) risks

There is a risk that questions during the treatment visits about mental health and mood state may upset the subject psychologically. Subjects are free to take a break from or to stop answering these questions at any time, and a study physician will be able to assist them if needed.

Due to the nature of affective disorders, it is possible that a subject may develop or experience an increase in suicidal ideation during their participation in the study. If it is determined that a subject has developed increased suicidal thinking, either through increased scores on the or through conversation with clinical study staff, a study physician and the subject's clinician will be called immediately.

b. Drug side effects and toxicities

N/A

c. Device complications/malfunctions

Risks Related to LFMS Device

LFMS technology does not use ionizing radiation. Instead, it uses electric field pulses that may stimulate the brain. There are no known hazards or risks associated with this technique. The LFMS device, unlike an MR scanner, has no permanent magnet and thus has no magnetic field when not in active operation. During treatment there is a small, low frequency magnetic field near the device. This field is less than 5 Gauss when further than 1.5 feet from the device. We plan to be conservative and follow the 5 Gauss guidelines for MRI sites and place a magnetic area sign in the doorway during treatment sessions, to warn anyone who may enter the room during the 20 minute treatment. Outside of the treatment time, there are no fields and thus no safety issues.

Persons with pacemakers, neurostimulators, or metal in head or neck will not be enrolled or allowed in the room during device operation.

There is a red button on the device that can be manually pushed in the event of a hardware failure or an emergency. This mechanically disconnects the coil from the power source and dumps the energy stored in the coil safely to a heat dissipative resistor. If the subject asks to terminate the experiment or experiences a medical emergency, there is a "stop" button on the interface that can be clicked with the computer mouse, and this will stop waveform execution.

Risks Related to Pregnancy

There are no known risks for pregnancy associated with this type of electromagnetic field exposure. However, in order to ensure subject safety, women who are pregnant, as confirmed by pregnancy test, will be excluded from this study.

Radiation Risks (statement provided by Radiation Safety Committee)

N/A

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals and/or to society

Potential benefits include the possibility of immediate and sustained mood improvement following the LFMS experimental treatments over a one-week period, and the further development of an antidepressant treatment for mood and anxiety disorders. LFMS may provide immediate improvement in mood, and a successful outcome to this study may lead to its use in emergency and acute treatment situations. However, it is also possible that this study may not be directly beneficial to the subject.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

A visit checklist is completed to ensure that all study procedures have been completed and documented. The study coordinator monitors all source documents to ensure that all study procedures have been completed and documented. The primary investigator will ensure that the study coordinator and clinical study staff are qualified to perform all duties delegated as outlined.

b. Safety monitoring (e.g., Data Safety Monitoring Board, etc.)

Subject safety and adverse events will be monitored and assessed by study staff during the study visit. If any events should occur, the subject can withdraw voluntarily or at the discretion of the PI.

Monitoring of the LFMS study will occur in two areas, and be primarily performed by two people. These two areas include 1) monitoring of LFMS device functions and 2) monitoring of patient information and mood assessments.

LFMS system functioning and records will be monitored by the coinvestigator, Dr. Rohan. These records will consist of a weekly check of LFMS computer log files, which contain the following information:

- Date of system operation
- Subject number
- Waveform used
- System completion status (“completed” “interrupted” or “system fault”)

These log files are only accessible by Dr. Rohan. These reports will be printed out and stored.

LFMS patient information will be monitored by the Study Coordinator. Data to be recorded include:

- Date of enrollment
- Subject number
- Diagnosis, if any
- Date of treatment
- Scores for mood rating scales before treatment
- Scores for mood rating scales after treatment
- Notes on any reports of side effects or sensations

Data will be recorded on a secure password protected computer and in REDCap, a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) extraction of de-identified data and 5) procedures for importing data from external sources. Collected data can be managed using REDCap electronic data capture tools, which are hosted at Partners HealthCare.

The investigating group (principal and co-investigators) will meet once a month to review the progress of this study. Patient information reports will be monitored with special attention paid to any reports of subject sensation or side effect.

c. Outcomes monitoring

Dr. Forester and colleagues will monitor and analyze the outcomes of this study.

d. Adverse event reporting guidelines

Adverse events related to the study procedures will be reported to Dr. Forester, the IRB, and appropriate clinicians so that timely and appropriate care can be given. Serious adverse events, non-serious unexpected adverse events that are

related or possibly related to the study, and unanticipated problems involving subjects or others will be reported to the PHRC within 5 business days/7 calendar days in accordance with PHRC unanticipated problems reporting guidelines. Events that do not fall into the above categories will be reported to the IRB in summary format at the time of the continuing review.

