**Official Study Title:**

Treatment of Depression with Connectivity Guided Robotically delivered rTMS

**NCT number:** NCT02802293

**IRB Approval Date:** 12.05.2018

**Unique Protocol ID:** HSC20160129H

# Protocol Template Form

| **Item 1 UTHSCSA Tracking Number** | HSC20160129H |
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| **Item 2 Abstract / Project Summary** | Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific.<br>**DO NOT EXCEED THE SPACE PROVIDED**. |
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**Background, Purpose/Objectives:** Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulatory treatment modality that is approved by regulatory bodies in the United States (FDA), Canada, Europe and Australia for Major Depressive Disorder (MDD). FDA approval for rTMS treatment of MDD was based on a double-blind, placebo-controlled (sham TMS), multi-center clinical trial. In that trial, the neuroanatomical location targeted was the left dorsolateral prefrontal cortex (DLPFC), based on functional neuroimaging evidence that its serves as a hub in a multi-node network dysregulated in MDD. However, these rTMS targeting methods are neurophysiologically, neuroanatomically and technically unsophisticated. Specifically, left DLPFC was located by reference to the hand region of primary motor cortex ($M1_{hand}$), rather than being based on per-subject anatomy or connectivity. The orientation in which the coil was positioned (with the E-field vector pointed toward the subject's nose) was (grossly) optimized for $M1_{hand}$, but did not account for differences in gyral anatomy between locations (DLPFC versus $M1_{hand}$) or between subjects; these studies were also not image-guided. This is the standard-of-care (SOC) TMS treatment of MDD. In the proposed trial, the treatment efficacy of TMS will be tested using a fundamentally new strategy to addresses this research gap.

**Research Design/Plan:** We propose a randomized, double-blind, trial of TMS to the left dorsolateral prefrontal cortex (DLPFC) for patients with MDD all of whom at the patient's treatment clinic are concurrently receiving pharmaceutical and psychotherapeutic interventions. Subjects will undergo TMS treatments for at least 4 weeks, but the duration of their TMS treatments may be extended (e.g. up to 8 weeks of treatment) if approved by the subject's third-party insurance plan. Arm 1 delivers active rTMS to the left DLPFC using the standard aiming strategy. Arm 2 delivers active rTMS to the left anterior DLPFC using connectivity-based, image-guided aiming. Arm 3 delivers active rTMS to the left posterior DLPFC using connectivity-based, image-guided aiming. In all three arms, rTMS is administered in an image-guided, robotically-positioned TMS (irTMS) manner to ensure therapist blinding and equivalent subject experiences across arms. In all three arms, the following stimulation protocol will be used: 10 Hz irTMS delivered in 4 sec trains with 26 sec inter-train intervals, 37.5 minutes/session (i.e. 3,000 pulses/session), 5 sessions/week, for at least 4 weeks. Neuroimaging will be used both for treatment planning and to characterize any TMS-induced network plasticity using resting-state functional magnetic resonance imaging (rs-fMRI) at week 4 of each treatment arm. Clinical assessments will be administered weekly throughout treatment at the subject's treatment clinic. Additional psychological tests will be performed at UT Health—San Antonio's Research Imaging Institute (RII) at the baseline and post-treatment visits in order to track subject progress.

**Clinical Relevance:** This will be the first study to determine the clinical effects of connectivity-guided irTMS in the treatment of MDD, to provide clues about the ideal neural networks (anterior DLPFC vs. posterior DLPFC) to target for more robust clinical outcomes, and to identify potential biomarkers of treatment response including changes in brain networks connectivity.


| **Item 3** Background | |
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| *Describe past experimental and/or clinical findings leading to the formulation of your study.*<br>*For research involving unapproved drugs, describe animal and human studies.*<br>*For research that involves approved drugs or devices, describe the FDA approved uses of* | There is pressing need for novel therapeutics for MDD, as up to a third of patients fail to respond to available options. rTMS applied at 10 Hz to the DLPFC is a noninvasive neuromodulatory therapy that is FDA-approved for MDD. Despite being FDA approved, the SOC rTMS targeting protocol is neurophysiologically, neuroanatomically and technically unsophisticated, being neither image-guided, nor connectomically informed, nor robotically delivered. Clinical trials of SOC DLPFC rTMS in MDD show moderate efficacy (effect size ~ 0.5) but high between-subject and between-study variability. This variability can best be attributed to i) inadequate neuroanatomical specification of treatment targets and, ii) delivery imprecision. This remains the case although a large body of neuroimaging research has established that MDD is characterized by functional (& structural) abnormalities in an extended network of emotive, cognitive and autonomic brain regions including subgenual cingulate (SGC; Brodmann Area (BA) 25), anterior cingulate cortex (ACC; BA 32), DLPFC (BA |

