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Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST – MST): Study Protocol for a Randomized Non-Inferiority Trial of Magnetic Seizure Therapy versus Electroconvulsive Therapy

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Abstract

Background: Electroconvulsive therapy (ECT) is well-established and effective for treatment resistant depression (TRD), but in Canada and the United States, less than 1% of patients with TRD receive ECT mainly due to its cognitive adverse effects (i.e., amnesia). Thus, new treatment alternatives for TRD are urgently needed. One such treatment is Magnetic Seizure Therapy (MST). ECT involves applying a train of high frequency electrical stimuli to induce a seizure, whereas MST involves applying a train of high frequency magnetic stimuli to induce a seizure.

Methods: In this manuscript, we introduce our international, two-site, double-blinded, randomized, non-inferiority clinical trial to develop MST as an effective and safe treatment for TRD. This trial will compare the efficacy of MST to right unilateral ultra-brief pulse width electroconvulsive therapy (RUL-UB-ECT) with a combined primary endpoint of remission of depression and superior cognitive adverse effects in 260 patients with TRD. Amelioration of suicidal ideation will be assessed as a secondary endpoint. Inpatients or outpatients, over 18 years of age with a MINI International Neuropsychiatric Interview (MINI) diagnosis of non-psychotic major depressive disorder (MDD) can be enrolled in the study provided that they meet illness severity and full eligibility criteria. Participants are randomized to receive MST or RUL-UB ECT, 2-3 days per week over seven weeks, or a maximum of 21 treatments. The study will involve before-, during-, and after-treatment assessments of depression severity, suicidal ideation, subjective side-effects, and cognitive performance consistent with an intent-to-treat study design approach.

Discussion: Positive results from this trial could have an immediate and tremendous impact for patients with TRD. If MST demonstrates comparable antidepressant treatment efficacy to ECT, but with greater cognitive safety, it could rapidly be adopted into clinical practice. Indeed, given that the administration of MST is nearly identical to ECT, the majority of ECT facilities in North

America could readily adopt MST. Furthermore, the potential for cognitive safety could lead to improved treatment acceptability. Healthcare providers, patients and care partners, and policymakers would therefore demand this form of convulsive therapy.

Trial Registration: Clinical Trials Gov NCT03191058

Keywords: Depression: Major Depressive Disorder; Treatment Resistant Depression; Magnetic Seizure Therapy; Electroconvulsive Therapy; Brain Stimulation

BACKGROUND

In this National Institute of Mental Health (NIMH) funded study, we aim to assess the efficacy and tolerability of Magnetic Seizure Therapy (MST) as an alternative to Electroconvulsive Therapy (ECT) for major depressive disorder (MDD). Even with multiple antidepressant medication trials, 30 - 40% of patients will experience a pharmacologically resistant form of MDD (i.e., treatment-resistant depression (TRD))[1]. In the United States (U.S.), the total economic burden of MDD as of 2010 was estimated to be $210.5 billion per year, representing a 21.5% increase from $173.2 billion per year in 2005[2]. The ineffectiveness of current antidepressant treatments coupled with the economic burden associated with depression provides a strong rationale for the development of new and safe antidepressant therapeutic interventions that can provide greater response and remission rates.

While ECT is a well-established and highly effective treatment for depression with remission rates ranging from 60% to 80%[3], less than 1% of patients with TRD receive ECT in Canada and the U.S. [4, 5]. One of the major reasons that providers, patients, and their families refuse to consider ECT, even when confronted with disabling and life-threatening depression, is concern about the ECT-induced cognitive side effects (e.g., amnesia). Regardless of treatment

delivery, ECT results in significant cognitive impairment including post-ictal disorientation, anterograde and retrograde amnesia, and executive dysfunction[6]. Disorientation immediately after ECT can last up to 60 minutes, regardless of electrode placement[7], which lengthens and can complicate recovery time after the procedure and causes patient distress and burden[8]. Anterograde amnesia, the inability to learn and retain new information, can appear at the first ECT treatment [9, 10] and persist for up to several months[11-14]. Retrograde amnesia, the inability to recall past personal and impersonal memories, remains one of the most distressing ECT cognitive adverse effects[15]. Retrograde amnesia has been found to be more severe with bitemporal than right unilateral (RUL) ECT, with high compared to low dosages, and with sine wave and brief pulse width relative to ultrabrief pulse width[6]. As recently highlighted by the U.S. Food and Drug Administration (FDA), the extent of anterograde and retrograde amnesia, and the degree to which memory remains impaired post-ECT is a significant problem for patients and their families[16]. Indeed, numerous patients and their families refuse ECT because of these adverse cognitive effects.

Several theories have been proposed to account for the ECT-induced adverse effects on memory. The most supported theory is that when an electrical seizure is initiated, the skull shunts the electrical current away from the stimulation site. This electrical current is propagated throughout the brain by the corticospinal fluid and ensures the electrical stimulus is non-focal[17, 18]. This diffuse electrical discharge spreads to deep brain regions, including medial temporal lobe structures (e.g., hippocampus), causing disruption of synaptic plasticity and long-term potentiation[19], which are neural substrates of learning and memory formation[20-23]. The development of a new treatment approach that can mitigate these adverse cognitive effects, while maintaining the robust efficacy of ECT, is significantly needed. MST offers a viable, and arguably

favourable, alternative to ECT with comparable antidepressant response/remission rates and a more favourable cognitive safety profile[24-26].

MST is an alternative form of convulsive therapy, that like ECT, involves the induction of a seizure to achieve a therapeutic effect[18]. However, the induction of a seizure occurs through high frequency, repetitive transcranial magnetic stimulation (rTMS) rather than high frequency, repetitive transcranial electrical stimulation. With magnetic stimulation, a rapid, high intensity, time-varying magnetic field is able to pass into the brain without resistance thereby limiting seizure spread. The induced magnetic field can be focally targeted to stimulate specific neurons based on geometry of the stimulating magnetic coil[27, 28]. Additionally, the magnetic field is not impeded nor shunted by non-conducting material (i.e., skull) and, therefore, results in focal brain activation[29, 30]. Specifically, compared to RUL-UB ECT, the electric field induced by MST is 5–10 times more focal[30, 31].

In an early study, White et al. compared 20 patients with severe depression openly allocated to receive ECT or MST. In the MST relative to the ECT group, time to orientation, a measure of post-ictal disorientation, was significantly shorter (4 vs. 18 minutes, $p<0.01$). The Hamilton Rating Scale for Depression-24 item (HRSD-24) total score improved from 32 to 14 in the MST group, while in the ECT group, the total score improved from 30 to 6 [32]. In another study, 20 patients with TRD were allocated to receive either RUL-ECT or MST. Comparable antidepressant response and no cognitive side effects were observed in the two groups [26]. Of note in that latter study, RUL-ECT was administered at 3 times the seizure threshold, which reduced the cognitive side effects and could have minimized the ECT-induced antidepressant benefits. A subsequent MST study conducted by the same group collated the data from the former study with 16 additional adults who received MST. Remission was achieved by 46% of the patients and no cognitive side

effects were observed. Fluorodeoxyglucose positron emission tomography (FDG-PET) scans (N=12) showed increased bilateral metabolic activity in the frontal cortex and decreased activity in the left striatum[33]. Based on theoretical calculations, Lee et al. found the electrical field to be 3-11 times stronger and the stimulated brain volume much larger (47-100% vs 21%) with ECT compared to MST. The improved focality and lower intensity of MST were suggested as a possible explanation for its favorable cognitive safety profile[31]. In a within-subject, non-human primate study, McClintock et al. compared the effects of electroconvulsive seizure (ECS), magnetic seizure (MS), and anesthesia alone on a measure of spatial working memory. ECS resulted in lower correlation between predicted and actual response patterns in 2 of 3 subjects, which suggested impaired planning ability. In all 3 subjects, reaction time was significantly longer in ECS relative to MS and sham[34]. Relative to ECS, this preclinical study substantiated the cognitive safety and superiority of MST.

In a recent published study from our group, we found support for favourable antidepressant effects of MST with a larger sample size in an open-label study design[35]. We evaluated the antidepressant and neurocognitive effects of MST applied over the prefrontal cortex at low (25Hz), medium (50 or 60Hz), and high (100Hz) frequencies. The primary analysis examined 86 adult patients with MDD who completed an adequate treatment course (i.e., 8 MST treatments or more) and 47 patients who completed the study per protocol either having achieved remission (i.e., HRSD-24 total score ≤ 10 and a comparative reduction of $> 60\%$ on two consecutive assessments) or received a maximum of 24 treatment sessions[35]. This study employed before-, during-, and after-treatment clinical and cognitive monitoring assessments. Response (i.e., 50% reduction on the HRSD-24) and remission were assessed weekly throughout the trial. High (100Hz) frequency MST produced the largest response and remission rates for both adequate trial completers (41.7%

and 33.3%, respectively) and protocol completers (60% and 53.3%, respectively). Furthermore, we found that MST has negligible effects on neurocognitive function. Overall, our findings suggest that the implementation of frontal stimulation at high frequency produces effective depression response and remission rates that may be comparable to ECT, but with greater cognitive safety.