X. REFERENCES

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Phase 2 of Protocol (September 17, 2018)

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September 17, 2018

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SITES WHERE THE STUDY WILL BE PERFORMED

Recruitment will take place in the geriatric outpatient clinic at McLean Hospital (South Belknap III) and the Seniors Aging Gracefully Everyday (SAGE) Program, also located in South Belknap. Treatments for this study will be performed at the McLean Hospital Imaging Center.

I. BACKGROUND AND SIGNIFICANCE (including preliminary studies).

d. Historical background

The Low Field Magnetic Stimulation (LFMS) procedure is an application of a series of electromagnetic pulses to the brain. The field and timing parameters of the LFMS pulses, such as pulse timing, duration, frequency, and electric and magnetic field distribution and direction are different from other neuro-stimulation methods. LFMS electromagnetic fields are significantly weaker (< 100x) than those used in ECT and rTMS.

LFMS was discovered at McLean Hospital and has thus far been studied as an experimental antidepressant treatment. LFMS is also being studied at Massachusetts General Hospital and 5 other hospitals in an NIH sponsored trial (RAPID) as well as in studies at Cornell-Weill School of Medicine. The mechanism of action for the antidepressant effects of LFMS is hypothesized to be an interaction between the electromagnetic fields and neurons in cortical regions, brought about by low level electrical stimulation applied with particular timing.

e. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research

LFMS is being investigated as a treatment for depression and anxiety at McLean Hospital in a program that includes a range of projects aimed at investigating mechanisms of action, optimizing treatments, and demonstrating effects of this potential new treatment. There have been three previous clinical studies of LFMS [1][2], a series of pre-clinical studies using the forced swim test [3], and mathematical and modeling solutions have been found for the electric fields inside the head during LFMS. These studies are listed below. During this time, there has also been a steady development effort in the laboratory in the measurement and analysis of low frequency electric fields in the air and in MRI systems.

The first clinical study was a human study using an MRS sequence, during which the antidepressant effects of LFMS were serendipitously discovered [1]. In this study, the LFMS electromagnetic fields were delivered by the MRI system. The second clinical study (2004-2006, 2004-P-002631) also used an MRI system to deliver LFMS. This study had low recruitment due to the difficulty and expense of scheduling subjects for time in a clinical MRI system. A recently completed single-visit study (2006-P-001655) used a specially designed “LFMS Device” to deliver LFMS. This device delivered the active portion of the MRI sequence using a tabletop sized coil and small amplifier. This device was reviewed by the FDA in 2006 and was declared to be a “non-significant risk” device. The LFMS device is a non-invasive device that does not present a potential for serious risk to the health, safety, or welfare of a subject. LFMS uses magnetic and electric fields that are at lower levels than those in MRI systems. The proposed multi-visit study will use this device.

Results from protocol 2006-P-001655 were published in Biological Psychology [2]. This study looked at the effects of a single LFMS experimental treatment in subjects with bipolar or unipolar depression. We found a significant reduction in depression symptoms in subjects who received active LFMS relative to sham treatment using the Hamilton Depression Rating Scale (HDRS) ($p < 0.009$), Visual Analog Scale (VAS) ($p < 0.006$) and in the secondary hypothesis using the

Positive and Negative Affect Scale (PANAS), positive scale ($p < 0.001$). The success of this study prompted the proposed study on the effects of LFMS in bipolar depression in a geriatric population.

f. Rationale behind the proposed research, and potential benefits to patients and/or society