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| *this drug/device in relation to your protocol.* | 9), medial frontal (BA 9/10) and inferior frontal cortex. In this MDD network, the most promising neuromodulatory targets are the SGC, ACC and DLPFC. SGC and ACC are too far from the scalp to be viable targets for rTMS but are being tested as targets for deep brain stimulation in MDD. Left DLPFC is accessible to rTMS and has been the target of the vast majority of TMS treatment trials in MDD, bipolar disorder, and other psychiatric disorders. The great majority of these trials, however, disregard the fact that the DLPFC is a large, functionally heterogeneous region with an anterior-to-posterior functional gradient. Anterior DLPFC is involved in higher order processes including emotion and has strong projections to SGC and ACC. Posterior DLPFC (i.e. closer to primary motor cortex) is involved in action control and has strong projections to the mid-cingulate and premotor cortex. Thus pathway-specific targeting of the anterior DLPFC should be more effective than the SOC protocol for rTMS in MDD. |
| **Item 4**<br>Purpose and rationale<br>*Insert purpose, objectives and research questions/hypotheses here.*<br>*If you cut and paste from another document, make sure the excerpted material answers the question* | We propose a randomized, double-blind, trial of irTMS to the left DLPFC for patients with MDD receiving treatment at the treatment clinic. In addition to treatment as usual, subjects will be randomized to receive irTMS in one of three treatment arms: Arm 1 delivers active irTMS to the left DLPFC using the SOC aiming strategy. Arm 2 delivers active irTMS to the left anterior DLPFC using connectivity-based, image-guided aiming. Arm 3 delivers active irTMS to the left posterior DLPFC using connectivity-based, image-guided aiming. In all three arms, repetitive TMS (rTMS) is administered in an image-guided, robotic manner to ensure therapist blinding and equivalent subject experiences across arms. In all three arms, the following stimulation protocol will be used: 10 Hz irTMS delivered in 4 sec trains with 26 sec inter-train intervals, 37.5 minutes/session (i.e. 3,000 pulses/session), 5 sessions/week, for at least 4 weeks. Neuroimaging will be used both for treatment planning and to characterize any TMS-induced network plasticity using resting-state fMRIs (rs-fMRIs) at week 4 of each treatment arm. Clinical assessments will be administered weekly throughout the TMS Treatment Phase. rs-fMRIs will be used both for treatment planning (baseline imaging), which guides the individualized positioning of the TMS coil, and to characterize irTMS-induced network connectivity (week 4). Clinical assessments using relevant clinician rated and self-report scales will be done weekly at the subject's treatment clinic. Other psychological tests will be performed at baseline, and week 4 when participants go to the RII for neuroimaging. Also, 1 and 3-month post-treatment clinical follow-ups will be conducted either in-person or over the phone to evaluate maintenance of clinical outcomes. If a subject's third-party insurance provider approves TMS treatment for more than 4 weeks, clinical assessments should continue on a weekly schedule and the 1 and 3-month post-treatment clinical follow-ups will be conducted (at their respective intervals) following that subject's last TMS treatment session.<br><br>***Aim 1. In persons with drug-resistant MDD compare the treatment efficacy of connectivity-image-guided rTMS targeting anterior DLPFC (Arm 1), posterior (Arm 2) DLPFC and the FDA-approved SOC rTMS targeting protocol (Arm 3). In all 3 arms, at least 4 weeks (5 days/week) of the FDA-approved SOC stimulation protocol (10 Hz x 37.5 minutes) will be used.***<br>• ***Hypothesis 1a.*** *Connectivity-based irTMS to the anterior left DLPFC will be superior to connectivity-based rTMS to the posterior left DLPFC and standard of care irTMS to the left DLPFC in relieving MDD symptoms.*<br>• ***Hypothesis 1b.*** *Connectivity-based rTMS to the posterior left DLPFC will be superior to the standard of care irTMS to the left DLPFC in relieving MDD symptoms.*<br>***Aim 2. Test for rTMS-induced changes in network functionality (plasticity) using rs-fMRI.***<br>• ***Hypothesis 2a.*** *Intrinsic connectivity will be attenuated by active irTMS in networks connected to the respective treatment sites, as tested by correlation with the number of sessions received at the time of scanning and by pre-treatment-to-post-treatment contrast.*<br>• ***Hypothesis 2b.*** *Treatment-induced decreases in connectivity will correlate with symptom improvement within and across treatment arms.* |