In this manuscript, we present our international, NIMH-funded, double-blinded, randomized, non-inferiority study protocol that evaluates the efficacy, tolerability, and cognitive adverse effects of MST compared to RUL-UB ECT (research protocol version 12.0; 21-Oct-2020). Several important areas of innovation are included in this study. First, is the use of a relatively new non-invasive neuromodulation therapy, MST. Second, is the non-inferiority clinical trial design to compare the efficacy of MST with ECT in adult patients with TRD. Finally, suicidal ideation – a symptom domain in TRD that has tremendous public health impact - is evaluated as a secondary outcome variable of interest. Other innovations include state-of-the-art combined TMS with electroencephalography (EEG) and analytic methods used to identify a neurophysiological GABAergic signal, and use of quantitative EEG to probe mechanisms of ECT-induced cognitive impairment. In the current manuscript, we outline the protocol for the clinical and cognitive outcomes of the trial. An accompanying second manuscript details the neurophysiology protocol[36].

METHODS

Study design and setting

The study involves a double-blinded, randomized, non-inferiority clinical trial with two treatment arms (see Figure 1: Study Design) conducted at two leading academic institutions in North America: the Temerty Centre for Therapeutic Brain Intervention at the Centre for Addiction and

Mental Health (CAMH) in Toronto, Ontario, Canada and University of Texas Southwestern (UT Southwestern) Medical Center in Dallas, Texas, United States of America. A total of 260 adult patients with MDD will be randomized to receive MST or RUL-UB-ECT.

Treatment is administered two to three days per week. Depression symptoms and severity are assessed with the HRSD-24[37] and suicidality is assessed with the Beck Scale for Suicidal Ideation (SSI)[38]. Remission is defined as HRSD-24 total score ≤ 10 and a $\geq 60\%$ decrease in total score from baseline on two consecutive ratings. Remission of suicidal ideation is defined as a score of 0 on the SSI. Therefore, there is no specific minimum number of treatments that patients must receive to be classified as remitters. However, patients who do not meet remission criteria after 21 treatment sessions are considered non-remitters and cease treatment sessions. This maximum treatment number was chosen to allow for the possibility that MST may require more treatment sessions to achieve remission, similar to RUL-UB ECT[39-41]. The study blind will not be broken to participants except in the case of physician safety concerns.

The clinical trial study was approved by the research ethics boards of CAMH (Reference Number 033-2017) and UT Southwestern (Reference Number STU 032017-022). The trial was issued an Investigational Device Exemption (IDE; Reference Number G170127) by the U.S. FDA and an Investigational Testing Authorization (ITA; Reference Number 270547) by Health Canada to assess the safety and efficacy of the MST MagPro XP with Cool Twin Coil device (MagVenture A/S, Farum, Denmark) within this clinical trial. The study is registered with ClinicalTrials.gov under the identifier NCT03191058 and results will be reported in a manner consistent with the international Consolidated Standards of Reporting Trials (CONSORT) guidelines. The research ethics boards of both study site institutions involved in the study are notified if any changes are made to the study protocol. The trial registration is also updated as appropriate. This protocol is in

accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[42] guidelines (see Additional file 1).

Recruitment and retention

To ensure we meet our recruitment goals, both sites have implemented new innovations including treatment care pathways that ensure many patients with TRD are offered brain stimulation treatments should they be unresponsive to initial pharmacological approaches. Brain stimulation psychiatrists are informed about clinical research and trained to screen all new referrals for potential recruitment. The CREST-MST study has recruitment milestones for overall recruitment as well as racial and ethnic minority recruitment to ensure a representative sample is obtained. Retention strategies have been implement to mitigate patient discontinuation throughout the study including constant communication between study staff and patient, weekly check-ins with the study psychiatrist, and an intent to treat (ITT) approach whereby patients continue to be followed and offered alternative treatment even if discontinued from the trial.

Eligibility criteria

Patients are included in the study if they: (1) are inpatients or outpatients; (2) are voluntary and competent to consent to treatment and research procedures according to an ECT/MST attending psychiatrist; (3) have a MINI International Neuropsychiatric Interview diagnosis of non-psychotic MDD; (4) are 18 years of age or older; (5) have a baseline HRSD-24 score ≥ 21; (6) are considered to be appropriate to receive convulsive therapy; (7) are agreeable to keeping their current antidepressant treatment constant during the intervention; (8) are likely able to adhere to the intervention schedule; (9) meet the MST safety criteria[43]; (10) if a woman of child-bearing

potential: is willing to provide a negative pregnancy test and agrees not to become pregnant during trial participation. Patients are excluded from the study if they: (1) have a history of a MINI diagnosis of substance dependence or abuse within the past three months; (2) have a concomitant major unstable medical illness; (3) are pregnant or intend to get pregnant during the study; (4) have a MINI diagnosis of any primary psychotic disorder; (5) have a MINI diagnosis of obsessive compulsive disorder, or post-traumatic stress disorder deemed to be primary and causing more functional impairment than the depressive disorder; (6) have probable dementia; (7) have any significant neurological disorder or condition likely to be associated with increased intracranial pressure or a space occupying brain lesion; (8) present with a medical condition, a medication, or a laboratory abnormality that could cause a major depressive episode or significant cognitive impairment in the opinion of the investigator; (9) have an intracranial implant or any other metal object within or near the head, excluding the mouth, that cannot be safely removed; (10) require a benzodiazepine with a dose > lorazepam 2 mg/day or equivalent or any anticonvulsant; (11) are unable to communicate in English fluently enough to complete the neuropsychological tests; (12) have a non-correctable clinically significant sensory impairment. These eligibility criteria are congruent with the criteria that have been used in the major ECT trials conducted during the past decade[6, 44, 45].

Informed consent procedures

At both study sites, general physicians or psychiatrists refer patients for an initial consultation with a brain stimulation psychiatrist to assess suitability for convulsive therapy and are then referred to qualified research personnel. The qualified research personnel will then explain the trial in terms suited to the patient's comprehension of the purposes, procedures, and potential

risks of the study, and of their rights as research participants. If participants would like to proceed an eligibility screening assessment is scheduled. Patients are provided with a consent form (Additional file 2) describing in detail the study intervention, study procedures, and risks, and all questions are answered. Written documentation of informed consent is required prior to initiating the screening visit to assess for eligibility. The consent form includes an additional signature line for the collection of neurophysiological biomarkers discussed in detail in an accompanying manuscript [36]. Once consent is obtained according to Institutional Review Board and Good Clinical Practice (GCP)/Tri-Council guidelines, the research personnel confirm inclusion/exclusion criteria is met with the site Principal Investigator (PI) before proceeding with baseline testing. Patients are informed that they can withdraw participation at any point during the study. Further, patients are informed of any approved protocol changes at their next study visit and re-consented if applicable. The rights and welfare of the participants are protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Randomization and blinding

Upon the completion of informed consent and the collection of baseline data, consenting and eligible participants are randomized to receive either MST or RUL-UB ECT using a permuted block method with a random number generator using blocks of varying sizes. Study personnel are blinded to the randomization block sizes. The Applied Health Research Centre (AHRC) at St. Michael's Hospital (SMH) centrally manages the randomization of participants. The random permuted blocks and central randomization ensure allocation concealment. Although the treatment team administering MST or ECT cannot be blind, all patients remain blind to their treatment

assignment during the course of the entire study. Similarly, the independent raters administering the efficacy and tolerability outcome assessments, as well as the neuropsychological raters, remain blind to treatment assignment during the entire study. Breaking the blind for a single patient will only be considered when knowledge of the treatment assignment is deemed essential by the physician for patient care. To assess the integrity of blinding procedures, participants and raters are asked to complete a conventional guess form asking them whether they believe participants received MST or RUL-UB ECT after the participant has received their first treatment.

Interventions

A total of up to 21 treatments are administered to participants, two to three times a week. At all sites, treatment with either MST or RUL-UB ECT is provided by trained study psychiatrists and follows standard protocols. Anesthesiologists experienced in convulsive therapy administer general anesthesia using methohexital or etomidate, muscle relaxation using succinylcholine, and mask ventilation with 100% oxygen. Following a standard established protocol[46], a study psychiatrist will determine the seizure threshold during the first treatment. MST treatments are administered using the MagPro XP MST device with a Cool Twin Coil (see Figure 2: MagPro XP). Stimulation is delivered over the frontal cortex at the midline position. By delivering convulsive stimuli to frontal brain regions, relative to other MST studies [35, 47-49], this study has an advanced MST treatment paradigm. The MST determination of seizure threshold is done using 100% machine output applied at 100 Hz at progressively escalating train durations, commencing at 2 seconds and increasing by 2 seconds with each subsequent stimulation until an adequate seizure is produced. During subsequent MST sessions, a single stimulation is delivered using a train duration that is 4 seconds longer than the train duration at threshold (up to a maximum

train duration of 10 seconds). ECT treatments are administered using the MECTA spECTrum 5000Q (MECTA Corporation, Tualatin, Oregon, USA). The ECT determination of seizure threshold and the adjustment of energy at subsequent ECT sessions is based on a standard published protocol [10]. Participants will receive RUL-UB ECT at six times the seizure threshold. This approach follows the treatment paradigms of prior ECT trials[44, 45].