LFMS and Depression. Results from our single-visit protocol (2006-P-001655) are encouraging, and demonstrate an immediate mood improvement from LFMS in depressed subjects. This indicates that LFMS continues to show potential as a treatment for depression. A study is currently underway, assessing the effects of multiple LFMS experimental treatments in subjects suffering from bipolar depression. One step in the development of LFMS is to extend these results to a similar but new population, geriatric bipolar depression (GBD), in addition to the evaluation of the effect of multiple treatments, as well as observation of the duration of the effect after a delay of one week in this population. The proposed protocol involves three treatments on consecutive days with one follow-up visit; this is a crossover study in which the treatments and follow-up are repeated after a one-week washout with the alternate (active, sham).
The mechanisms of depression in a geriatric population may differ from those in a younger population. In particular, brain structures and connectivity have changed, and there is the increased risk of comorbid diagnoses such as dementia that might confound treatment and assessment. In this study we will extend the findings of LFMS in the general population to directly address the treatment of bipolar depression in a geriatric population. The LFMS group at McLean is currently pursuing a multi-treatment, parallel design study in subjects with bipolar disorder (2012-P-002380) using a similar treatment protocol, and the results from this study will be comparable to the results from that study because of this similarity.

Potential benefits to subjects include the possibility of immediate mood improvement following LFMS. The need for immediate mood improving treatments in crisis and acute scenarios is important. The current delay between the start of anti-depressant therapy and the relief of symptoms is weeks, and is not effective in crisis situations. The discovery of a treatment with immediate effect would be an important addition to the treatment of depression. Additionally, current treatments for depression are not satisfactory for all patients, and any additional therapy alleviating symptoms would benefit patients and society. Finally, the response rate of patients to anti-depressant medication is low and the incidence of treatment resistance is high; this means that additional therapies are needed. The lack of demonstrated side effects from LFMS to date will allow widespread use, either as a monotherapy or as an adjunct therapy, without significant risks.

LFMS and Anxiety. In previous studies we found that LFMS affected symptoms of anxiety, in addition to depression. These results lead us to believe that LFMS should be explored for use in anxiety disorders. A detailed examination of the responses to the Hamilton Depression Rating Scale (HDRS) in the recent study shows that the largest effects are in the "psychic anxiety" and "somatic anxiety" items, along with "depressed mood" and "work and interest." A similar examination of the Positive and Negative Affect Schedule (PANAS) results shows that the improvement is in many of the anxiety-related items on the negative scale such as " distressed," "upset," "scared," "irritable" and "jittery" along with changes in many items on the positive scale such as "enthusiasm," "pride" and "inspiration." Based on this pattern of results, we propose that LFMS may offer relief from symptoms of depressed mood, anxiety, and irritability.

II. SPECIFIC AIMS (Research Objectives)

b. Specify objectives and hypotheses to be tested in the research project

Aim 1: To assess the safety and efficacy of regular LFMS in treating symptoms of depression in older adults suffering from bipolar depression.

- Hypothesis 1: We hypothesize that subjects will show long-term improvement in mood following the five days of LFMS experimental treatment, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).

Aim 2: To assess the efficacy of regular LFMS in treating symptoms of anxiety in older adults suffering from bipolar depression.

- Hypothesis 2: We hypothesize that subjects will show long-term improvement over one week in anxiety following the first LFMS experimental treatment, as measured by the Hamilton Anxiety Rating Scale (HARS).

Aim 3: To assess any cognitive benefits from regular LFMS in older adults suffering from bipolar depression.

- Hypothesis 3: We hypothesize that subjects will show cognitive improvement, as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), at the follow-up visit as compared to baseline.

III. SUBJECT SELECTION

Up to 64 subjects will be enrolled in order to achieve our target of 32 completers of the treatment protocol. Subjects will be referred by clinicians from the Division of Geriatric Psychiatry at McLean Hospital.

d. Inclusion/Exclusion criteria

Inclusion criteria:

6. Subjects will be men or women aged 55 years or older.
7. Subjects will have a diagnosis of Bipolar Disorder Type I or II, current episode depressed as measure by a MADRS $\geq$ 20.
8. Subjects must be maintained on a stable dose of all psychotropic medications for a period of at least two weeks prior to screening.
9. Subjects must be capable of providing informed consent.
10. Subjects must live within 2 hours of McLean Hospital.
11. Subjects must have a treating psychiatrist within 2 hours of McLean Hospital.