| **Item 5**<br>Study Population(s) Being Recruited<br><br>In your recruitment plan, how many different populations of prospective patients do you plan to target? Provide number: 1<br><br>*e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc.*<br><br><u>List each different population</u> on a separate row and provide a short descriptive **label**:<br>*(e.g., normal-healthy, diabetics, parents, children, etc.)*<br><br>*To add rows use copy & paste* | Identify the criteria for **inclusion**: | Identify the criteria for **exclusion**: |
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| Individuals diagnosed with MDD. | **1)** Males or females 18-65 years of age;<br>**2)** Meeting clinical diagnostic criteria for MDD according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V);<br>**3)** Having depressive symptom scores > 14 on the Patient Health Questionnaire-9 (PHQ-9 > 14);<br>**4)** Having third-party insurance payers and meeting Insurer's criteria for payment of at least 20 sessions of TMS Depression treatments;<br>**5)** If patient is currently receiving other psychotropic medication treatment, having been stable on that treatment for at least 8 weeks;<br>**6)** Able to provide written informed consent and able to read English. | **1)** Patients with a diagnostic history of bipolar disorder, schizophrenia or schizoaffective disorder or currently exhibiting psychotic features;<br>**2)** Serious, active suicidal risk as assessed by evaluating psychiatrist. Serious active suicidal risk is reflected by patient having a plan and intent to end his or her life. History of suicidality in itself is not an exclusion;<br>**3)** Except for Mild or Moderate Alcohol Use Disorder according to DSM-V criteria, having any other substance use disorder during the 3 months prior to screening;<br>**4)** Any history or signs of serious medical or neurological illness including a) seizure disorders, b) structural brain damage due to a penetrating head injury, or c) structural and/or functional brain damage due to stroke. Except for seizures, patients with a clinical abnormality may be included only if the study clinician considers the illness will not introduce additional risk and will not interfere with the study procedures;<br>**5)** Females will be excluded if they are pregnant (i.e. positive pregnancy test identified after their intake at the treatment clinic);<br>**6)** Recent history (e.g. within the past two years) of traumatic brain injury (TBI) with loss of consciousness for 20 minutes or more;<br>7) Any history or signs of metal objects (e.g. surgical clips, cardiac pacemakers, metal implants, etc.) in the body at the time of screening. MRI can have risks |

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| | | for persons with foreign bodies implanted in their body. |

**Item 6**
**Research Plan / Description of the Research Methods** ***a.*** *Provide a* ***comprehensive narrative*** *describing the* ***research methods****.*
*Provide the* ***plan for data analysis*** *(include as applicable the* ***sample size calculation).***

Step-by-Step Methods: We propose to study 150 subjects (i.e. 50 per arm) who meet criteria for 1) MDD as determined by the MINI and 2) treatment resistance as determined by the MADRS) and the outlined study inclusion criteria. We anticipate recruiting and screening approximately 300 male and female subjects, in order to meet the target enrollment goals. To account for subject dropouts and retain a sample of 150 subjects completing the double-blind treatment phase (50 per treatment group), 198 eligible subjects (66 in each group) meeting MDD criteria, as determined by the MADRS, and the study inclusion criteria outlined above, will be randomized for the study. Subjects will be recruited at their treatment clinic from the institution's MDD out-patient program by the Site-Principal Investigator's team. Subjects will be screened for pregnancy and for metal objects in the body before enrolling in the study. The RII Principal Investigator's (PI) team will randomly assign subjects to one of the three treatment arms as part of the generation of neuroimaging-based treatment plans. In addition to rTMS treatments, all subjects will also complete treatment as usual at their treatment clinic, including regular medication management encounters with their attending psychiatrist and therapy sessions as part of their MDD treatment. An effort will made to limit the disruptions in subjects' treatment by working research assessments and rTMS around their expected programing. Once enrolled, all subjects (N=198, 66 per treatment arm, expecting to retain 50 completers) will be imaged at the RII using a research-dedicated 3T Siemens TIM/Trio MRI scanner (Siemens, Erlangen, Germany) with an eight-channel phased array coil. Structural imaging will be obtained only once, upon enrollment. Structural images will be used for rTMS treatment planning (described below) and for spatial normalization to a standard anatomical template. Functional images will be obtained two times (i.e. pre-treatment and post-treatment-week 4) across the course of the study and used to detect symptom-specific network abnormalities and treatment-induced plasticity. Each subject will wear foam earplugs during each image acquisition session and each rTMS treatment session to protect subjects from the high decibel level produced by the MRI gradient and rTMS coil. See also Table of Study Procedures below.

**Recruitment**
Subjects will be recruited at their treatment clinic from that institution's MDD out-patient program by the study staff supervised by the Site-Principal Investigator's team. Upon admission to their treatment clinic, subjects will be informed about this treatment trial by either their staff psychiatrist or a member of the treatment clinic's research team. Each subject will be given an information sheet describing the study. If interested in participating, each subject will be shown a video describing the treatment trial and each of the tools/treatments used throughout the study (i.e. MRI and TMS).

As part of the treatment clinic's standard of care assessments, potential subjects will be asked to complete the following assessment at the subject's treatment clinic:

> *Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001).* The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the DSM diagnostic criteria for Major Depressive Disorder (MDD). Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The PHQ-9 has high internal consistency (e.g., alpha ranging from .83 to .92; Cameron, Crawford, Lawton, & Reid, 2008), and correlates strongly with other measures of depression (Kroenke et al., 2001).