During all sessions, the seizure quality will be monitored using fronto-mastoid EEG. Congruent with published criteria, seizures will be considered adequate if they result in generalized tonic-clonic activity > 15 seconds of motor tonic-clonic activity[45, 50, 51], including the duration of the stimulus[52]. The anaesthetic dosing and MST or ECT parameters will be reviewed and optimized in the event of inadequate seizures. If the seizure produced is inadequate, a second stimulation is administered during the same session at stimulus intensity 25% above the level that resulted in the inadequate seizure, up to a maximum output of 568.3 mC for ECT or using a train duration that is 1 second longer to a maximum of 10 seconds for MST. If seizure duration still remains below the motor duration cut-off, then the seizure is accepted for that particular treatment.

Medications that may be used to treat MST or ECT related side effects include, but are not limited to: granisetron, ondansetron, or dymenhydrinate for nausea; ketorolac, or acetaminophen, ibuprofen for headaches or muscle pain; and esmolol or labetolol for treatment related hypertension. Prolonged seizures (i.e., seizures longer in duration than two minutes as recorded either through EEG (spike-wave complexes) or through prolonged tonic-clonic muscular activity) will be treated with either repeat administration of the anesthetic (i.e., methohexital) or midazolam. Midazolam will be used as judiciously as possible owing to its potential to prolong reorientation times after treatment. Medications are used at doses within labeling.

If the patient fails to achieve an equal or greater than 25% decrease on the HRSD-24 total score from baseline following treatment six, the charge is increased by approximately 50% for ECT or increased by 200 pulses for MST. This process is repeated based on the HRSD-24 total scores from both treatments 9 and 12, and parameters are adjusted accordingly. If at any point the patient is already at maximum stimulation (568.3 mC or 1000 pulses) the treatment continues with the parameters unchanged.

Participants are discontinued from the treatment if they cannot safely continue the study based on any of the following criteria: (1) experience worsening in depression severity, defined as an increase in the HRSD-24 total score from baseline of more than 30% on two consecutive assessments; (2) experience clinically significant increase in suicidal ideation with imminent intent (based on the SSI) or attempt suicide; (3) develop clinically significant hypomanic or manic symptoms; (4) emergence of catatonia; (5) withdraw consent; (6) the PI believes that for safety reasons it is in the best interest of the participant to stop participation; (7) participant engages in a serious attempt to harm others; (8) missed seizures (i.e. no induced seizure) on 2 consecutive treatment sessions despite parameter and anaesthesia optimization; (9) non-compliant with treatment schedule. Consistent with an ITT approach, willing participants who are discontinued from treatment will not be removed from the trial entirely. They will continue to be followed and will complete post-treatment assessments to the extent possible, contingent upon patient agreement. The study PI reserves the right to fully discontinue participants from the trial if they believe it is in the best interests of the participant or study staff.

Study schedule

The study schedule of events is described in Table 1: Study Measures. Prior to screening, capacity to consent to treatment and research procedures will be assessed and documented as previously described. Prior to the acute treatment phase, baseline data is collected using clinical and cognitive outcome measures. Data is collected by trained and certified clinical and cognitive raters directly into the electronic data capture system, Medidata Rave (RAVE), or onto paper source documents where necessary. Rater administered clinical assessments are captured in RAVE while self-report questionnaires and cognitive assessments are completed on paper and transcribed into the RAVE database. Hard copy completed data collection forms are stored at each site. Clinical outcome measures are completed at baseline, after every three or four treatments immediately prior to the next treatment session, within four days of the last treatment session, and then six months post-treatment. This latter time point is part of an exploratory analysis to study the long-term clinical and cognitive outcomes post- ECT or post-MST treatment. The cognitive battery was designed to comprehensively examine cognitive dimensions that are affected by seizure therapies while minimizing assessment burden on participants[19]. Assessments included in the cognitive battery measure performance validity, global cognitive function, estimated pre-morbid intellectual ability, attention, processing speed, verbal fluency, verbal and visual learning and memory, autobiographical memory, working memory, and executive functions (e.g., complex planning, inhibition, cognitive flexibility). Neurocognitive assessments are completed at baseline, upon participant termination of treatment, and six months post-treatment. Raters inquire about adverse events (AE) at every treatment and study visit; any event endorsed by a patient is recorded in the RAVE database. In addition to the clinical and neurocognitive measurements, neurophysiological measures for biomarkers are completed both at baseline and upon participant termination of treatment[36].

Outcomes

The primary objective for this trial is to assess the efficacy and cognitive adverse effects of MST compared to RUL-UB ECT in patients with MDD. The primary hypotheses include: (1) MST will result in remission rates that is non-inferior to that of RUL-UB ECT; and (2) MST will have a superior cognitive adverse effect and tolerability profile compared to RUL-UB ECT. Primary clinical outcome measures are assessed using the HRSD-24 and primary cognitive outcome measures are assessed using the Autobiographical Memory Test (AMT). The secondary objective is to evaluate the efficacy of MST compared to RUL-UB ECT in ameliorating suicidal ideation in patients with MDD. The secondary hypothesis is that MST will have a non-inferior remission rate on the SSI compared to RUL-UB-ECT in patients with depression. Secondary clinical outcome measures include the SSI. Time to Reorientation, measuring patients' reorientation time after treatment, will be completed after the first three treatments. For a detailed overview of all study assessments and information about the schedule of measures in relation to the study timeline see Table 1. In addition, a tertiary objective for this trial involves the development of candidate neurophysiological biomarkers, which may predict response to treatment[36].

Statistical methods

We are using a combined primary effectiveness endpoint where: (1) MST will result in remission rates on the HRSD-24 that is non-inferior to that of RUL-UB ECT; AND (2) MST will have a superior cognitive adverse effect and tolerability profile compared to RUL-UB ECT assessed with the AMT.

In the primary outcome analysis, baseline variables will be summarized for each group by descriptive statistics. As per Senn et al. and Pocock et. al. [53, 54] significance tests between groups on baseline characteristics in a randomized trial are ill-advised and will not be done.

The primary efficacy analysis will be carried out in two stages. The first stage will test for non-inferiority of MST compared to ECT on remission. The second stage is a superiority comparison on cognitive function. If non-inferiority is established, then the second stage analysis will be carried out. This closed testing procedure ensures that the Type I error will not exceed the nominal alpha of 0.05.

The Stage 1 analysis hypothesis to be tested is $H_0: \pi_{ECT}-\pi_{MST} \geq 0.15$ versus $H_1: \pi_{ECT}-\pi_{MST}<0.15$ where π_{ECT} and π_{MST} are the probabilities of remission in the ECT and MST groups respectively. The primary comparison will be a one-sided Z-test in difference of proportions, compared against the non-inferiority margin of 15%. The 15% non-inferiority margin was chosen as a remission rate of 35% remains clinically meaningful in this difficult to treat sample and still higher than more conventional, less invasive treatments for treatment resistant depression (e.g., rTMS at about 20% remission[55] and 14% with antidepressants[56]). The absolute risk difference will be calculated along with 90% and 95% confidence intervals, using standard normal approximations. Since ITT analysis introduces a conservatism that is undesirable for non-inferiority trials, both ITT (i.e., all randomized participants) and completer analyses (i.e., 8 treatments or met remission criteria) will be performed. The primary analysis for Stage 1 will be a completer analysis and a sensitivity ITT analysis will be done secondarily. We plan to collect the primary outcome data from all patients regardless of treatment compliance to minimize missing data in the outcomes. If outcomes are missing in more than 5% of the patients in the ITT analysis, inverse probability weighting will be employed to assess and mitigate the effect of missing data.

It is only necessary for non-inferiority to be established in this analysis in order to proceed to the stage 2 analysis although additional secondary analyses of this outcome will be performed.

An adjusted analysis will be performed using generalized linear models for binary data. Clinical variables known to be associated with remission will be included (see again Senn et al., [53] and Pocock et. al., [54]). The following variables will be included in the analysis, which have been shown to be related to response/remission in this population: number of failed antidepressant trials, duration of most recent major depressive episode, number of major depressive episodes, and benzodiazepine use. The purpose of the adjusted analysis is to ensure the robustness of the non-inferiority findings when accounting for the variance in our model attributable to predictors of outcome. This will be examined in two ways. First, the unadjusted odds ratio and 95% confidence interval will be compared with the adjusted for consistency. Second, the fitted logistic regression model will be used to estimate the probability of response for each subject. An adjusted difference in proportions will be estimated by averaging the predicted probabilities within group and taking the difference. A bootstrap will then be used to generate a distribution of this measurement from which the bias corrected percentiles can be obtained to compare with the 15% non-inferiority margin.

Upon the determination of non-inferiority, we will move to Stage 2 of the analysis which will examine cognitive superiority using the AMT. The binary outcome is defined as a worsening of > 25% on the AMT total score. The hypothesis to be tested is $H_0: \pi_{ECT}-\pi_{MST}=0$ versus $H_1: \pi_{ECT}-\pi_{MST}\neq 0$ where π_{ECT} and π_{MST} are the probabilities of deterioration in the ECT and MST groups respectively. This primary analysis will be ITT. The hypothesis will be tested with a chi-square test. The absolute risk difference and 95% confidence interval will be computed using standard methods.