Exclusion criteria:

8. Dangerous or active suicidal ideation.
9. Subjects meeting DSM-V criteria for any Axis I disorder other than Bipolar Disorder or an anxiety disorder (e.g. Major Depressive Disorder, dementia).
10. Subject has an MMSE score $\leq$ 24.
11. Subject is pregnant or plans on becoming pregnant.
12. Subject has recent history (within 7 days of screening) of ECT or TMS treatment.
13. Subject has recent history of substance abuse (cannot meet DSM-V criteria for substance abuse, no significant drug abuse within last 3 months, no history of dependence in last year, no drug use within last month, other than marijuana use).
14. Subject is experiencing active psychosis as determined by "yes" answers to questions K12 and K13 in the Mini International Neuropsychiatric Interview (MINI).
15. Subject has any contraindication for MRI (i.e. Presence of a pacemaker, neurostimulator, or metal in head or neck).

For safety purposes, use of the LFMS device follows standard MRI procedures. The LFMS device is assessed by the McLean Hospital Biomedical Engineering department annually to ensure the device operates within safe parameters.

e. Withdrawal Criteria:

Participation in this research study is voluntary. Subjects will be informed that they may withdraw from this study at any time. Subjects also will be informed that study staff may terminate participation at any time if they feel that it is in the best interest of the subject or study.

Objective criteria for removing a subject from the study include: if they become no longer eligible for the study between screening and treatment per inclusion/exclusion criteria (e.g. drug use or pregnancy), if they have dangerous or active suicidal ideation at any time during the study (as determined by C-SSRS and suicide related questions on the MADRS and the opinion of a study clinician), or if their CGI-I score, determined as part of the Safety Measures, shows a change of $\geq$ 8, or if any intolerable discomfort from the study procedures occurs.

f. Source of subjects and recruitment methods

Study subjects will be recruited via clinician referrals from the Geriatric Psychiatry Mood and Anxiety Disorders Outpatient Clinic (GPMADOC) and the SAGE Program, located in South Belknap. Clinicians associated with these

programs will identify patients from their group that may be potential subjects. We have also obtained permission from the clinical directors of these programs to have a research coordinator look through electronic patient charts using Epic to identify eligible subjects. Once a potential subject has been identified, study staff will discuss the possibility of study participation with the patient's doctor and/or case manager to determine if the study would be appropriate. Potential subjects may be given an informational flyer about the study by clinical staff. The clinicians and staff members will not discuss aspects of the study with potential subjects so as to prevent the patient from experiencing undue pressure from their provider. We expect that potential subjects may be confused and/or upset if they were contacted by research staff at McLean without prior knowledge. Therefore, involving clinical staff as the first point of contact is essential to bridge patient communication between the two institutions. Clinicians will not be required or pressured to enroll patients in the study and patients' routine clinical care will not be jeopardized in any way if they choose not to participate. Potential subjects will be told that participation is completely voluntary and can be terminated at any time, for any reason by the patient.

A clinical research study staff member will contact interested and viable study candidates to explain the study procedures, answer any questions that the potential subject may have and conduct a pre-screening interview over the phone. Pre-screen interviews will be reviewed with the principal investigator on a weekly basis. Potential subjects who pass the pre-screen interview and are still interested in the study will be scheduled for an informed consent and prescreening visit at McLean Hospital.

Acceptance will rely on approval by one of the study physicians, in addition to satisfying all other criteria.

Subjects will be paid $30.00 for each visit (not including phone follow-ups) to help cover the cost of travel and meals. Subjects may earn a maximum of $240.00 over the course of the 8 visits.

IV. SUBJECT ENROLLMENT

d. Methods of enrollment, including procedures for patient registration and/or randomization

A clinical study staff member will contact potential subjects to explain the study procedures and answer any questions that potential subjects may have. If potential subjects are interested, treatment visits will be scheduled.

e. Procedures for obtaining informed consent (including timing of consent process)

Informed Consent will be obtained by either a doctoral-level psychologist or by a CITI certified research assistant. If a research assistant obtains Informed Consent then a study psychologist will be available on site as back-up during the consent process, and subjects will be offered the option of speaking with a study psychologist or physician before consenting. The PI will also be available to answer questions if requested by the subject. Any discussion with additional study staff will be recorded in the consent log. Informed Consent will be obtained using an informed consent for approved by the Partners Healthcare IRB.

Subjects will be given ample time to review study procedures before consenting and will receive a copy of the signed consent document to keep. Consent will be signed under conditions that give free power of choice without intervention or undue duress, persuasion, coercion, or deception. The clinical study staff will sign the consent after confirming the subject understands the conditions of participation. Signed consent forms will be stored in a locked filing cabinet in a locked office.

f. Treatment assignment, and randomization (if applicable)

This is a randomized, double-blind, sham-controlled study. There is no physical sensation associated with the treatment, and all operating sounds are duplicated during sham, so that the operator, rater, and subject are all blinded. An inaccessible log file records the treatment condition, time and date of each system use for confirmation after the study is un-blinded.