Results from this assessment may be used to assess each patient's inclusion/exclusion criteria and as the PHQ-9 baseline assessment for the patient.

**Pre-Screening at Treatment Clinic Intake**
Under an IRB approved HIPAA Waiver of Authorization, Waiver of Informed Consent, and Waiver of Documentation of Informed Consent, study personnel will conduct a brief pre-screening intake interview where the basic study inclusion and exclusion criteria will be reviewed to help the individual determine if he or she meets the study criteria or has obvious exclusions from the study protocol. This information will be maintained as a secure file with the following information: name, phone number, name of study, referral date, referral source, potential eligibility status, reason if not eligible, and verbal permission to contact the caller in the future for other studies. Patients who agree to study participation will be referred to the RII for consent and baseline assessments and a member of the research team will schedule an appointment to visit the RII—where they will sign a consent document before any further screening will take place. Any individually identifiable information and Protected Health Information (PHI) collected on individuals who do not consent to participation will not become part of the research data. If patients agree to participate in the research, the identifiable data collected will become part of their research records and will be stored according to the research confidentiality plan.

**Consent Process**
Once the subject has completed the psychological assessments required to determine inclusion/exclusion criteria at the subject's treatment clinic, eligible participants will then schedule an appointment at the RII to proceed with the study. An authorized and trained member of the research team will engage the potential participant in an interactive explanation of the study guided by the informed consent document (ICD). After the participant has read the ICD, he or she will be given the opportunity to consider participation and discuss the research with family and friends. Once the potential participant has reached a decision, the advising staff member will review the purpose of study, duration of study, study procedures, the experimental components of the study, the potential risks and discomforts, the potential benefits, any alternatives to participation, protection of participant's confidentiality, and the contact information for both the researchers and the regulatory bodies overseeing the conduct of the study with the participant to ensure the participant has an understanding of the study. If the individual is agreeable to participation the advising staff member will then have the individual sign the consent form in the presence of a witness. A copy of the signed ICD will be given to the participant for their reference. Over the course of the study, the Research Team will be available to answer any questions about the research. Following consent, the participant meets regularly with the research staff. Ongoing discussions occur to ensure the participant's questions and concerns are addressed during the course of the study. Potential participants will have the study explained to them in a safe and private location before any assessments are conducted.

**Phase I: Baseline Assessment at the RII.** When the participant arrives for their appointment at the RII and has signed the ICD, the participant will undergo a review of the metal screening history and will complete the PHQ-9 and the Montgomery and Asberg Depression Rating Scale (MADRS). The MADRS is a standardized clinical assessment instrument to ascertain depressed mood and neurovegetative signs and symptoms of depression. These assessments will be performed by a trained member of the RII's research team.

**Baseline MRI.** Immediately after their MADRS is evaluated, the participant will undergo an anatomical and functional magnetic resonance imaging (MRI) session. Earplugs will be provided at every MRI session. MRIs use strong magnets and radio waves to non-invasively acquire images of organs and tissues. Unlike X-rays, MRIs do not expose subjects to radiation, therefore it is considered safe to obtain many MRIs in a single scanning session or over multiple days; the initial MRI scans may take up to 1.25 hours. In the event that the participant cannot tolerate the MRI procedure, they will be withdrawn from the study. Participants will be imaged at the RII using a research-dedicated 3T Siemens TIM/Trio MRI scanner (Siemens, Erlangen, Germany) with an eight-channel phased array coil. Structural imaging will be obtained only once, upon enrollment. Structural images will be used for irTMS treatment planning (described below) and for spatial normalization to a standard anatomical template. MRI images will be obtained two times (i.e. pre-treatment and post-treatment) and used to detect symptom-specific network abnormalities and treatment-induced plasticity. We will also perform motor threshold assessments for each subject (at pre-treatment and post-treatment, immediately after each MRI) to determine the correct intensity and train durations needed to safely deliver irTMS in each subject's TMS Treatment Phase. The post-treatment motor threshold assessment are important to the future establishment of safety guidelines for irTMS treatment of MDD.

