STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST – MST)

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Title:	Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST – MST)
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1.0 BACKGROUND, OBJECTIVE AND SPECIFIC AIMS

1.1.1 The Need for Novel Therapeutic Approaches for Depression

In this proposal, we aim to assess the efficacy and tolerability of Magnetic Seizure Therapy (MST) as an alternative to electroconvulsive therapy (ECT) for depression. Even with multiple medication trials, 30 - 40% of patients will experience a pharmacologically resistant form of illness [1]. In Canada, estimates have quantified the total mental health burden of MDD to be $14.4 billion in 1998 (not accounting for decreased productivity associated with the illness estimated to be about $6 billion [2]). The ineffectiveness of current treatments for major depressive disorder (MDD) coupled with the economic burden associated with the disorder engenders a need for novel therapeutic interventions that can provide greater response and remission rates.

The need to optimize our therapeutic approach to depression is twofold. First, 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 treatment resistant depression (TRD) receive ECT in Canada and the United States [4, 5]. One of the major reasons that providers, patients and their families refuse to consider ECT - even when confronted with a disabling depression - is their concern about the cognitive side effects associated with ECT. The cognitive impairment includes anterograde and retrograde amnesia and prolonged post-treatment disorientation that is distressing to patients and mitigates the improvements in depressive symptomatology. MST offers a viable alternative to ECT with comparable response/remission rates and a more favourable cognitive adverse effect profile [6-8]. Second, it is vital to gain insight into the biological mechanisms underlying treatment response in order to better understand the physiological underpinnings of illness and treatment. To this end, we will evaluate the role of cortical inhibition (CI) from the dorsolateral prefrontal cortex as a biological target that can potentially predict MST and ECT treatment response. This will serve to deepen and enrich our biological models of depression, with the hope for more effective and personalized treatments.

1.1.2. Electroconvulsive Therapy (ECT) is Efficacious But Has Cognitive Adverse Effects

ECT is currently the most effective intervention for depression[9]. Despite evidence of significant efficacy (i.e., up to 75 percent remission rates in treatment resistant depression[9], ECT is complicated by its negative stigma and adverse cognitive effects. Regardless of treatment delivery, ECT results in significant post-ictal disorientation, and anterograde and retrograde amnesia[10]. Disorientation immediately after ECT can last up to 40 minutes, regardless of electrode placement[11], which lengthens the procedure and causes patients distress and burden[12]. Anterograde amnesia, the inability to learn and retain new information, can appear at the first ECT treatment [13, 14] and persist for up to several months [15-18]. Retrograde amnesia, the inability to recall past personal and impersonal memories, remains the most serious ECT cognitive adverse effect[19]. Retrograde amnesia is more severe with bilateral ECT (i.e., bifrontal or bitemporal) than right unilateral (RUL) ECT, with high compared to low dosages, and with brief pulse width relative to ultrabrief pulse width[10]. As recently highlighted by the US 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[20]. Numerous patients refuse ECT because of these adverse cognitive effects.

Several theories have been proposed to account for the adverse effects of ECT on memory. The most supported theory is that when an electrical seizure is initiated, the skull shunts electrical current away from the stimulation site. This electrical current is propagated throughout the brain by the corticospinal fluid (CSF) and ensures the electrical stimulus is non-focal[21, 22]. This diffuse electrical discharge spreads to deep brain regions, including medial temporal lobe structures (e.g., hippocampus) where it causes a disruption of synaptic plasticity and long-term potentiation[23], which are neural substrates of memory formation[24-27]. The development of a new treatment approach that can mitigate these adverse cognitive effects, following this theory of how ECT results in cognitive adverse effects while maintaining the robust efficacy of ECT, is needed.

The proposed study will employ a relatively new approach to delivering ECT through right unilateral electrode placement combined with ultrabrief pulse width (RUL-UB ECT; 0.3 msec). Animal and human studies have demonstrated that ultrabrief pulse widths induce more efficient seizures compared to standard pulse widths (0.5 to 1 msec)[28]. When applied at six times the seizure threshold, RUL-UB ECT was shown to be as effective as standard pulse width RUL ECT but with significantly fewer and more attenuated cognitive adverse effects[10]. Although RUL-UB ECT does seem to reduce cognitive adverse effects, a greater number of treatments are required to produce comparable therapeutic effects to standard pulse width ECT[29-31] with increased cognitive impairments emerging after more treatment. Thus, patients treated with RUL-UB ECT still experience significant memory impairment compared to baseline.