Subjects will be distributed equally into two groups. One group will receive active LFMS during the treatment week and the other group will receive sham LFMS during the treatment week. Treatment assignments will be randomized and balanced within blocks of 10. Randomization is performed automatically on the first treatment visit. The LFMS Device contains a pre-randomized folder of subject treatment links that are assigned to subjects as they arrive for their first treatment. This list was randomized in ten-subject blocks at the start of the study (using a random number generator). This randomization schedule has since been updated to reflect the parallel-group, 5-day design of this protocol.

V. STUDY PROCEDURES

Study Overview

b. Study visits and parameters to be measured (e.g., laboratory tests, x-rays, and other testing)

This study will consist of a screening visit; a baseline visit; we will aim to administer four or five daily LFMS treatment or sham treatment visits over a period of five days and one in-person follow-up visit for ratings on the Monday after the treatment week. If a subject is unable to attend only one treatment visit in the five day window, this will not be considered a protocol violation. Follow-up rating scales will be administered by phone once per week for two weeks following the last visit.

Visits and Procedures	*Screening*	*Baseline*	*LFMS experimental treatment*					*Follow-Up Visit*	*Follow-Up Phone Call*	*Follow-Up Phone Call*
	Visit 1	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*	*Visit 6*	*Visit 7*	*Visit 8*		
LFMS			X	X	X	X	X			
M.I.N.I International Neuro-Psychiatric Interview (MINI)	X									
Cumulative Illness Rating Scale (CIRS-G)	X									
Mini-Mental State Exam	X									
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)		X						X		
LFMS Demographics Form	X									
LFMS Medical Screening Form	X									
LFMS Medications Form	X									
Drug Test	X									
Pregnancy Test	X		X	X	X	X	X			
Montgomey-Asberg Rating Scale (MADRS)	X	X	X		X		X	X	X	X
Hamilton Anxiety Rating Scale (HARS)		X	X		X		X	X	X	X
Positive and Negative Affect Schedule (PANAS)*		X	X	X	X	X	X	X	X	X
Young Mania Rating Scale (YMRS)	X	X	X	X	X	X	X	X	X	X

Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X
Clinical Global Impressions-Improvement Scale (CGI-I)			X	X	X	X	X	X	X	X
Clinical Global Impressions-Baseline		X								
Adverse Events Check-in		X	X	X	X	X	X	X	X	X

*Administered twice per visit, immediately before and immediately after LFMS treatment.

Safety Procedures

h. Suicidality Procedures

Suicidal ideation (SI) is not uncommon in people suffering from GBD. Suicidality will be assessed throughout the study during the screening visit, treatment visits and follow-up visits. Using the C-SSRS. The GPMADOC suicidality SOP will be prompted by over threshold responses for certain items on mood rating scales or by spontaneous report of suicidal ideation at any time. Specifically,

- The use of the GPMADOC Suicidality SOP will be triggered by spontaneous report of suicidal ideation or by over-threshold responses to specific items on mood ratings.
- The Suicidality SOP instructs the use of the C-SSRS and uses the responses to questions 4 and 5 as a threshold for physician involvement. If the responses to these two questions are "yes" then the study physician will be contacted for in-person assessment or for phone call-back assessment as appropriate. The C-SSRS will be completed while awaiting the physician.
- The following mood rating items and thresholds trigger use of the Suicidality SOP: C-SSRS, "yes" to questions 4 and 5; MINI, "yes" on items B7, B9 or B10; MADRS, 4 or 6 on item 10.