*Structural MRI.* T1- and T2-weighted structural MRIs will be used for treatment-plan computation (described below) and for spatial normalization of functional images. T1-weighted images are obtained in 3D modes (1.0 mm cubic voxels) with acquisition parameters of: repetition time (TR) = 1900 ms, echo time (TE) = 2.26 ms, tip

angle = 9˚, slice thickness = 1.0 mm, in-plane resolution = 1.0 x 1.0 $mm^2$ acquiring 256 volumes. T2-weighted images will be obtained with and without fat suppression (turbo spin echo, 34 axial slices, matrix size = 640 x 640, voxel size = 0.4 x 0.4 x 5.2 $mm^3$, flip angle = 120°, TR/TE = 14000/93 ms, turbo factor 18). Total structural MRI scan time is approximately 20 minutes. To ensure accurate irTMS treatment planning, we will also acquire diffusion tensor images (DTI). DTI will be obtained from the diffusion-weighted images using a single-shot echo-planar gradient-recalled echo, T2-weighted, sequence to acquire diffusion-weighted data with the spatial resolution of 2.0 x 2.0 x 2.0 mm and TE/TR = 85/9300. The diffusion-weighted scans will have 64 different non-collinear diffusion sensitization directions, consisting of diffusion-weighted images at b = 700 $mm^2/s$ and one non-diffusion weighted image at b = 0 $mm^2/s$. The total DTI sequence acquisition time will be 20 min.

*BOLD fMRI for motor threshold assessment.* Functional images will also be used to identify each subject's primary motor cortex for motor threshold assessment. BOLD fMRI will be acquired in a block design paradigm utilizing gradient echo planar images with the following parameters: TR = 2.5 s, TE = 30 ms, a flip angle of 90**º**, and slice thickness = 4.0 mm. Thirty-six continuous slices will be acquired, with an in-plane spatial resolution of 1.7 x 1.7 $mm^2$. During the BOLD fMRI scan, participants will perform abduction and adduction of the right index finger (in a block design); this has been shown to maximally activate the first dorsal interosseous muscle area of the hand's motor cortex. The task and rest periods are 50 seconds long and are interleaved during the 6 minutes of data acquisition. During the rest period, the participants will be instructed to remain motionless, to keep their eyes open, and to perform no behavioral task.

*Intrinsic Connectivity by Blood-Oxygen-Level-Dependent (BOLD) fMRI for computing treatment plans.* Intrinsic connectivity networks will be measured using blood oxygen dependent (BOLD) fMRI. BOLD fMRI is the most robust and widely used pulse sequence for intrinsic connectivity modeling. BOLD images will be used for computing treatment plans and for testing for intrinsic connectivity changes by symptom score and with treatment. BOLD data will be acquired as 360 whole-brain volumes acquired with a TR = 2500 ms, TE = 30 ms, tip angle = 90˚, 128 x 128 voxels, 1.7 mm x 1.7 mm, and 36 slices (4.0 mm thickness). This sequence requires ~ 15 minutes. Resting-state BOLD (15-min acquisition) will be used to map (per-subject) the voxel-wise intrinsic connectivity of DLPFC with the anterior cingulate cortex (ACC) and Precuneus; this will guide aiming parameters.

**Motor Threshold Assessment.** After the baseline MRI session, each subject will undergo a brief motor threshold assessment by single pulse TMS to their primary motor cortex hand region which elicits a contraction of the targeted hand muscle. The motor threshold assessment begins by locating the hand region and applying single pulses of TMS—with at least 5 seconds between successive pulses—at increasing levels of TMS intensity. We continue to ramp up the TMS intensity with each TMS pulse until we observe a contraction of the targeted hand muscle in 5 out of 10 pulses at a given TMS intensity. This TMS intensity will then be recorded as that subject's resting motor threshold.

**Random Assignment.** Prior to the TMS Treatment Phase, participants will be randomly assigned by a member of the RII's research team (using a statistically generated randomization program) to 1 of 3 active irTMS treatment arms. An irTMS treatment plan will be developed specifically for each participant, which will be securely-transmitted to the irTMS treatment team at the subject's treatment clinic. The master list of treatment arm enrollment will be securely-stored (i.e. password-encrypted) on UTHSCSA's XNAT server and will not be available to members of the research team until all of the participant's treatment sessions and symptom assessments have been completed. Therefore, all members of the subject's treatment clinic's irTMS treatment team will be blinded to which treatment arm each participant is assigned. irTMS treatment visits will take place at the subject's treatment clinic within two week's after the Baseline scan and development of the treatment plan. This ensures that the subject's scores on the PHQ-9 and the MADRS reflect their current state of depression.

**Phase II: TMS Treatment Phase.**
*irTMS Treatment Planning.* All irTMS treatments will be planned for robotic, image-guided irTMS delivery—which will be performed at their treatment clinic. The acquired MRI images will be used to compute a subject-specific, treatment plan, which will be stored and used during their respective irTMS session at their treatment clinic. Image guidance will be based on treatment plans developed from high-resolution structural MRI and resting-state BOLD fMRI acquired at the RII. From the T1-weighted MRI (described above), two surface models are computed: a model of the scalp surface, for use in registration of the subject to the treatment plan; and, a model of the cortical surface including cortical surface normals. Both models are created using a modification of the dividing cubes algorithm following automated tissue segmentation. The scalp surface

model is based on the air-scalp interface, which is readily obtained by simple thresholding. The cortical surface model is based on pre-classification of brain tissue into gray, white and CSF surfaces, using the FMRIB's Automated Segmentation Tool.