1.1.3. Magnetic Seizure Therapy (MST) is a New Convulsive Neuromodulation Therapy

MST is an alternative form of convulsive therapy, that like ECT, involves the induction of a seizure to achieve a therapeutic response[22]. However, the induction of a seizure occurs through the use of high frequency, 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 and stimulate neurons thereby limiting seizure spread as the induced magnetic field can be focally targeted based on geometry of the stimulating magnetic coil[32, 33]. Additionally, the magnetic field is not impeded nor shunted by non-conducting material (i.e., skull) and, therefore, the field results in focal brain activation[34, 35]. Specifically, compared to right unilateral ultrabrief pulse ECT (RUL-UB-ECT), the electric field induced by MST is 5–10 times more focal[35, 36].

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 was much shorter (4 vs. 18 minutes, $p<0.01$). The Hamilton Rating Scale for Depression-24 item (HRSD-24) score improved from 32 to 14 in the MST group, while in the ECT group the score improved from 30 to 6[37]. In another study, 20 TRD patients were allocated to receive either right unilateral (RUL) ECT or MST. Comparable antidepressant response and no cognitive side effects were observed in both groups[8]. Note that in the latter study, RUL ECT was administered at 3 times the seizure threshold, which reduced the cognitive side effects, but might hinder the response to ECT. A subsequent MST study done by the same group collated the data from the former study with 16

additional MST subjects. Remission was achieved by 46% of the patients, and no cognitive side effects were observed. FDG-PET scans (N=12) showed increased bilateral metabolic activity in the frontal cortex and decreased activity in the left striatum[38]. 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%) in ECT compared to MST. The improved focality and lower intensity of MST was suggested as a possible explanation for its favorable side effects profile[36]. In a within subject, non-human primate study, McClintock et al. (collaborator, UT Southwestern) 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[39]. This preclinical study further substantiates the cognitive superiority of MST.

1.2.1 Neurophysiological Targets of Suicidal Ideation in TRD

The NIMH Research Domain Criteria (RDoC) proposes to use symptom clusters that cut across neuropsychiatric diagnoses as opposed to strict diagnostic classifications that have often failed to adequately capture recent advances in our understanding of the pathophysiology of severe psychiatric disorders[40]. To this end, several symptom constructs have been put forward to identify the depressive phenotype that is most closely associated with its underlying mechanism[41]. Suicidal ideation is a construct that is not part of the current RDoC matrix, but rather a construct that has been linked to maladaptive behaviors including hopelessness[42, 43], negative affect, and attentional biases[44]. These maladaptive behaviors are in the RDoC negative valence domain, specifically the RDoC constructs of loss, sustained threat, and frustrative non-reward[40]. Suicidal ideation has been posited to be a construct that shows heritability, state independence, and biological/clinical face validity[45]. It has been suggested that suicidal ideation may be more responsive to ECT than depressive symptoms[46, 47] and ECT is used as a first line treatment in TRD patients with significant suicidal ideation[46]. Therefore, suicidal ideation represents a symptom construct that is of major public health concern and associated with the TRD phenotype.

From a mechanistic viewpoint, suicidal ideation has been linked to the γ-aminobutyric acid (GABA)ergic system. Indeed, previous studies found abnormal GABA neurotransmission in suicidal patients, particularly in those with depression[48, 49]. Merali et al.[50] found that frontal mRNA expression of the $GABA_A$ subunit, was reduced in depressed suicide victims compared to controls. Poulter et al.[51] reported that there was dysfunctional DNA methylation in the $GABA_A$ receptor α1 subunit promoter region which was under expressed in MDD suicide brains compared to patients who did not die as a result of suicide. Moreover, relative to non-depressed suicide patients, mRNA expression of several genes related to the $GABA_A$ receptor is increased in depressed suicide patients[52]. It stands to reason that neurophysiological measures that assess GABAergic neurotransmission, such as integrated transcranial magnetic stimulation (TMS) and electroencephalography (EEG; TMS-EEG) can represent an important neurophysiological target. Conceptually, reduced GABAergic inhibitory neurotransmission may result in lack of control over one's own thoughts, which can become ruminative, persistent, and translate in a desire to die. This may explain our group's previous findings that relative to non-TRD patients, TRD was

associated with greater deficits in cortical inhibition (CI)[53], which is mediated by GABA inhibitory interneurons. In summary, for the treatment of suicidal ideation, evidence suggests that prefrontal GABAergic inhibitory neurotransmission may represent an important neurophysiological target.