We note that the CGI is used for withdrawal criteria, but this scale is not used for suicidality assessment, but rather to ensure safe continuation of the study.

i. Medication or Therapy Changes

At the phone screen and on site screening, potential subjects are informed that we do not ask them to discontinue their medications or treatments. However, we ask that they do not make changes to their medications or therapy prior to or during the experimental study period. Stable medication is not a confound. Subjects are also told that if their clinician believes it is in their best interest to make this change, they should do so. They will be asked to inform us if this is the case. We will not ask the subject to withdraw from the study, but their data will be excluded from analyses. If a subject withdraws from the study due to a change in medication, pregnancy or any other reason not related to the actual LFMS procedures and would like to return to the study in the future, they will be allowed to re-enroll. However, they must go through a 2 month washout period. The subject will be partially rescreened to confirm mood state and inclusion/exclusion criteria prior to their first treatment visit.

j. Study visits and parameters to be measured (e.g., laboratory tests, x-rays, and other testing)

Measures

Screening measures

- M.I.N.I International Neuro-Psychiatric Interview (MINI)
- Cumulative Illness Rating Scale – Geriatrics (CIRS-G)

- Montgomery Asberg Depression Rating Scale (MADRS)
- Mini Mental State Exam (MMSE)
- Hamilton Anxiety Rating Scale (HARS)
- Positive and Negative Affect Schedule (PANAS)
- LFMS Medical Screening Form
- LFMS Medications Form
- Clinical Global Impressions – Baseline (CGI-B)

Safety Measures
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Clinical Global Impressions – Improvement Scale (CGI-I)

Long-term measures
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HARS)
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Young Mania Rating Scale (YMRS)

Short-term measures
- Positive and Negative Affect Schedule (PANAS)

Screening (Visit 1) Procedures

A study staff member will obtain informed consent (see consent procedures above IV.b.). If informed consent is obtained, then the screening procedures will proceed.

During the screening visit, a trained clinical study staff member will interview and assess the subject using the Screening Measures, during which a detailed medical history will be obtained and current medications noted. Suicidality risk is assessed as part of the Safety Measures; a positive response to items 4 or 5 of the C-SSRS will prompt the use of the Suicidality SOP.

A urine drug screen and, if female, a pregnancy test will be performed. Subjects will be accepted for the treatment trial based on the interview and review of results by a study physician.

The screening visit, including the rating scales and physical exam, will take approximately 2 hours and will be done up to one week before the baseline visit. If subjects meet study criteria after the screening visit, a baseline visit will be scheduled.

Baseline (Visit 2) Procedures

Contingent on a successful screening visit, subjects will come in for a baseline visit on the Thursday or Friday prior to the 5 days of consecutive LFMS treatment. This visit will take about 1 hour to complete. Subjects will be administered Long- and Short-Term mood scales as well as the Safety Measures. A positive response to items 4 or 5 on the C-SSRS will prompt the use of the Suicidality SOP (see 'Suicidality Procedures' above).

LFMS (Visits 3-7) Procedures

Subjects will come in for 5 daily consecutive LFMS treatments over a period of five days, Monday-Friday. If subjects are unable to come in for five consecutive days due to a scheduling conflict, we will accept a schedule of four consecutive days without considering this a protocol deviation. Women of childbearing potential will be required to complete a urine pregnancy screen at screening and before each LFMS procedure.

The Safety Measures will be administered. As part of these, the C-SSRS will be used as a suicidality risk assessment and any positive response to items 4 or 5 will prompt the use of the Suicidality SOP (see 'Suicidality Procedures' above). The second part of the Safety Measures is the CGI-I, which will be used to ensure safe continuation of the study; a score of 6 or more will prompt a consultation with the study physician and potential withdrawal from the study (see "Withdrawal Criteria" above). Medication and/or treatment changes will be asked about and noted. Changes in treatment will not prompt withdrawal but will indicate that data will be excluded from analysis (see "Medication and Therapy Change Procedures" above). A brief progress note will be recorded. The Short- and Long-Term mood scales will be

administered, and LFMS procedures will begin immediately after these mood ratings are completed. HARS and MADRS Long-Term mood scales will only be administered on Visits 3, 5, and 7.

Randomization occurs automatically when the subject number is entered on the LFMS Device during the first treatment visit.

For LFMS procedures, the subject will lie down on the patient table with his/her head positioned inside the device cylinder, and the operator will start the LFMS device. The device has been designed so that the cylinder does not extend below the eyes in order to reduce claustrophobia. Subjects will be instructed to remain silent during the treatment, except in cases of discomfort, desire to discontinue treatment, or similar situations related to subject safety and study participation. Subjects will be given one 20 minute exposure to either the LFMS or sham electromagnetic field treatment. Subjects will be told they may receive either the active treatment or a sham, inactive treatment.