Our secondary effectiveness endpoint outlines that MST will have a non-inferior remission rate on the SSI compared to RUL-UB-ECT in patients with depression. This will be determined using similar methods to those described above.

Sample size

Our sample size calculations are based on non-inferiority trial calculations that are sufficiently large enough to minimize Type II error [54]and are consistent with previous large, multi-centre ECT trials[44]. RUL-UB ECT and MST have been found to achieve remission in approximately 60% of patients with TRD[57, 58]. Non-inferiority trials, such as this study, specify a tolerance threshold, with a tolerance of 15% denoting equivalence between the two treatments when the effectiveness of MST can be concluded to be not less than 35%. The total sample size is derived as a function of tolerance and power with a significance level of 0.05. Using these methods, a total sample size of 260 participants (130 per group) yields 80% power to confirm a non-inferior difference in HRSD-24 remission rates of 15% between the two study groups. This sample size also provides >95% power to detect a minimally important difference > 25% (absolute risk difference) change on the AMT total score. The primary analysis will proceed once a minimum of 260 participants achieve an adequate trial of treatment. The overall rate of dropout in a similar past trial at CAMH was less than 3%.

Adverse Event Analysis

The analysis of all AEs will include incidence tables by severity, relationship to treatment and baseline parameters. AE rates will be compared between the study groups. We anticipate that

there will be no significant differences in side effects between these two treatments and will conduct comparisons of safety endpoints at trial conclusion.

Data Management

Study staff are trained to collect complete and accurate source data and document all participant information in study specific case report forms. Data is stored in an electronic data capture system, Medidata Rave (RAVE), designed specifically for the needs of our study. The study data manager and AHRC at the Li Ka Shing Knowledge Institute of SMH in Toronto, Canada will manage the trial database. The electronic data capture system was designed to automatically complete range checks for all values and flag any deviant entries. The study data manager will conduct routine monitoring of study data including adherence to the protocol, data completion, and AE. All database activity is tracked through the electronic audit trail maintained by the database. Data quality checks of paper source documentation are conducted by verifying that the transcription into the eCRF database has been properly complete for two participatns selected at random out of every 10 participants.

Confidentiality

Participants are given a unique study ID upon entry and no identifying information is stored on study documents or within the RAVE database. Any personal identifying information is stored in a locked file on secure servers, at each respective site. Personal information is not shared between sites.

Safety monitoring

Proactive site monitoring is overseen by the Office of Clinical Research (OCR) through the NIMH prior, during, and after the study to ensure that GCP is followed and maintained throughout the duration of the study. The OCR regularly visits both sites for trial oversight and is responsible for the creation and maintenance of a data safety monitoring board (DSMB). The DSMB is comprised of an independent group of researchers and experts based out of the NIMH. Its role is to monitor patient safety and treatment efficacy data during the conduct of this trial. Members of the group meet regularly, approximately every four months in order to review participant safety, study conduct, and study progress.

Throughout the study, notification of any Serious Adverse Events (SAEs) as well as any proposed investigator-initiated changes in the protocol are submitted to the NIMH DSMB, the U.S. FDA and Health Canada. The NIMH DSMB may at any time request additional information from the PI. All SAEs and AEs will be tabulated and submitted to the NIMH DSMB, and central and local research ethics boards in the triannual DSMB data reports or at the time of study continued review. Based on review of safety data, the NIMH DSMB can issue directives concerning the conduct of the study.

Convulsive therapy is an involved treatment and there are potential side effects that are anticipated over the course of the trial. Safety and AEs are queried and documented at each study visit. The following AEs are anticipated in a sub-sample of the participant population: reversible cardiac ectopy, transient hypertension, uncomplicated asystole, fatigue, headache, aching/stiffness in muscles, nausea and vomiting, acute post-treatment delirium, post-ictal agitation, disorientation, neurocognitive impairment (e.g., anterograde and retrograde amnesia), prolonged seizures, treatment emergent mania, treatment emergent anxiety and fear, laryngospasm, peripheral nerve palsies, and aspiration, wakening paralysis, intravenous (IV) infiltration, other complications due

to anesthesia (e.g., sore throat, headache, shivering), dental injury, lip lacerations and falls. All AEs are recorded and reported to the site PI for consideration of further action. Participants receive care as appropriate for any harm that arises as a result of study participation.

Dissemination plan

This study is conducted in accordance with the publication and data sharing policies and regulations of the National Institute of Health (NIH) Public Access Policy. This policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will also comply with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information and U.S. FDA Clinical Trials Registration and Results Information Submission rule. As such, this trial is registered at ClinicalTrials.gov.

Data from this study is submitted to the NIMH Data Archive (NDA) approximately every 6 months. The NDA is a data repository operated by the NIMH that allows researchers studying mental illness to collect and share deidentified information with each other. During and after the study, the researchers will send deidentified information collected from participants to NDA.

A further goal of this research is to inform and educate the wider community, both professional and public, about the potential of MST in the treatment of MDD/TRD. To this end, the study team will present the findings of this research at both national and international conferences and submit results for peer-reviewed publication to affirm the significance of potential findings. In addition, the study team will foster awareness in the community through the dissemination of any results in an accessible manner to help educate and promote understanding of convulsive therapy in general and MST in particular.

DISCUSSION

Patients with TRD in the U.S. use more health care resources and have significantly higher overall health care payments compared to non-TRD patients[59]. Yet treatment options for this population are limited; moreover, those available antidepressant therapies such as ECT, are highly stigmatized and produce significant cognitive adverse effects such as amnesia and executive dysfunction[6]. An alternative first-line convulsive therapy, such as MST, with high remission rates in severely ill patients and those with TRD would be transformative for the field. The specific aims of the protocol described in this paper are to conduct a randomized non-inferiority trial evaluating the efficacy, tolerability, and cognitive adverse effects of two different forms of convulsive therapy (MST and RUL-UB ECT) for MDD/TRD, to assess the efficacy of two forms of convulsive therapy in ameliorating suicidal ideation in patients with depression, and to identify a neurophysiological biomarker of a clinically meaningful treatment response indicator. If MST demonstrates comparable efficacy to ECT, but with cognitive safety, it should be rapidly adopted into clinical practice as providers, patients and their families may be far more likely to accept this treatment.

The strengths of our protocol include: (1) the use of a new treatment option, MST, for difficult to treat depression complete with preliminary evidence that supports its safety and efficacy; (2) intensive clinical and neurocognitive study assessments pre-, during-, and post-treatment to monitor progression and ensure safety of participants; (3) longitudinal follow-up post-treatment to monitor long term outcomes of patients who did and did not respond to convulsive therapy; (4) trial oversight by an interdisciplinary team of experts in convulsive therapy across two leading North American institutions along with study monitoring by the NIMH OCR; (5) a linked

non-inferiority/superiority gated analysis statistical approach and comprehensive dissemination plan.

Although this protocol is clinically significant and strong, there are some limitations. First, recruitment is limited to two institutions in North America: CAMH and UT Southwestern. That being said, efforts to recruit a representative and generalizable study sample will be made by both study sites from the outset. Through our study design, careful data collection practices, and the appropriate statistical analyses, our data will be internally valid allowing us to draw firm conclusions about the true treatment effect in our population of interest. Second, historically it has been shown in multiple studies that the acceptability of convulsive therapy as a treatment option is underrepresented in minority populations as opposed to patients who identify as white[60, 61]. As outlined above, we will endeavour to recruit an ethnically diverse sample across both sites; however, this may prove challenging based on prior study findings. Our efforts in community engagement and education as described in our dissemination plan will go a long way towards fulfilling this aim and dispelling some of the stigma associated with convulsive therapy.

Recently published evidence from our open-label pilot clinical trial conducted at CAMH provides promising support for MST as an effective and safe treatment for adult patients with difficult to treat depression. For example, patients who received high-frequency MST (100Hz) achieved response and remission rates of 41.7% and 33.3%, respectively, for adequate trial completers (i.e., 8 treatments or more); and 60% and 53.3%, respectively, for protocol completers (i.e., 24 treatments)[35]. For both groups, the remission rates with high-frequency MST were significantly greater than the remission rates for low-frequency (25Hz) MST supporting further investigation of 100Hz MST. Additionally, an important use of ECT is rapid relief of acute suicidal ideation, and Weissman et al., (2020) found remission of suicidal ideation was achieved in 47.8%

of patients who endorsed suicidality at baseline in the MST open-label trial[62]. Findings from the pilot study also suggested that MST is cognitively safe [35]. Thus, should the clinical efficacy and safer cognitive effects of MST be replicated in this study, our results could lead to confirmation of a new potential treatment alternative to ECT.

The underlying interest in MST is that it is expected to have better cognitive outcomes than ECT and so would be preferred if it is at least as effective in relieving clinical symptoms as ECT is. This reasoning implies that unless MST is no worse than ECT with respect to clinical symptoms, its impact on cognitive outcomes is not important given MST would not be indicated if it is worse than ECT. The staged approach to the analysis reflects these realities and permits both questions to be answered in a single trial rather than two trials; a non-inferiority trial for clinical outcomes follow by a superiority trial for cognitive outcomes. With the staged approach, a sufficient sample size, and valid data, our statistical analyses will be robust and answer the underlying clinical management question. If our hypotheses are confirmed, the results of this trial will be presented to the FDA in support of marketing MST for patients with TRD.