1.3.1 Innovation

Several important areas of innovation are included in this study. We will conduct a randomized non-inferiority clinical trial designed to compare the efficacy of MST with ECT in patients with TRD. Suicidal ideation – a symptom domain in TRD that has tremendous public health impact - will be evaluated as the primary outcome variable of interest. In this study, we will follow an experimental medicine approach and evaluate CI as a potential mechanism through which MST and ECT may result in attenuation of suicidal ideation. Specific innovations include: 1) use of a new convulsive therapy, MST, 2) state-of-the-art combined TMS with EEG and analytic methods used to identify a neurophysiological GABAergic signal, and 3) use of quantitative EEG to probe mechanisms of ECT-induced cognitive impairment.

1.3.2 Pilot Data Support Innovative Study Methodology and Feasibility: Transcranial Magnetic Stimulation Measurement of CI in TRD

TMS can provide an index of GABA receptor-mediated inhibition in the cortex because it differentially stimulates inhibitory interneurons and pyramidal neurons. We have demonstrated TMS paradigms that provide a measure of GABA receptor-mediated inhibitory neurotransmission including the cortical silent period (CSP) and long interval cortical inhibition (LICI)[54-57]. The CSP relies on motor cortical stimulation superimposed on background electromyography (EMG) activity. At high stimulus intensities, a cessation of all EMG activity occurs (thus the 'silent' period). The duration of this 'silent' period provides a metric of GABAergic inhibition in the motor cortex[58]. LICI involves a suprathreshold conditioning stimulus (CS) preceding a suprathreshold test stimulus (TS) by 50-200 ms, resulting in recruitment of inhibitory interneurons and inhibition of the motor evoked potential (MEP) by 50 %[54].

Evidence suggest that LICI and CSP are mediated by cortical $GABA_B$ interneurons[54, 55, 57, 59]. We have demonstrated evidence for deficient CI in patients with MDD and Bipolar Disorder using the above TMS inhibitory paradigms[53, 60]. Levinson et al.[53] found that all patients with MDD demonstrated significant CSP deficits. However, these studies were limited as measurement of CI was confined to the motor cortex and recorded in hand muscles through EMG. This limitation is problematic as the motor cortex has not been traditionally viewed as a key brain structure underlying the pathophysiology of MDD.

1.3.3 Recording CI from the dorsolateral prefrontal cortex (DLPFC) Using TMS-EEG. TMS-EEG is a powerful method to assess CI, excitability, connectivity and plasticity in non-motor cortical regions. Single and paired pulse TMS-EEG studies have identified several TMS-EEG indices associated with cortical inhibitory mechanisms associated with GABAergic neurotransmission[61-65]. In TMS-EEG, the application of single TMS pulse to the motor and prefrontal cortices results in generation of a series of TMS-induced cortical evoked potentials within the first 300 ms of the TMS pulse that results in descending corticospinal volleys and a

MEP. A series of studies including pharmacological probing and simultaneous recording of EEG and EMG response at the periphery have associated the N100 components with $GABA_B$ receptor mediated inhibitory mechanisms [61-65]. In addition, we have previously reported LICI can be generated from the DLPFC[62] and both N100 and LICI have high test-retest reliability[66, 67].

1.3.4 Predicting Remission of Suicidal Ideation

Baseline Prediction: In relation to target engagement, we used TMS-EEG to identify the neurophysiological predictors of decreased suicidal ideation associated with MST treatment[68]. We applied single and paired pulse TMS-EEG to the left DLPFC at baseline prior to MST treatment in 27 TRD patients. Our recently published study[68]demonstrated that the amplitude of the N100 and the extent of LICI in frontal and central midline region significantly correlated with remission of suicidal ideation based on the Scale for Suicidal Ideation[69]. This relationship was specific to the DLPFC and was not observed when N100 and LICI were assessed in the motor cortex. Additionally, we demonstrated that N100 and LICI in the frontal cortex predicted remission of suicidal ideation with 90% sensitivity and 89% specificity[68].

Target engagement: LICI was derived from the left DLPFC in 20 TRD patients prior to and after a course of MST treatment. Change in LICI predicted remission of suicidal ideation correctly with 85.7% sensitivity and 100% specificity (AUC = 0.98, p = 0.002). This pilot data suggests that LICI is modified by MST and that individualized changes in LICI by MST may underlie the differential treatment response for suicidal ideation.