For each subject, one of three left DLPFC treatment target locations will be determined (according to their randomization group): 1) 5-cm (e.g. standard of care) aiming to the left DLPFC brain region with the coil oriented towards the subject's nose; 2) connectivity-based aiming to the left, anterior (nearer the front) DLPFC brain region with the coil's E-field aligned according to the cortical column cosine model at the target site; 3) connectivity-based aiming to the left, posterior (nearer the back) DLPFC brain region with the coil's E-field aligned according to the cortical column cosine model at the target site. Stimulation intensity will be delivered in the same fashion as other TMS treatment trials for MDD: 120% of the subject's resting motor threshold (which was obtained at the Baseline MRI visit).

*irTMS Position/Holding.* For each subject, the coil pose will be pre-computed from structural and functional MRI (above) and stored as an individualized treatment plan. Each subject's treatment plan will be registered to his/her head by creating a scalp model with a high-resolution digitizer, an integrated component of the irTMS system. In each arm, the TMS coil will be positioned and held by the robot (under the TMS treatment technician's supervision).

*irTMS Treatment Sessions*. All participants will continue with their TAU at the subject's treatment clinic including regular medication management, encounters with their attending psychiatrist, and therapy sessions. An effort will be made to limit the disruptions in subjects' TAU by working research assessments and irTMS treatment sessions around their expected TAU programming. irTMS treatment visits will take place at their treatment clinic starting as soon as possible after the treatment plan is completed, expected to be 1-10 working days following baseline scanning. At the respective TMS treatment target site, the treatment cliinic's team will deliver rTMS using the FDA-approved rTMS treatment protocol for MDD. This TMS protocol consists of 4 seconds of 10 Hz rTMS followed by a 26 second rest period; the treatment lasts for a total of 37.5 minutes (e.g. 3,000 rTMS pulses/session). Treatment is 5 days per week for at least 4 weeks in all arms. All treatments will delivered using a liquid cooled figure-8 MagPro coil (MagVenture, Denmark). If study participants decide that they cannot tolerate the prescribed dose of irTMS (e.g. 120% of resting motor threshold), they will be withdrawn from the study (see Discontinuation and Withdrawal of Patients Section below).

**Phase II: Post-Treatment Follow-Up**
*Post-treatment MRI.* Immediately following the last irTMS treatment at the end of the 4th week, a second functional MRI scan will be conducted to assess treatment effects. The post-MRI will occur any time after last treatment with up to a 3-day window for completion. After the post-treatment MRI session, each subject will also undergo another brief motor threshold assessment in order to document any changes—which may be used to report on the safety of this TMS treatment protocol. This second scanning visit should take approximately 1 hour.

*Participant Blind Form.* The Participant Blind Form measures the participant's best guess about the study treatment that they received, level of confidence in this guess, and how unblinding could potentially have occurred. This form will be used at treatment completion and follow-up for all of the RII's double-blind irTMS studies.

*Independent Evaluator Blind Form.* The Independent Evaluator Blind Form measures the independent evaluator's best guess about the study treatment that the subject received, level of confidence in this guess, and how unblinding could potentially have occurred.

**Phase III: 1 Month/3 Month Follow-Up**
One month and three months after the final irTMS treatment session, participants will be interviewed (either in-person or over the telephone) by a member of the research team. Results from these assessments will be stored on the RII's secure XNAT server..

**Table of Study Procedures:**

| Phase | Pre-Study | | | TMS Treatment Phase (at the clinic & the RII) | | | | Post-Treatment (at the RII) | 1 Month/ 3 Month Follow-Up (in-person or via telephone) |
|---|---|---|---|---|---|---|---|---|---|
| | Clinic Intake | Baseline | MRI Appt | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 5 | Wk 8/Wk16 |
| Review Medical History | X | | | | | | | | |
| Informed Consent | | X | | | | | | | |
| Metal Screening | | X | | | | | | | |
| Patient Health Questionnaire-9 (PHQ-9) | | X | | X | X | X | X | X | X |
| Montgomery-Ashberg Depression Rating Scale (MADRS) | | | X | | | | | X | X |
| Adverse Events Monitoring | | | X | X-X | X-X | X-X | X-X | X | X |
| Concomitant Medications/Treatment | | X | | X-X | X-X | X-X | X-X | X | X |
| Structural MRI | | | X | | | | | | |
| Intrinsic Connectivity by Blood-Oxygen-Level-Dependent Functional MRI | | | X | | | | | X | |
| Motor threshold assessment | | | X | | | | | X | |
| irTMS Treatment (at least 20 weekdays) | | | | X-X | X-X | X-X | X-X | | |
| Participant Blind Form | | | | | | | X | | |
| Independent Evaluator Blind Form | | | | | | | X | | |

Data Protection. Data will be coded using an assigned number. Data collected during treatment will be placed into locked cabinets at the subject's treatment clinic's offices. Every member of the research team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the research team strictly controls access to study data. No identified data (either copies or originals) will be maintained at the study site. The study site will maintain a list of assignment numbers for the purpose of linking subsequent research materials.