After treatment, the Short-Term Measures will be completed again to obtain post-treatment scores. Subjects will also be asked about possible side effects or sensations. After the treatment and mood ratings, subjects may leave immediately or rest in the Imaging Center waiting area until they are ready to leave or return to the GPMADOC and the SAGE Program, located in South Belknap.

Follow-up Visit (Visit 8)

The Monday following the set of 5 treatments (visits 3-7), subjects will meet with the study staff for a non-treatment follow-up visit. This visit will last up to 1 hour. During this visit, the Safety measures will be administered. As part of these, the C-SSRS will be used as a suicidality risk assessment and any positive response to items 4 or 5 will prompt the use of the Suicidality SOP (see 'Suicidality Procedures' above). Medication and/or treatment changes will be asked about and noted. Changes in treatment will not prompt withdrawal but will indicate that data will be excluded from analysis (see "Medication and Therapy Change Procedures" above).

The Long-term measures will be completed, as well as the PANAS. Subjects will be asked if they have experienced any change in their mood or noticed any effects. In addition, subjects will be asked whether they think they received active or sham LFMS.

Follow-up Phone Calls

In order to determine whether any effects are still felt after treatment stops, study staff will make one follow-up phone call each week on Monday for the 2 weeks after the Follow-up Visit. Short- and Long-Term Measures will be administered, and study staff will ask whether the subject has experienced any adverse side-effects. Safety Measures including the C-SSRS and the CGI-I will be administered, and a positive response to question 4 or 5 on the C-SSRS will trigger the Suicidality SOP.

k. Drugs to be used (dose, method, schedule of administration, dose modifications, toxicities), include Toxicity Grading Scale (if applicable)

N/A

l. Devices to be used

The LFMS Device is an electromagnetic coil situated on a cylinder with an inside diameter of 13.2 inches. It produces weak electromagnetic fields at a frequency of about 1000Hz; the magnetic fields are less than 30 Gauss and the electric fields are up to 1.43 V/m. A fully detailed description of the electromagnetic field distribution and waveform has been presented in the IDE submission to the FDA (and determined to be a non-significant risk device).

m. Procedures/surgical interventions, etc.

N/A

n. Data to be collected and when the data is to be collected

During the treatment visits, research data will be obtained through mood rating scales before and after the LFMS procedures, and through self-report from the subjects. Research data will also be obtained from subjects through mood rating scales at the follow-up visits, one week after the start of the set of 5 experimental LFMS procedures.

VI. BIOSTATISTICAL ANALYSIS

d. Specific data variables being collected for the study (e.g., data collection sheets).

The primary long-term measures will be the change in MADRS and HARS scores at one week compared to baseline across the treatment week. This analysis will be a repeated measures ANOVA with a baseline covariate. The primary short-term analyses using the PANAS scores, which provide additional insight into the details of mood change, will be performed in the same way.

e. Study endpoints

The main endpoint of this study is that participants will well tolerate 5 daily active treatments. A secondary endpoint is the expectation that participants will experience a persistent increase in positive mood at one week after the start of treatment. Change in mood over the first treatment is an additional measure that will ensure comparability of the study to previous studies.

f. Statistical methods and Power analysis

This is an exploratory study being performed to characterize the effects of LFMS over daily treatments and at one week in a target population. As the endpoints are safety and tolerance by the participants, no power analysis has been performed. We expect to be able to make the first estimate of an effect size based on the results of this study.

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

d. Complications of surgical and non-surgical procedures, etc.

Risks Related to Confidentiality and Privacy

There is a risk that a breach of privacy or confidentiality could occur. But, all study staff are trained in how to preserve confidentiality and privacy. Risks will be minimized by storing subject data and personal information on a password protected computer or in a locked filing cabinet in a locked office, accessible only to study staff.

Psychosocial (non-medical) risks

There is a risk that questions during the treatment visits about mental health and mood state may upset the subject psychologically. Subjects are free to take a break from or to stop answering these questions at any time, and a study physician will be able to assist them if needed.