1.3.5 Predicting ECT-Induced Cognitive Impairment through Multi-Scale Entropy

Additional data from our group suggests that resting EEG can be used to predict cognitive adverse effects following a course of seizure therapy. We obtained resting-state EEG from 34 patients receiving MST or ECT, and employed multi-scale entropy to quantify the complexity of brain temporal dynamics before and after seizure therapy. Temporal complexity represents the temporal fluctuations in resting state neurophysiological signals. The more complex the signal, the less recurring temporal patterns it contains. In ECT, but not MST, complexity of brain temporal dynamics in coarse time scales was significantly increased. In a subset of 19 patients we obtained scores of global cognitive function using the Montreal Cognitive Assessment (MoCA)[70] before and after ECT (n = 6) and MST (n =13) treatment. We found that increased complexity in coarse time scales derived through multi-scale entropy from EEG predicted change in MoCA with over 90 percent accuracy.

1.4.1 Specific Aims

The specific aims of this proposal are: (1) to conduct a randomized non-inferiority trial evaluating the efficacy, tolerability and cognitive adverse effects of two different forms of convulsive therapy for depression, (2) to assess the efficacy of two forms of convulsive therapy in ameliorating suicidal ideation in patients with depression and (3) to identify a neurophysiological biomarker of a clinically meaningful treatment response indicator. Two of the least invasive forms of convulsive therapy will be compared: RUL-UB ECT and a novel form of convulsive therapy that uses high intensity repetitive magnetic field pulses, called MST. MST has been shown to have

similar efficacy to RUL-UB ECT with minimal cognitive adverse effects. Pilot data from our naturalistic study of MST in 70 patients with depression demonstrates strong evidence for MST treatment efficacy. Our data also demonstrates that MST produces significant remission of suicidal ideation and minimal cognitive adverse effects.

Biomarkers of convulsive therapy response could further improve treatment efficiency and efficacy by identifying the patients who are most likely to benefit from these treatments. In this regard, we have developed a promising neurophysiological biomarker– cortical inhibition - that can predict treatment response through remission of suicidal ideation following a course of MST with 90 percent sensitivity and specificity.

Overall, this proposal will have transformative real-world clinical impact if MST demonstrates non-inferior efficacy compared to RUL-UB ECT. Healthcare providers, patients and policy makers would consequently demand this form of convulsive therapy. This is because only 1% of patients with depression accept a course of ECT owing to the cognitive adverse effects and negative stigma associated with ECT [4, 5]. A more acceptable and cognitive sparing form of convulsive therapy is desperately needed for patients with depression. Finally, the development of a reliable biomarker to guide response prediction will help identify those patients who are most likely to benefit from convulsive therapies.

2.0 RISK/BENEFIT ASSESSMENT

2.1.1 Known Potential Risks

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 [71] and these are summarized below. The most likely additional risk with MST would be the risk of a missed seizure. However, missed seizures have a very low rate of occurrence from our CAMH open-label trial (i.e., <1/100 treatments). If the patient has clinically significant suicidal ideation with imminent intent or attempted suicide and requires hospitalization then Dr. Blumberger at CAMH, Dr. Tamminga at UT Southwestern or Dr. Daskalakis at UCSD will be notified and the patient will be seen and assessed to determine the most appropriate plan of care. Patients may experience side-effects after each MST 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. Treatment is available and will be provided by medical staff in the event of study-related injury or adverse event.

Known Risks of Seizure Therapies (ECT/MST) include**:**

1) Risks of general anesthesia, which involves about 1/100,000 treatments risk of death.
2) Risks of non-terminating seizures in about 1/100. 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 1/100. This usually resolves on its own, but is monitored.
4) Risks of high blood pressure in about 1/100. 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 hypomanic or manic symptoms. Emergent hypomanic or manic symptoms is possible with any antidepressant therapy. A measure of manic symptoms (see Section 5.1.5) is included in the weekly assessments to monitor and document the presence or absence of hypomanic or manic symptoms.
9) Risk of suicidal or depressive symptom worsening: There will be a psychiatrist available to our study participants. In addition, our participants will be notified that in the event of serious symptom worsening they should visit the respective study site's ER or another ER that is closer in proximity to receive immediate care.

2.1.2 Known Potential Benefits

The potential benefits of the proposed research include: 1) a significant decrease in suicidal ideation and depressive symptoms, 2) significantly fewer memory impairments with MST compared to ECT, 3) faster recovery or orientation immediately following treatment with MST versus ECT. Our preliminary data suggests response rates of over 50 percent and extensive research on ECT has illustrated a remission rate of between 50-75 percent.