Our study team has put forth great effort to ensure data collected from the two sites will be generalizable and accurately reflect the treatment effect and clinical practice for the U.S. population. Furthermore, our inclusion and exclusion criteria have been designed to closely mirror the typical clinical presentation of the population that receives ECT and that has been used in previous ECT treatment trials[41, 44, 45, 63]. This strategy will help to maximize both the internal and external validity (i.e., generalizability) of our findings. This study has been accepted by the U.S. FDA in support of a 510(k) premarket notification of intent to market the MagVenture MST MagPro XP device with a Cool Twin Coil for patients with depression. The MagProXP device has already received International Electrotechnical Commission certification and we expect a

marketing submission for this device to be submitted to the U.S. FDA approximately 6 months after study completion. Data generated from this study will be pivotal in supporting the approval of MST for use in TRD and accessibility of this potentially ground-breaking new antidepressant treatment to a wider population.

In conclusion, the CREST-MST protocol was predicated on existing pilot data that supported the safety and efficacy of MST for MDD and through strong collaborations with an integrated-healthcare study team including experts in the fields of psychiatry, convulsive therapy, TRD, anesthesiology, clinical neuropsychology, and neurophysiology. Should the results of this trial support MST as non-inferior and cognitively superior to ECT, MST could become a standard antidepressant treatment for patients with TRD. Existing ECT suites can easily accommodate MST without major modifications. Indeed, given that the administration of MST is nearly identical to ECT, the majority of ECT facilities in North America would be able to readily adopt MST into their established convulsive therapy programs. By establishing MST as a safe and effective treatment for severe depression, this trial will provide a new antidepressant therapy to advance the care of depression in adults and improve overall health outcomes.

Abbreviations

AE: Adverse event; AHRC: Applied Health Research Centre; AMT: Autobiographical Memory Test; CAMH: Centre for Addiction and Mental Health; CONSORT: Consolidated Standards of Reporting Trials; DSMB: data safety monitoring board; ECT: Electroconvulsive therapy; ECS: electroconvulsive seizure; EEG: electroencephalography; FDA: Food and Drug Administration; FDG-PET: fluorodeoxyglucose positron emission tomography; GCP: Good Clinical Practice; HRSD-24: 24 item-Hamilton Rating Scale for Depression; IDE: Investigational Device Exemption; ITA: Investigational Testing Authorization; ITT: intention to treat; IV: intravenous; MDD: Major depressive disorder; MINI: Mini-International Neuropsychiatric Interview; MS: magnetic seizure; MST: Magnetic Seizure Therapy; NIH: National Institute of Health; NIMH: National Institute of Mental Health; NDA: NIMH Data Archive; OCR: Office of Clinical Research; PI: Principal Investigator; RAVE: Medidata Rave; RUL: Right Unilateral; RUL-UB-

ECT: Right Unilateral Ultrabrief ECT; rTMS: repetitive transcranial magnetic stimulation; SAE: Serious Adverse Event; SMH: St. Michael's Hospital; SSI: Beck Scale for Suicidal Ideation; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TRD: treatment-resistant depression; U.S.: United States; UT Southwestern: University of Texas Southwestern

DECLARATIONS

Ethics approval and consent to participate

Ethics approval was obtained by the Centre for Addiction and Mental Health Research Ethics Board (reference number 033-2017) and the University of Texas Southwestern Medical Center Institutional Research Board (reference number STU 032017-022). All participants provide written informed consent to participate in this trial using the "Documentation of Consent for Study" and a completed consent form describing in detail the study intervention, study procedures, and risks is also provided to the participant via email.

Consent for publication

Does not apply

Availability of data and materials

The final de-dentified dataset generated from the current protocol will be available as part of the NIMH Data Archive (NDA) and from the corresponding author on reasonable request.

Competing Interests

The study received in-kind equipment support from MagVenture A/S (Farum, Denmark) for this investigator-initiated research. In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work is supported by the Canadian Institutes of Health Research (CIHR), the National Institutes of Mental Health (NIMH), Brain Canada and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute. FF has no competing interest related to this trial. FF received funding from NARSAD (Grand ID: 22317). She has also received funding form Michael Smith Foundation for Health Research (Scholar Award), NSERC, and CIHR. SMH has received research support from NIH. He is a consultant to Pearson Assessment. He received a teaching honoraria from Duke University School of Medicine. DMB has received research support from CIHR, NIH, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Family Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd and MagVenture Inc. He is the site principal investigator for three sponsor-initiated studies for Brainsway Ltd.He received medication supplies for an investigator-initiated trial from Indivior.

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Authors' contributions

All authors contributed to the writing, critically reviewed, and approved the final manuscript. All authors adhere to the authorship guidelines of *Trials*; all have agreed to the publication and contributed to the writing of the manuscript.

Conception: ZJD, DMB
Development of protocol: ZJD, CT, AT, LP, JD, FF, KET, SMM, DMB
Development of methodology: ZJD, SMM, FF, KET, DMB
Statistical analysis: KET

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TRIAL STATUS

Enrollment for this study began on June 26, 2018. At the time of submission, we have enrolled and randomized 89 participants.

Trial Registration

Registration: June 19, 2017 (NCT03191058), https://clinicaltrials.gov/ct2/show/NCT03191058
Primary sponsor:
Daniel Blumberger (DMB), Principal Investigator
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Contact for scientific queries: ZJD, Zdaskalakis@health.ucsd.edu

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FIGURE 1: Study Design

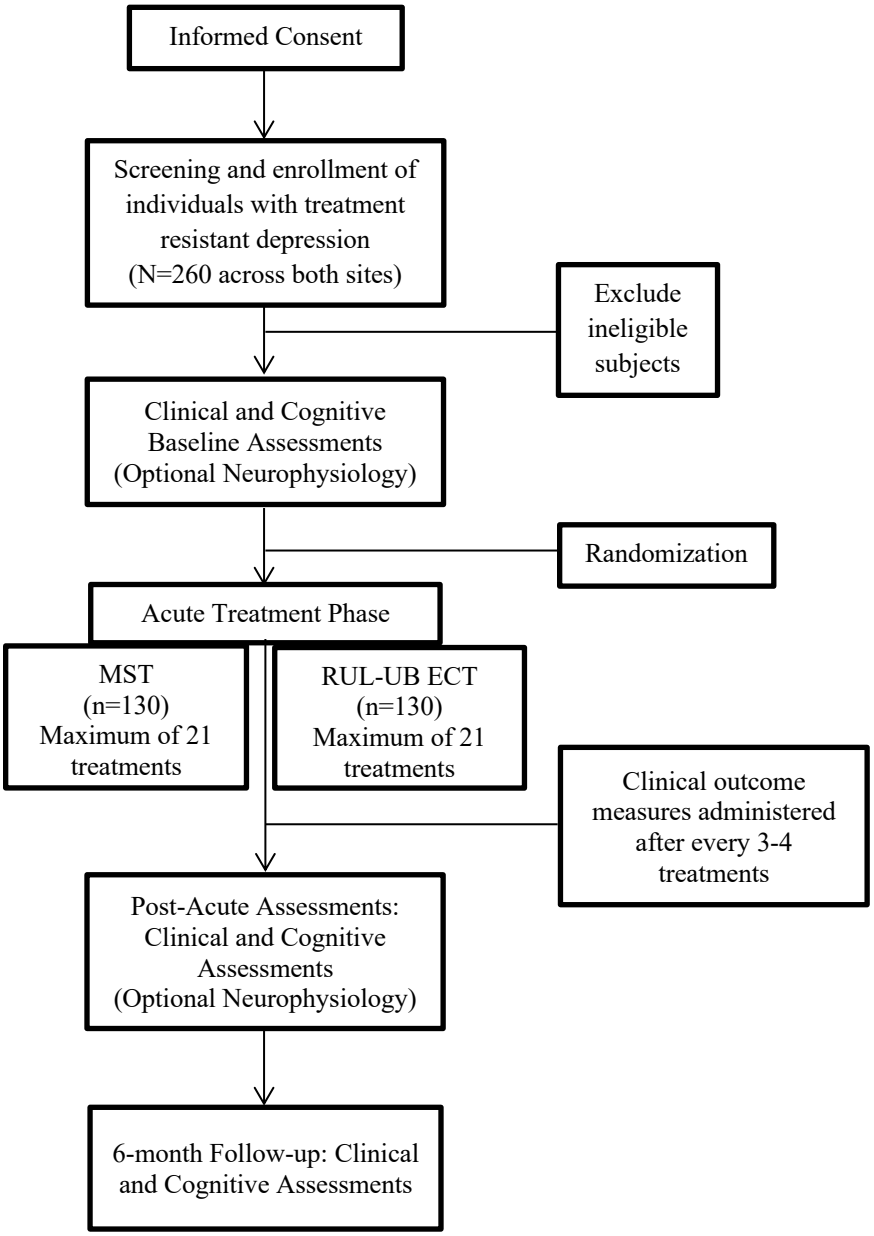

FIGURE 2: MagPro XP with Cool Twin Coil device (MagVenture A/S, Farum, Denmark)