Due to the nature of affective disorders, it is possible that a subject may develop or experience an increase in suicidal ideation during their participation in the study. If it is determined that a subject has developed increased suicidal thinking, either through increased scores on the or through conversation with clinical study staff, a study physician and the subject's clinician will be called immediately.

e. Drug side effects and toxicities

N/A

f. Device complications/malfunctions

Risks Related to LFMS Device

LFMS technology does not use ionizing radiation. Instead, it uses electric field pulses that may stimulate the brain. There are no known hazards or risks associated with this technique. The LFMS device, unlike an MR scanner, has no permanent magnet and thus has no magnetic field when not in active operation. During treatment there is a small, low frequency magnetic field near the device. This field is less than 5 Gauss when further than 1.5 feet from the device. We plan to be conservative and follow the 5 Gauss guidelines for MRI sites and place a magnetic area sign in the doorway during treatment sessions, to warn anyone who may enter the room during the 20 minute treatment. Outside of the treatment time, there are no fields and thus no safety issues.

Persons with pacemakers, neurostimulators, or metal in head or neck will not be enrolled or allowed in the room during device operation.

There is a red button on the device that can be manually pushed in the event of a hardware failure or an emergency. This mechanically disconnects the coil from the power source and dumps the energy stored in the coil safely to a heat dissipative resistor. If the subject asks to terminate the experiment or experiences a medical emergency, there is a "stop" button on the interface that can be clicked with the computer mouse, and this will stop waveform execution.

Risks Related to Pregnancy

There are no known risks for pregnancy associated with this type of electromagnetic field exposure. However, in order to ensure subject safety, women who are pregnant, as confirmed by pregnancy test, will be excluded from this study.

Radiation Risks (statement provided by Radiation Safety Committee)

N/A

VIII. POTENTIAL BENEFITS

b. Potential benefits to participating individuals and/or to society

Potential benefits include the possibility of immediate and sustained mood improvement following the LFMS experimental treatments over a one-week period, and the further development of an antidepressant treatment for mood and anxiety disorders. LFMS may provide immediate improvement in mood, and a successful outcome to this study may lead to its use in emergency and acute treatment situations. However, it is also possible that this study may not be directly beneficial to the subject.

IX. MONITORING AND QUALITY ASSURANCE

c. Independent monitoring of source data

A visit checklist is completed to ensure that all study procedures have been completed and documented. The study coordinator monitors all source documents to ensure that all study procedures have been completed and documented. The primary investigator will ensure that the study coordinator and clinical study staff are qualified to perform all duties delegated as outlined.

d. Safety monitoring (e.g., Data Safety Monitoring Board, etc.)

Subject safety and adverse events will be monitored and assessed by study staff during the study visit. If any events should occur, the subject can withdraw voluntarily or at the discretion of the PI.

Monitoring of the LFMS study will occur in two areas, and be primarily performed by two people. These two areas include 1) monitoring of LFMS device functions and 2) monitoring of patient information and mood assessments.

LFMS system functioning and records will be monitored by the coinvestigator, Dr. Rohan. These records will consist of a weekly check of LFMS computer log files, which contain the following information:

- Date of system operation
- Subject number
- Waveform used
- System completion status ("completed" "interrupted" or "system fault")

These log files are only accessible by Dr. Rohan. These reports will be printed out and stored.

LFMS patient information will be monitored by the Study Coordinator. Data to be recorded include:

- Date of enrollment
- Subject number
- Diagnosis, if any
- Date of treatment
- Scores for mood rating scales before treatment
- Scores for mood rating scales after treatment
- Notes on any reports of side effects or sensations

Data will be recorded on a secure password protected computer and in REDCap, a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) extraction of de-identified data and 5) procedures for importing data from external sources. Collected data can be managed using REDCap electronic data capture tools, which are hosted at Partners HealthCare.

The investigating group (principal and co-investigators) will meet once a month to review the progress of this study. Patient information reports will be monitored with special attention paid to any reports of subject sensation or side effect.

e. Outcomes monitoring

Dr. Forester and colleagues will monitor and analyze the outcomes of this study.

f. Adverse event reporting guidelines

Adverse events related to the study procedures will be reported to Dr. Forester, the IRB, and appropriate clinicians so that timely and appropriate care can be given. Serious adverse events, non-serious unexpected adverse events that are related or possibly related to the study, and unanticipated problems involving subjects or others will be reported to the PHRC within 5 business days/7 calendar days in accordance with PHRC unanticipated problems reporting guidelines. Events that do not fall into the above categories will be reported to the IRB in summary format at the time of the continuing review.

X. REFERENCES

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