2.1.3 Safety of TMS-EEG

EEG recordings are not associated with any known risks to health and there is no evidence that there are either short-term or long-term side effects though some scalp discomfort during the procedure which can occur in a small proportion of patients.

Magnetic stimulators capitalize on the ability of time-varying magnetic fields to induce eddy currents in biologic tissue via the principal of electromagnetic induction. The magnetic stimulator stores electrical current and then discharges it in brief pulses through a stimulating coil. A magnetic field forms around the coil; with the magnetic flux lines perpendicular to the current flow. When the resultant magnetic field is applied to a conducting medium, such as nervous tissue, an electrical current is induced in that medium that results in neuronal depolarization. This technique has been used to stimulate peripheral nerves and the central nervous system and has now become a tool for clinical neurophysiology. The ability of TMS to non-invasively stimulate brain areas presents a significant advance beyond techniques that require the invasive method of direct cortical or transcranial electrical stimulation. Magnetic fields pass through scalp and skull without the impedance encountered by direct electrical stimulation, permitting enhanced control over the site and intensity of stimulation.

In numerous studies[72], single pulse TMS has been found to pose no significant health risk to properly screened healthy volunteers. Prospective studies designed to systematically evaluate

health effects have not found changes in EEG, blood pressure, heart rate, serum cortisol, serum prolactin, cerebral blood flow, memory or cognition. Single pulse TMS of the motor cortex has been used in children and infants as young as 2 weeks of age with no adverse effects reported. Single pulse TMS is now in routine clinical diagnostic use in hundreds of neurophysiological laboratories worldwide. The induced electrical current is well below that which is expected to cause harm to nervous tissue. The US FDA has concluded that stimulation at <1 Hz carries virtually no risk seizure and is therefore classified as a non-significant risk device[73].

3.0 OBJECTIVES AND HYPOTHESES

Primary objective: To assess the efficacy and cognitive adverse effects of MST compared to RUL-UB ECT in patients with depression.

Primary hypothesis/combined effectiveness endpoint: (1) MST will result in remission rates on the 24-item Hamilton Rating Scale for Depression (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 as assessed with the Autobiographical Memory Test (AMT).

Secondary objective: To assess the efficacy MST compared to RUL-UB ECT in ameliorating suicidal ideation in patients with depression.

Secondary hypothesis/effectiveness endpoint: MST will have a non-inferior remission rate on the SSI compared to RUL-UB-ECT in patients with depression.

Tertiary objective: To refine and develop candidate neurophysiological biomarker, cortical inhibition (CI), using combined transcranial magnetic stimulation and electroencephalography (TMS-EEG) that may predict response to treatment using remission of suicidal ideation as a meaningful clinical indicator.

Tertiary hypothesis/effectiveness endpoint: (1) Change in CI in the DLPFC following MST will significantly predict SSI reduction; (2) Following MST and ECT, increased complexity in course time scales derived through multi-scale entropy will be associated with change in the AMT scores in patients with depression.

4.0 SIGNIFICANCE

An alternative first-line convulsive therapy with high remission rates in severely ill patients and those with treatment resistance would be transformative for the field. Novel pharmacotherapies and other neurostimulation treatments such as rTMS only yield remission rates around 30% leaving a significant proportion of patients struggling with persistent symptoms. Yet, few accept ECT because of the negative stigma and cognitive adverse effects despite an impressive remission rate that is nearly double all other treatments for TRD. The results of this RCT could have significant impact on the treatment of depression. First, if MST demonstrates comparable efficacy to ECT, but without its cognitive adverse effects, it should be rapidly adopted into clinical practice as providers, patients and their families will likely accept this treatment. During our

open-label pilot clinical trial, patients were much more open to the idea of convulsive therapy if the cognitive adverse effects were known to be lower. Thus, the improved cognitive profile of MST will certainly lead to improved treatment acceptability. Fortunately, ECT suites can easily accommodate MST without major modifications. Reduced duration of post-treatment disorientation will substantially improve patients' experience and minimize their time in the clinic. By establishing MST as a safe and effective treatment for severe depression, this trial will advance the care of depression—a disabling illness for which there are few alternatives.