TABLE 1: Study Measures

Clinical Measures

Measure	Study Period					
	Prior to acute phase			Active study phase	Follow-up	
	Enrolment	Screening	Baseline	Acute Phase[1]	Post-Acute[2]	6 Months
Informed Consent	X					
MINI		X				
Demographics Form		X				
Medical History Form		X				
TASS		X				
HRSD-24		X		X	X	X
ATHF			X	X	X	X
SSI			X	X	X	X
BSI			X	X	X	X
CGI			X		X	X
Q-LES-Q			X		X	X
YMRS			X	X	X	
Columbia ECT Side effects Schedule			X	X	X	X
Concomitant Meds		X	X	X	X	X

Neurocognitive Measures

Measure	Study Period				
	Prior to acute phase		Active study phase	Follow-up	
	Screening	Baseline	Acute Phase[1]	Post-Acute[2]	6 Months
TOPF		X			
MoCA		X		X	X
DKEFS Verbal Fluency Test		X		X	X
DKEFS Color Word Interference Test		X		X	X
DKEFS Tower Test		X		X	X
CVLT-3		X		X	X
AMT		X		X	X
NIH Toolbox: Flanker Test		X		X	X
NIH Toolbox: Picture Sequence Test		X		X	X
NIH Toolbox: List Sorting Working Memory Test		X		X	X

[1]Acute treatments are delivered 2-3 times a week. Acute assessments are delivered after every 3-4 treatments

[2] ≤ 4 days post-acute phase

Abbreviations:

MINI International Neuropsychiatric Interview diagnosis V6.0 (MINI), Transcranial Magnetic Stimulation Adult Safety Screen (TASS), 24-item Hamilton Depression Rating Scale (HRSD-24), Antidepressant Treatment History Form (ATHF), Scale for Suicidal Ideation (SSI), Brief Symptom Inventory (BSI), Clinical Global Impression Scale (CGI), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Young Mania Rating scale (YMRS), Test of Premorbid Function (TOPF), Montreal Cognitive Assessment (MoCA), Delis Kaplan Executive Function System (DKEFS), California Verbal Learning Test- Third Edition (CVLT-3), Autobiographical Memory Test (AMT), National Institutes of Health (NIH) Toolbox: Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, List Sorting Working Memory Test

SPIRIT Checklist for *Trials*

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Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 6	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 8, line 206	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 29, line 722	
Protocol version	#3	Date and version identifier	Page 7, line 169	

Funding	#4	Sources and types of financial, material, and other support	Page 27, line 667	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 28, line 686	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 29, line 724	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 27, line 667	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 21, line 482; Page 27, line 667	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3, line 78	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 3, line 89	
Objectives	#7	Specific objectives or hypotheses	Page 15, line 370	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 7, line 183	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7, line 183	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 9 line 225	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 12, line 287	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 14, line 330	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests). Also relevant for non-pharmacological RCTs.	Page 20, line 463	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 10, line 225	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 16, line 370	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 14, line 345	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 19, line 442	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9, line 213	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 11, line 271	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page, 11, line 271	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11, line 271	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11, line 271	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 11, line 271	
Methods: Data collection, management, and analysis				

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 14, line 345 (Table 1)	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9, line 213	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 20, line 463	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 16, line 387	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 18, line 431	

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17, line 410	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 20, line 482	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A	Not applicable as this study was not designed with an interim analysis
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 15, page 364	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 20, line 471; Page 20, line 482	
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval including the committee's reference number (if applicable)	Page 8, line 200	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Page 11, line 265	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 10, page 251	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 10, page 251	
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 20, line 476	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 27, line 649	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 27, line 645	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 15, line 354	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 21, line 510	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A	Not applicable as there is no intent to use professional writers. All author contributions outline on Page 29
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 21, line 510	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Consent Attached. See Additional file 2.	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	Not applicable as no biological specimens were collected as part of this trial.

camh Temerty Centre for Therapeutic Brain Intervention

INFORMED CONSENT AND INFORMATION SHEET

Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression: CREST-MST

Dr. Daniel Blumberger

This Informed Consent form has 2 parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be offered a copy of the full informed consent form.

Part I: Information Sheet

Introduction

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary. There is a section at the end of this document that explains how the study may be conducted remotely when extra precautions are required and how some of the procedures may differ.

Background and Purpose

- You have been asked to take part in this research study because you have a diagnosis of Major Depressive Disorder and are interested in pursuing brain stimulation therapy, as prescribed by your clinical physician.
- Electroconvulsive Therapy (ECT) is the most established type of brain stimulation therapy, and uses electrical stimulation to stimulate the brain and induce a seizure.
- ECT is effective to treat depression but may cause memory loss.
- With this study we would like to investigate a recently developed treatment, Magnetic Seizure Therapy (MST). It is hoped that MST will prove to be as good as ECT in treating depression, but with less memory loss.
- For both treatments, a seizure is induced while you are under general anesthesia.

- At this time, MST is an investigational treatment and has not yet been approved by Health Canada for clinical use outside of research studies like this one. ECT, on the other hand, has been in use for several decades and there is extensive research documenting its efficacy.
- This study will compare these two different treatments to see if they have the same or different effectiveness in treating major depression. If MST proves to be as good as ECT in treating depression, but with fewer side effects including memory loss, it will be an important treatment option in future years.
- About 260 people will participate in the study. They will come from the University of Texas – Southwestern Medical Center and the Centre for Addiction and Mental Health.
- If new information emerges about the treatments in this study that alters the risks or benefits of participation you will be notified.

Study Design

- This study compares the effectiveness of two different kinds of treatments: MST and ECT.
- Whether you receive MST or ECT will be decided randomly (by chance). The number of people getting treatment in each study group will be ~130, so you will have a 1 in 2 chance of receiving MST and a 1 in 2 chance of receiving ECT.
- This study will be blinded. This means that neither you nor the study team member, who follows your progress, will know which kind of treatment you are receiving until the study is finished. This information can be found out at any time in case of an emergency.
- You will undergo treatment in this study for approximately 7 weeks (or a maximum of 21 treatments).
- There will be one screening visit lasting around 1 – 1.5 hours, and two baseline visits, each lasting between 1 - 1.5 hours.
- There will be a maximum of 21 treatment visits (Monday, Wednesday and Friday for 7 weeks). There will be a post-treatment visit conducted after you end treatment, lasting approximately 3 hours. There will also be a follow-up visit 6 months after treatment completion (lasting approximately 3 hours).
- You will also have the choice to complete an additional component involving testing sessions before and after your treatment course that examine your brain's physiology. These processes are known as cortical inhibition and multi-scale entropy. These sessions will only be offered if non-essential research is deemed safe to conduct, according to hospital directives.

Important Precautions

You should be aware that the magnetic fields generated by the stimulator might damage magnetic cards, watches and some electrical devices. *Please remove any such items before testing*.

Exposure to magnetic stimulation or any strong magnetic field is **not permitted** in people who have a pacemaker, an implanted medication pump, a metal plate in the skull, or metal objects inside the eye or skull (for example, after brain surgery or a shrapnel wound). *Please inform investigators if you have any of these*.

Study Visits and Procedures

Screening Visit: The first study visit will be a screening visit. This visit will involve an interview to confirm your diagnosis of major depressive disorder and rule out other psychiatric diagnoses that might interfere with treatment, and to confirm that you can safely undergo MST or ECT. The results of the tests/questions at the screening visit help the researchers to decide whether you can continue in this study. The results of all tests and interviews are completely confidential. There are also clinical procedures which you will be asked to complete, including bloodwork and an electrocardiogram (ECG). Additionally, a consult with the anesthesiologist will be scheduled to review your bloodwork and ECG, and ensure that it is medically safe for you to undergo anesthesia.

Baseline Visit: This visit will be conducted after your screening visit once your eligibility for this study has been confirmed. You will undergo some interviews and fill out questionnaires regarding your symptoms. You will also complete about one and half hours of cognitive assessments that will assess your memory and executive functioning. These require two separate visits both located here at the Queen St. location of CAMH.

Treatment Visits 1-21: The treatments will take place over a 7 week time frame, three days a week (Monday, Wednesday and Friday). You will be asked to attend for treatment in the morning when the clinic opens. The treatment procedure is approximately 10 minutes, followed by a recovery period of approximately 30 minutes until you are stable and feeling well enough to be escorted home. Please note that the duration of your visit to CAMH will vary based on wait times in the clinic. *It is required that you have an escort to take you home after each treatment visit. An escort may be a relative, friend, neighbour, case worker, etc. A taxi driver is not considered a suitable escort.*

If you miss more than 2 scheduled treatment sessions, your treatment as part of the study will be stopped, as missing treatment sessions compromises the efficacy of the treatment.

Monitoring Visits: The study team will follow your progress with additional monitoring visits after every 3 - 4 treatments. It should take around 30-45 minutes to complete this monitoring visit.