**Risk/Benefit Assessment.**

**Risks and Side Effects related to the irTMS applied to Dorsolateral Prefrontal Cortex Brain Region:**

- Likely, some may be serious. In 100 people, approximately 20-30 may have:
  - Mild headache
  - Scalp and/or Facial pain/discomfort
  - Scalp and/or Facial Muscle Twitching
  - Neck pain
- Less Likely, some may be serious. In 100 people, approximately 5-10 may have:
  - Dizziness
  - Sleepiness
- Rare and Serious. In 100 people, approximately 1-2 may have:
  - Seizures

**Risks and Side Effects related to the Robot placement of the irTMS include those which are:**

- Rare and Serious. In 100 people, approximately 0-1 may have:

- Physical injury from the robotic device.

**Risks and Side Effects related to the MRI include those which are:**

- Rare and Not Serious. In 100 people, approximately 1 may have:
  - Claustrophobia (fear of tight spaces). During the MRI scan, participants will be asked to remain perfectly still.
- Rare and Serious. In 100 people, approximately 1-2 may have:
  - Foreign bodies which may interact with the magnetic field of the MRI

**Risks related to the Psychological Assessments include those which are:**

- Less likely (less than 5-20 patients out of 100) and Not Serious:
  - Emotional distress including experiencing an initial increase of MDD symptoms due to the discussion of traumatic events.
- Rare (less than 5 patients out of 100) and Serious:
  - Breach of confidentiality.

**Risks of having a diagnosis of MDD regardless of participation in this research or not:** Individuals with MDD may have suicidal thoughts or attempt suicide. This is a risk to you whether you are being treated for MDD or not. Therefore, the risk of suicide is not any higher in the study than it would be if you were not in this study.

**Risk Minimization.**

- To physical injury by the robotic device. Robotic devices must be used with caution in the presence of persons. The robotic device used here (KUKA®) poses no significant risk. The KUKA® moves slowly, so that it can easily be stopped prior to any collision. Loss of electrical power renders the KUKA® robot immobile in its current position, (i.e., it does not return to a "parking" position or make any sudden motions). The KUKA® robot requires a key and a recessed button to actuate, being used only under direct supervision. Collectively, these features make the KUKA® robot safe for use by and with humans.
- To claustrophobia in the MRI.
- To injury during the MRI from foreign bodies interacting with the magnetic field. MRI can have risk for persons with foreign bodies implanted in their body. Cardiac pacemakers and cochlear implants may cease to function and can be permanently damaged by the MRI. Surgical clips on aneurysms and intestines may be moved by the magnetic field. Ferrous metal filings in the eye (e.g., in machinists) can be moved by the magnetic field. Foreign body risk is minimized by including only volunteers with no known foreign bodies and no exposure to circumstances, which might predispose to foreign bodies (e.g., metal machine workers). Before receiving an MRI, participants will be asked about any metal objects that may be in their body.
- To emotional distress during psychological assessments. All clinical staff associated with assessment have experience in psychiatric evaluation and will implement protocol procedures in a sensitive and supportive manner. Interviews will be stopped if subjects become distressed or object to answering questions. Measures implemented to minimize risks are: 1) Before participating, subjects undergo careful psychiatric and medical evaluation. 2) An experienced study clinicians are available at all times during the sessions to provide medical a psychiatric monitoring for subjects experiencing any difficulties during treatment. 3) All subjects will be seen weekly for ongoing assessment of behavioral symptoms. 4) If a subject's clinical condition significantly worsens, he or she will be withdrawn from the research protocol to continue TAU at their treatment clinic. Any indication that a participant's suicidality has worsened from baseline will be handled using processes at their treatment clinic.
- To breach of confidentiality. Study participants will be treated in individual offices located at their treatment clinic. Data a will be stored by an assigned participant code number so that data records and specimens can be viewed by password-authenticated, authorized investigators and Consortium personnel. Digital audio recordings of assessments will be labeled with the participant's study id number and saved on a secure password protected server. Those recordings to be reviewed for fidelity to ensure that the assessment is being delivered in accordance with Consortium standardized procedures. There is no option for the reviewers to download or otherwise save the recordings to their computers. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Only authorized study staff, and members of the Data Management and Biostatistics Core will have access to either the raw data or electronic study data.

**Potential Benefits.**

- The potential benefit to participants is the potential for MDD symptom relief.