5.0 APPROACH

5.1.1 Research Design and Methods

The trial will be registered in an international clinical trial registry (clinicaltrials.gov) and results will be reported in a manner consistent with the international CONSORT guidelines. The study will involve a randomized, double blind, parallel-group clinical trial with two treatment arms conducted at three leading academic institutions in North America: CAMH, University of Texas Southwestern in Dallas, and University of California, San Diego (UCSD). Based on our power analysis (Section 5.7.1), a total of 260 participants with depression will be randomized to receive MST or RUL-UB-ECT. We plan to enroll four to five participants per month across the three study sites over 54 months.

Treatment will be administered two to three days per week. Depression symptoms will be assessed with the 24-item Hamilton Depression Rating Scale (HRSD-24) [74] and suicidality will be assessed with the Scale for Suicidal Ideation (SSI) [69]. Remission will be defined as HRSD-24 $\leq$ 10 and a > 60% decrease in scores from baseline on two consecutive ratings. Once a participant reaches remission, a second rating to confirm remission will be conducted immediately before their next scheduled treatment. If remission is confirmed, they will then be considered a completer of the acute treatment course. Remission of suicidal ideation is defined as a score of 0 on the SSI. Therefore, there will be 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 will be considered non-remitters and will cease treatment sessions. This maximum treatment number was chosen allowing for the possibility that MST may require more treatment sessions to achieve remission, similar to RUL-UB ECT [29-31]. The blind will not be broken to participants until the completion of the entire study. Following completion of the acute treatment course, participants who achieve response (defined as a 50% reduction in symptoms on the HRSD-24 from baseline) or remission will be referred to a maintenance treatment trial.

5.1.2 Subjects

Inclusion Criteria

Patients will be included if they:

(1) are inpatients or outpatients;

(2) are voluntary and competent to consent to treatment and research procedures according to ECT/MST attending psychiatrist (Section 5.1.4);

(3) have a MINI International Neuropsychiatric Interview diagnosis, Version 6 (MINI–6.0) 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 as assessed by an ECT attending psychiatrist and a consultant anesthesiologist
(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 [75];
(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.

Exclusion Criteria

Patients will be excluded if they:
(1) have a history of 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 based on study investigator assessment;
(7) have any significant neurological disorder or condition likely to be associated with increased intracranial pressure or a space occupying brain lesion, e.g., cerebral aneurysm;
(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 (e.g., hypothyroidism with low TSH, rheumatoid arthritis requiring high dose prednisone, or Cushing's disease);
(9) have an intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) 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 due to the potential of these medications to limit the efficacy of both MST and ECT;
(11) are unable to communicate in English fluently enough to complete the neuropsychological tests (Section 5.1.5);
(12) have a non-correctable clinically significant sensory impairment (i.e., cannot hear or see well enough to complete the neuropsychological tests).
These eligibility criteria are congruent with the criteria that have been used in the major ECT trials conducted during the past decade [9, 10, 76].

5.1.3 Strategies for Recruitment and Retention

Seizure therapies and human neurophysiological recordings will be conducted in the Temerty Centre for Therapeutic Brain Intervention at the Centre for Addition and Mental Health (CAMH), UT Southwestern Medical Center, and the University of California San Diego (UCSD). Subjects at

CAMH will be recruited through both the Temerty Centre and the Mood and Anxiety Division. The Temerty Centre directly receives referrals from psychiatrists across the province to assess patients with TRD. The Mood and Anxiety division is one of the largest in North America and includes over 30 psychiatrists who annually evaluate over 11 thousand patients.

To ensure we meet our recruitment goals, we have already implemented two new innovations. The first is our TRD integrated care pathway (ICP) that ensures many patients with TRD are offered brain stimulation treatments (e.g., rTMS, MST, ECT) should they be unresponsive to initial pharmacological approaches. This process outlines the indications for each of the brain stimulation modalities used in this ICP and defines successive treatment steps and criteria, thus providing a structured brain stimulation care algorithm to enhance efficiency of recruitment. The second innovative recruitment strategy is the Clinical Engagement and Research Recruitment (CLEARR) model. This strategy was approved by the CAMH Medical Advisory Committee and Research Ethics Board, and carefully screens all new referrals to the CAMH clinics and ensures that all patients are informed about clinical research at the time of their initial clinical assessment. During this initial assessment, patients are pre-identified for potential recruitment and informed about clinical research opportunities. Importantly, the World Health Organization (WHO) designated the Centre for Addiction and Mental Health as one of four international Centers of Excellence. The Temerty Centre is one of five evidence based brain stimulation centers in the world.