Post-Treatment Monitoring Visit: After your final treatment you will undergo the same interviews and questionnaires as you did in your baseline visit, as well as the cognitive tasks to measure your executive function. This visit should take around 2.5 – 3 hours.

Follow-up Monitoring Visits: A final follow-up visit, lasting around 3 hours, will take place 6

months after you end treatment.

Should you withdraw or be discontinued from treatment prior to completing the full course, we aim to continue to follow you at the regularly scheduled time points described above. This allows us to collect more complete data regarding the efficacy of these treatments.

Additional Sessions to Measure Brain Physiology: Transcranial magnetic stimulation (TMS) is a method used to measure brain inhibition. TMS excites nerves over the area of the brain involved in moving your hand muscles. When the nerves are stimulated, this causes the muscles in your hand to move, which will be recorded and later analyzed. Brain activity and inhibition during TMS will be assessed using electroencephalography (EEG) and electromyography (EMG).

- You will be seated in a comfortable chair and we will attach soft foam electrodes to the skin surface over your hand muscles; these electrodes will then be connected to a recorder that will record the activity of your hand muscles.
- It takes approximately 30 minutes to put on the EEG cap and get it ready for recording. The cap contains many recorders that record your brain activity. There is gel on the inside of the cap that may be sticky; you will be allowed to rinse it out after the test.
- A magnetic coil will be held on the surface of your scalp
- When the magnetic stimulation is applied, you will feel a twitch or small movement in your hand, but there should be no pain.
- The TMS measures of brain physiology will be taken from your motor cortex (the part of the brain that controls movement) and the prefrontal cortex (the part of the brain that controls thinking).

If you choose to participate in these sessions, there will be one scheduled before your first treatment session, and one after your treatment course is complete, each lasting around 2 – 2.5 hours. As mentioned above, these sessions are optional and will only be offered if non-essential research is deemed safe according to hospital directives.

Calendar of Visits

Boxes marked with an X show what will happen at each visit:

Visit	Interview and Question-naires	Cognitive Assessments	Clinical Lab[e]/ Consult	TMS-EEG (optional)[f]	Treatment (MST or ECT)	Time
Screening Visit	X		X[d]			1.5 – 2.5 hours
Baseline Visit 1	X		X			1 hour

Baseline Visit 2		X		X (2 – 2.5 hours)		1.5 hours
Visits1-21[a]					X	
Visits 4, 7, 10, 13, 16 and 19[c]	X				X	30-45 minutes[b]
Post-treatment Monitoring Visit	X	X		X (2 – 2.5 hours)		2.5-3 hours
6 month post-treatment Monitoring Visit	X	X				2.5-3 hours

[a]For these visits, we cannot provide an exact estimate of the total duration of time, as this will be affected by wait times at the facility on a given day.
[b]The time duration listed for visits 4, 7, 10, 13, 16 and 19 only accounts for the interview and questionnaire portion.
[c]There is some flexibility with the interview and questionnaire monitoring visits, as they may be rescheduled to facilitate treatment scheduling.
[d]This will include an anesthesia consult, which will likely require that you are on site for longer.
[e]Clinical labs may be completed at a time point other than the Screening Visit, but this information should be available for review at the first visit.
[f] These sessions are optional and will only be offered if non-essential research is deemed safe according to hospital directives.

Planning for Treatment Visits

Because you will be receiving a general anaesthetic you cannot have anything to eat or drink after midnight the night before your treatment.

You MUST have an escort to take you home after each of your treatments. An escort may be a relative, friend, neighbour, case worker, etc. A taxi driver is not considered a suitable escort.

Prior to treatment start you will be seen by a brain stimulation physician, during this visit you may be asked to change a medication that could interfere with the MST or ECT procedure. The limiting or discontinuation of any medications prior to treatment start is a clinical decision and all risks associated with this will be reviewed with the brain stimulation physician or your clinical physician.

Taking a benzodiazepine at a dose greater than lorazepam 2 mg or equivalent or taking a non-benzodiazepine anticonvulsant medication is not permitted in the study as it could interfere with the MST or ECT procedure

Should you be required clinically to start any new medication, please ensure to inform the research team. We also ask you to please refrain from starting any new "over the counter" or "as needed" medications without discussing this with the research team first. This includes medication to treat anxiety or insomnia such as lorazepam or clonazepam.

After each treatment, you will spend some time in the recovery room where your vitals will be measured, nursing staff will monitor your status and you will be asked some questions by study staff to check your orientation (e.g. name, DOB, place, etc.). There will be other patients in this space who will be at various stages of recovery and reorientation. Current practise standards aimed at maintaining confidentiality will be applied throughout this process.

Reminders

It is important to remember the following things during this study:

- Ask your study team about anything that worries you.
- Tell study staff anything about your health that has changed.
- Tell study staff if you are considering any changes to your medications or doses.
- Tell study staff if you have changed any of your medications or doses.
- Tell study staff if you become pregnant during the study.
- Tell study staff if your depression becomes worse.
- Tell study staff if you are having thoughts about hurting yourself or anyone else.
- Tell study staff if you have noticed changes to your memory
- Tell your study team if you change your mind about being in this study.

Risks Related to Being in the Study

Based on safety studies over the last decade, the known risks of the magnetically-induced seizures of MST are not greater than the known risks of electrically-induced seizures in ECT (these are summarized below). There is a possibility that you may also experience a worsening of your symptoms during the course of the trial. You may experience side-effects after each treatment. This can be caused by the treatment itself, the anesthetic medication or not having anything to eat or drink for a long period of time. The most common side-effects are headache, dizziness, nausea or vomiting, muscle aches and fatigue. There is also a small risk of experiencing difficulty breathing after each treatment. If this happens, the treating physician and anesthesiologist will adjust the doses of the medications administered during the treatment to ensure that this does not happen again. Some of these side effects can be reduced, therefore we encourage you to let the research staff know if you experience any of these. Treatment is available and will be provided by medical staff in the event of study-related injury or adverse event.

Known risks of electrically-induced convulsive therapy include:
1) Risks of general anesthesia, which involves about 1/100, 000 treatments risk of death.
2) Risks of non-terminating seizures in about 1/1000. This is usually treated with a medication

given to the patient by the doctor monitoring the anesthesia.
3) Risks of decreased heart rate in about 1/1000. This usually resolves on its own.
4) Risks of high blood pressure in about 1/1000. This usually resolves on its own but is monitored. The anesthetist may also administer a fast-acting medication to reverse severe high blood pressure.
5) Risks of increased brain pressure in about 1/100, 000. This effect, again, is usually temporary, and patients with conditions that would increase this risk are identified during the initial ECT screening.
6) Risks of temporary decline in blood oxygen during the seizure. Again, this is usually temporary and is monitored throughout the duration of the seizure.
7) Risks associated with a confusional state, including agitation and risk of injury due to falls from the ECT bed following the seizure. This is minimized by close supervision. In rare cases, brief sedation is used to avoid fall/injury.
8) Risks of emergence of hypomania or mania. A measure of manic symptoms is included in the monitoring visits to screen for this.
9) ECT and MST can cause confusion and memory loss. This may start immediately after treatment and may continue after treatment is stopped. Memory loss can affect new memories (for example, it may be hard to learn or remember new information) or old memories (you might not be able to remember past experiences or other memories). These side effects can range from mild (unsettling to the participant) to severe (impact daily activity and cause distress for participants).

You may find it helpful to write down things you want to remember and use a calendar for appointments and important details. You may want to keep important contact information in a place you can easily find. The study team will also provide you with a wallet card detailing study contact information. Please talk to the study team if you have any questions or are worried about this.

The overall mortality rate for ECT is currently around 1 per 100, 000 treatments according to statistics maintained by the American Psychiatric Association.

If you have further concerns, you may contact your study doctor at any time.

A study physician will be present at all times during the treatment component of this study and will promptly assess and treat any side effects you may experience in consultation with one of the anesthesiologists.

<u>Incidental Findings</u>

Research scans are not subject to clinical review and the psychological test and interviews are not used for diagnostic purposes. However, any incidental findings will be communicated to you and, upon your request, to your clinical physician.

Risks Related to Pregnancy

There are no known risks of MST or ECT during pregnancy. However, there is always a possibility that if you are pregnant, MST or ECT may have risks that we do not know about. For this reason, you cannot participate in the study if you are pregnant. We also ask that you not actively try to become pregnant while participating in this trial.

Benefits to Being in the Study

You may or may not receive any direct benefit from being in this study. MST or ECT may improve your symptoms of depression, or may have no effect. Information learned from this study may help other people undergoing a convulsive therapy for major depression in the future.

Right to refuse or withdraw from the study

Your participation in this study is voluntary. You may refuse to participate or stop your participation at any time without penalty and without jeopardizing your continuing medical care at this institution.

Should you choose to withdraw from the treatment portion of the study or are unable to finish all of the scheduled treatment appointments due to unforeseen circumstances, you may still agree to participate in the remaining clinical assessments as scheduled.

Throughout your participation in this study you may continue your regular appointments with your original treating physician.