**Adverse Events, Unanticipated Problems, and Deviations.**
Adverse Events will be assessed and monitored according to the established RII's SOPs and the IRB of record's policies and procedures. Reporting Adverse Events, Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), and Deviations to the Office of the IRB. All adverse events, unanticipated problems involving risk to subjects or others, and deviations will be reported to the Institutional Review Board (IRB) in accordance with current IRB policy. UPIRSOs and recurrent non-compliance with study procedures will be reported promptly to the IRB. All adverse events that do not meet the UPIRSO criteria and deviations that are not non-compliance will be summarized at Continuing Review per the IRB of record's policy.

**Research Monitor.**
The study Research Monitor, Karen Nijland, BPharm, will oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The IRB assigned Research Monitor's duties include: Act as an advocate regarding complaints or concerns from subjects; verify the IRB approved safety monitoring plan is being followed; verify that UPIRSO determinations are made in a timely fashion; and concurrently review UPIRSO reports submitted by PI to the IRB. In addition, the Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators, interview subjects, and consult with others outside of the study about the research; shall have authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

**Data Analysis**
Neuroimaging Data Analysis Plan: *Structural MRI: The* T1- and T2-weighted images will be pre-processed using FSL's Brain Extraction Tool (Smith, 2002), then segmented into three tissue classes: gray, white and ventricular components, using the FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001). Acquisition of both the T1- and T2-weighted images allow more accurate tissue segmentation and TMS treatment planning; the gray-matter surface normal will be used for treatment planning. Images will be spatially normalized to Montreal Neurological Institute space for group-wise analyses. The DTI data will be pre-processed using FSL's diffusion toolbox.

*BOLD fMRI for motor threshold assessment.* Each subject's BOLD fMRI will be analyzed using FSL's FEAT program to determine his/her primary motor cortex targets for motor threshold assessment. This information will be used to determine the TMS intensity needed for each subject's irTMS treatment plan and it will also inform the train durations of each treatment session so that the intensity of these pulses falls within the published safety limits of TMS delivered at 10 Hz.

*Intrinsic Connectivity by BOLD fMRI.* Data will be analyzed using FSL's FEAT program. Head movements are corrected by affine registration using a 2-pass procedure. BOLD data will be normalized to MNI space single-subject template using the "unified segmentation" approach, followed by a 5-mm full width at half maximum Gaussian smoothing. Spurious correlations with nuisance variables are removed using a recently validated framework. Data are band-pass filtered preserving frequencies between 0.01 and 0.08 Hz. The time course of each seed region's BOLD signal will be extracted as the first eigenvariate of activity in all gray-matter voxels located within the respective cluster. To quantify resting-state functional connectivity linear (Pearson) correlation coefficients between the time series of the seeds (targeted DLPFC nodes of each subject's DLPFC-limbic and DLPFC-motor networks) and any other gray matter voxel will be computed. Voxel-wise correlation coefficients will be transformed into Fisher´s Z-scores (with non-sphericity correction). These images will be used for irTMS treatment planning. The resting-state fMRI scan will also be used to assess, network-specific functional connectivity differences between each subject's pre-treatment and post-treatment scans.

*Clinical Outcomes Data Analysis plan.* All pre-treatment and post-treatment MRIs will be acquired and analyzed at the RII, however, all of the statistical analysis of the symptom scores for this project will be done upon completion of recruitment and termination group blinding. The primary efficacy outcome measure will be the PHQ-9 for MDD symptoms assessed pre-treatment, weekly during treatment, post-treatment, and 1/3-months following the completion of treatment and the MADRS for the diagnosis of MDD assessed pre-treatment, post-treatment, and 1/3-months following the completion of treatment. The primary analysis will use

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| | mixed effects regression models. Secondary analysis will focus on changes in MDD symptoms clusters, effects of the intervention in mood symptoms, functioning and cognitive outcomes. Types and rates of adverse events will be summarized and compared across the study groups. The durability of benefit and the clinical significance of PHQ-9 changes will be explored. Non-compliance to protocol as defined as missing three consecutive irTMS sessions or receiving less than 10 irTMS sessions during treatment at their treatment clinicwill be assessed for and evaluated in data analysis.<br><br>**Discontinuation of Subjects.** Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are: 1) Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment; 2) Clinical deterioration: The following are objective criteria for clinical deterioration, a 25% increase in the PHQ-9 at any time during the study and/or the onset of active suicidality as assessed by the study clinicians requiring treatment outside of the study protocol; 3) Evidence of intolerable adverse reaction, or unable to tolerate irTMS or MRI; 4) Non-compliance to protocol by missing three consecutive irTMS sessions or as judged by the investigator; 5) Safety reasons as judged by the investigator. |

**Item 7 Risks Section:**

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

| **Research procedures** | **Risks** |
|---|---|
| *example:*<br>• History and physical<br>• Questionnaire<br>• Laboratory tests<br><br>*Add or delete rows as needed* | List the reasonably expected risks under the following categories as appropriate: |