The Principal Investigators at all sites will monitor enrollment and retention of participants. The progress of the study, including recruitment, enrollment, retention, and management of the research team will be reviewed at weekly meetings to ensure any barriers to research participation and retention are addressed. At CAMH the CLEARR recruitment model will ensure all new clinic referrals are assessed for eligibility for the CREST-MST study, while at UT Southwestern and UCSD, Drs. Tamminga and Daskalakis will contact community psychiatrists to encourage appropriate referrals for the study. To review the conduct of the entire trial, Drs. Blumberger, Daskalakis and Tamminga will have weekly teleconference investigator meetings.

Efforts to recruit a representative and ethnically diverse sample will be made by all study sites. The Mood and Anxiety Program at CAMH services a very diverse inner city population through numerous satellite clinics in several minority neighborhoods throughout the city. Toronto is a city with diverse cultural representation as almost 75% of its population age 15 and older have direct ties to immigration. The largest of these populations have immigrated from China, India, or the Philippines. Moreover, CAMH prides itself on inclusion and diversity programs working closely with numerous community resources to provide access to patients with TRD who are often over-represented in these populations. In the present study, we anticipate the CAMH site will recruit the following ethnic distribution: White/non-Hispanic, 50%; Asian 20%, Southeast Asian 15%, Black/non-Hispanic, 10%; Hispanic, 5%. We also expect that 60 percent of our subjects enrolled at the CAMH site will be female based on our prior experience of brain stimulation clinical trials in TRD.

At UT Southwestern, efforts will include raising awareness of referring minority psychiatrists and psychiatrists treating underserved populations of the Dallas community such as the psychiatrists at Texas MHMR Metrocare Services, which serves 53,000 patients in 2015, including 11,847 with major depressive disorder (MDD), of whom 69% were from ethnic minorities (5,872 African American and 2,303 Hispanic patients) and Parkland Memorial Health which provides treatment to adult patients with any number of psychiatric disorders (including depression, bipolar disorder, schizophrenia, anxiety). They see on average about 8,500 patients a year from the Dallas community. We will provide services to psychiatrists and mental health staff to encourage appropriate referrals for the CREST-MST study. To foster trust between researchers and the underserved Dallas community, there is a plan in place to provide high quality, inclusion and diversity training to the research interviewers. The training will cover topics such as how to approach patients and introduce the study, and optimal ways to communicate about confidentiality and voluntary participation. The research interviewers will be well trained in research skills and experienced in working with ethnic minority participants. Additional outreach procedures will include the development of educational materials about the clinical trial for community physicians and the use of support groups to facilitate trial participation as a part of our alternate referral sources. These efforts will maximize the recruitment of ethnic minorities, without coercing or biasing good clinical practices. In the present study, we anticipate the UT Southwestern site will recruit the following ethnic distribution: White/non-Hispanic, 50%; Asian 20%, Southeast Asian 15%, Black/non-Hispanic, 10%; Hispanic, 5%. We also expect that 60 percent of our subjects enrolled at the UT Southwestern site will be female based on our prior experience of brain stimulation clinical trials in TRD.

With UCSD clinics located across San Diego, Outpatient Services-La Jolla, -Hillcrest and -Dove Canyon, we provide over 25,000 patient visits per year. The UCSD School of Medicine and Department of Psychiatry are also affiliated with the VA San Diego HealthCare System, which provides services, including comprehensive mental health treatment, to over 200,000 veterans in the region. Additionally, the patient population seen at UCSD is comprised of Medicare and Medicaid (Medi-cal) patients, therefore improving access to the trial for our historically underserved communities. We will provide services to psychiatrists and mental health staff to encourage appropriate referrals for the CREST-MST study. To foster trust between researchers and the underserved Dallas community, there is a plan in place to provide high quality, inclusion and diversity training to the research interviewers. The training will cover topics such as how to approach patients and introduce the study, and optimal ways to communicate about confidentiality and voluntary participation. The research interviewers will be well trained in research skills and experienced in working with ethnic minority participants. Additional outreach procedures will include the development of educational materials about the clinical trial for community physicians and the use of support groups to facilitate trial participation as a part of our alternate referral sources. These efforts will maximize the recruitment of ethnic minorities, without coercing or biasing good clinical practices. San Diego County is 33.4% Hispanic, 46.2% White, 11.9% Asian/Pacific Islander, 4.7% Black, 0.4% American Indian/Alaska Native, and 3.5% other or 2 or more races. The patient population at UCSD seen clinically for outpatient general psychiatry and brain stimulation consists of 66% White, 15.5% Mixed Race, 7.5% Asian/Pacific Islander, 5% African American, and 1% American Indian/Alaska Native, and 1% are Other. 16%

are Hispanic/Latino. Approximately 60% of the subjects will be females based on our previous research recruitment experience.