Discontinuation

It should be noted that your treatment may be discontinued without your consent under the following conditions:

- if you miss more than two scheduled treatment sessions
- the study physician decides to stop your convulsive therapy treatment for safety reasons
- you are lost to follow-up
- you are not compliant with the requirements of the study, which include the inclusion/exclusion criteria
- the study is stopped or halted prematurely
- the investigator believes that it is in your best interest (e.g., you experience a serious adverse event) to stop treatment
- you become pregnant
- you experience a significant worsening in depression
- you experience a significant increase in suicidal ideation with imminent intent or attempt suicide
- you develop signs of mania or hypomania

- a seizure cannot be induced on two consecutive treatment sessions, despite optimization of treatment parameters and anesthesia

If you stop treatment early, we will complete the scheduled post-treatment and follow-up visits as outlined above.

Alternatives to Being in the Study

You do not have to join this study to receive treatment for your condition. ECT is offered in a non-research setting at various hospitals in Toronto and elsewhere. There are also many other approved medications/interventions for major depression:

- There are many antidepressant medications that are available alternatives to participation in this study. Your psychiatrist or family doctor can help you decide on the best antidepressant medication for your illness.
- Psychotherapies such as cognitive behavioral therapy (CBT), interpersonal therapy (IPT), or mindfulness-based cognitive therapy (MBCT).
- Other forms of brain stimulation therapy such as bilateral electroconvulsive therapy, for depression that is severe or unresponsive to other treatments.
- There are also other research studies looking at other brain stimulation treatments for your condition.
- You may also choose not to have any treatment for your condition.

Your doctor will discuss any of these options with you.

Confidentiality

The confidentiality of the data collected and identity of the individuals participating in this study will be strictly maintained. The names and identity of the participants will not be revealed in any discussion of this work.

To determine if you meet the requirements to participate in this study, a member of the research team will need to access your CAMH Health Record.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law. The information regarding this clinical trial will be entered into a databank.

As part of the Research Services Quality Assurance Program, this study may be monitored and/or audited by a member of the Quality Assurance Team. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law.

A description of the research study will be available at www.clinicaltrials.gov. This website will not include information that can identify you in any way. At most, the website will include a summary of the results. You can search this website for the study at any time.

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental illness to collect and share deidentified information with each other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send deidentified information about your health and behavior and in some cases, your genetic information, to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers around the world treat future children and adults with mental illnesses so that they have better outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at http://data-archive.nimh.gov.

Personal Health Information

If you agree to join this study, the study doctor will look at your personal health information for clinical reasons only. Your personal health information will not be recorded in the study records. Personal health information is any information that could be used to identify you and includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area (secure

server for electronic data) by the study doctor for 25 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study will also be recorded in your medical record at this hospital. The following people may also come to the hospital to look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines:

- Representatives of Canadian, U.S. or health regulatory agencies (e.g. Health Canada, Food and Drug Administration)
- Representatives of CAMH, UT Southwestern Medical Center or the National Institutes of Mental Health (NIMH)

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. If you consent to be re-contacted for future research studies, some basic information as described below may be shared with other authorized research personnel affiliated with the Temerty Centre. You will not be named in any reports, publications, or presentations that may come from this study. If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

With your permission, some basic information (e.g. demographics, medications, safety screening, brain stimulation history, etc.) gathered as part of the screening process will be stored in a centralized electronic database and may be shared with other research personnel affiliated with the Temerty Centre. This data will be used to safely track your participation and to better match you with current and future studies that you may be eligible for if you consent to be re-contacted. Only investigators/research teams affiliated with the Temerty Centre will have access to this secured database, and will adhere to all appropriate measures to safeguard the confidentiality of your information.

Because this is a treatment study, your signed consent form will be scanned and sent to the CAMH medical records department for your file.

New Information

If new information becomes available that is relevant to your participation to continue in the study, you will be informed in a timely manner.

In Case You Are Harmed in the Study

If you become ill, injured or harmed as a result of taking part in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness or harm that is directly a result of being in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent

form.

Expenses Associated with Participating in the Study

You will not have to pay for any of the treatments or other procedures involved with this study.

Modified Procedures

All study visits, except for ECT/MST treatments and TMS-EEG sessions, will be conducted virtually using videocoference software (Webex), or the telephone if you are not able to use the videoconference software. Like online shopping, videoconferencing technology has some privacy and security risks. It is possible that information could be intercepted by unauthorized people (hacked) or otherwise shared by accident. This risk can't be completely eliminated, however CAMH has approved the use of WebEx for videoconferencing sessions because the appointments take place over a secure encrypted network. We want to make sure you are aware of this. The research team will confirm your identity at the beginning of the call and may also ask to see a piece of government-issued ID, via video, during the session.

Video sessions can be conducted using your cell phone, tablet or personal computer enabled with a camera/microphone and internet connection. You should use your home computer or personal device, and not a shared or work device, and use a home (private) Wi-Fi network, and not free (public) Wi-Fi for your internet connection. To use WebEx, an e-mail will be sent to you including the instructions for how to log-in. Self-report questionnaires will be completed using screen share, or verbally completed over Webex or telephone.

Do we have your consent to send you information by e-mail? The security of information sent by e-mail cannot be guaranteed.

☐ No

☐ Yes

The security of information sent by e-mail cannot be guaranteed. Please do not communicate personal sensitive information by e-mail. E-mail is not routinely monitored outside of work hours. Please do not use e-mail to communicate emergency or urgent health matters – please contact your clinician or family doctor. If it is a medical emergency, call 911.

For your safety, the research team will ask you for an emergency contact number, alternate phone number and your address before they start the call. They may follow-up with you after the session if you leave early. If at any time, we are concerned for your safety, we may contact you, your emergency contact or emergency responders to follow-up.
For these videoconference sessions, please try to find a quiet place where you can be by yourself and will not be disturbed and use earphones if you can. It's a good idea to test out the system a few minutes before the session to make sure the connection and sound are working. You or the research team can stop the session at any time, including if there are technical difficulties. If there are technical issues, one of our technical staff may join the call to provide

support. Some of the cognitive assessments cannot be completed remotely so the baseline, post-treatment, and follow-up visits will be shorter when they are conducted by video or telephone. During one of the cognitive assessments the research staff will take a screen shot of work you have done, your face will not be included.

ECT/MST treatments will be conducted in person. You will be told ahead of time what time you should arrive for your treatment in order to minimize the number of people in the waiting room. Prior to entering CAMH each day, every person is screened for COVID-19 symptoms and contacts. Any person who is found to have symptoms or contacts as per the screening protocol (known as a positive screen) will not be permitted to enter CAMH. If you are found to be a positive screen on any given day during the study, treatment will not be allowed to continue that day. Depending on the determination of the Infection Prevention and Control team at CAMH, we may or may not be able to resume treatments. If you miss more than 2 scheduled treatments due to a positive screen it will be at the discretion of the treatment team whether or not you can continue to receive treatment. If you do not have COVID-19 symptoms or contacts as per the screening protocol (known as a negative screen), you will be given a wristband to indicate you have been screened for that day. A CAMH staff will then escort you to the waiting room. Once you have recovered from the treatment the CAMH staff will take you to the person who is escorting you home.

During the optional brain physiology sessions, you will be required to wear a mask. The research staff will be wearing a mask, face shield and gloves. The research staff will maintain a physical distance whenever possible but there will be extended periods where they will be within 6ft/2m. All of the equipment and furniture that they use will be disinfected before and after the session. You will not be allowed to rinse out your hair at the end of the session, but we will provide you with a cap for your commute home.

Part II: Certificate of Consent

I have been invited to participate in this research treatment study and have read the attached information sheet. The discomforts and possible risks have been described to me. I understand that I can ask further questions during any stage of the study.

I understand that I may withdraw from the study at any time without affecting my treatment with my original treating physician. My identity will not be disclosed in any reference to the study or its results. I have also been offered a copy of the consent form.

Questions About the Study

Dr. Blumberger is responsible for the study. If you have any questions, please contact him at 416-535-8501 x33662. Dr. Robert Levitan (Chair, Research Ethics Board) is the external contact should you have further questions about participant rights. He can be reached at 416-535-8501 x 34020.

I voluntarily consent to participate in this study.

_____	_____	_____
Participant's Name (Print)	Signature	Date
_____	_____	_____
Name of Person Obtaining Consent (Print)	Signature	Date

I voluntarily consent to participate in two additional TMS-EEG sessions to measure cortical inhibition (*check here*) ☐
I do not agree to complete the optional TMS-EEG sessions (*check here*) ☐

_____	_____
Signature	Date

I authorize _____ to disclose my personal health information,
(name of treating physician)
consisting of psychiatric or medical conditions, illnesses or psychiatric procedures that may influence my ability to participate in this study to the research analyst and/or Dr. Blumberger. I understand the purpose for disclosing this personal health information.

_____ _____
Signature Date

Should I be interested in future research studies, I agree to be contacted in the future.

_____ _____
Signature Date

Note- In addition, to ensure your safe participation in this study, you are being asked to designate someone whom the research team can contact about your depression symptoms and participation in the study, and who the research team can contact if they have questions about/are concerned about your well-being and/or are unable to reach you. This should be someone who has frequent contact with you and can contact the study staff in case of emergencies.

_____
Name of contact person

_____ _____
Telephone number Alternate telephone number

Or

□ I do not wish to provide a contact.