Participants will not receive compensation for choosing to participate in this study, nor will they be required to pay for any of the treatments or other procedures involved with this study.

5.1.4 Randomization and Blinding

Participants will be randomized into the study using a permuted block method with a random number generator using blocks of varying sizes. The study statistician will prepare the randomization scheme. Study personnel will be blinded to the randomization block sizes. As per our service agreement (see Section 6.4) with the Applied Health Research Centre (AHRC), they will centrally manage the randomization of participants. The unique participant ID number and treatment type (i.e. MST or RUL-UB ECT) will be assigned after the participant details have been obtained. While the treatment team administering MST or ECT cannot be blind, all participants will 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 technicians, will remain blind to treatment assignments during the entire study. Participants will be prepared for both treatment procedures and both MST and ECT machines will be on and operational in the room prior to the participant entering the suite. All additional aspects of ECT (e.g., skin prep) will be applied in MST to optimally blind the treatment condition. To maintain the blind, the treatment team will have minimal contact with the participants between sessions. To assess the integrity of blinding procedures, participants and raters will be asked to complete a conventional guess form asking them whether they believe participants received MST or RUL-UB ECT as treatment after the participant has received their first treatment.

5.1.5 Clinical and Cognitive Measures

<u>Screening and Baseline evaluation:</u>

Prior to screening, potential participants will be seen for a consultation by an ECT/MST attending psychiatrist. Capacity to consent to treatment and research procedures will be assessed and documented. Participants will be screened with the MINI V 6.0 and HRSD-24 to determine eligibility. The MINI V 6.0 assesses current and lifetime depression and other psychiatric disorders. It will be used to clarify psychiatric inclusion and exclusion criteria. Furthermore, a score of greater than or equal to 21 on the HRSD-24 will used to establish eligibility. The Transcranial Magnetic Stimulation Adult Safety Screen will be used to assess for potential MST risk factors[75]. The Antidepressant Treatment History Form (ATHF) will be used to quantify level of treatment resistance[77, 78]. Demographic information, medical history and concomitant medications information will also be collected at the screening visit. The Clinical Global Impression Scale-Severity (CGI-S)[46] and Young Mania Rating scale (YMRS) will also be completed at baseline. The schedule of assessments is depicted in Table 1 (Appendix A).

<u>Clinical Assessments During and After Treatment:</u>

Clinical outcome measures will be completed at baseline, after every three treatments (or every four treatments to facilitate treatment scheduling) 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 will be part of an exploratory analysis to study the long-term clinical and cognitive outcomes post- ECT or post-MST treatment. The HRSD-24 [74] will be the primary outcome measure. Secondary outcome measures will include the Scale for Suicidal Ideation (SSI)[69], Brief Symptom Inventory (BSI)[79], Clinical Global Impression Severity/Improvement Scale (CGI-S, CGI-I)[80], Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[81], and the Columbia ECT Subjective Side Effects Schedule[82].

Cognitive Assessments

The cognitive battery was designed to comprehensively examine cognitive dimensions that are affected by seizure therapies while minimizing burden on participants[23]. Assessments included in the cognitive battery measure global cognitive function, intellectual abilities, attention, processing speed, verbal fluency, anterograde and retrograde memory, and executive functions. Specific cognitive measures include:

(1) Test of Premorbid Function (TOPF)[83] - measures premorbid IQ - baseline only

(2) Montreal Cognitive Assessment (MoCA)[70, 84] - measures global cognitive function – baseline, end of treatment, follow-up

(3) three tests from the Delis Kaplan Executive Function System (D-KEFS)[85]: Verbal Fluency, Color-Word Interference, and Tower Test—measures executive functions including verbal fluency, inhibition, cognitive flexibility, and planning—baseline, end of treatment, follow-up

(4) California Verbal Learning Test- Third Edition (CVLT-3)[86] - measures verbal learning and memory, and effort – baseline, end of treatment, follow-up

(5) Autobiographical Memory Test (AMT)[87] - measures autobiographical memory recall and specificity – baseline, end of treatment, follow-up

(6) NIH Toolbox: Flanker Test, Picture Sequence Test, List Sorting Working Memory Test [88]—measures processing speed, attention, visuospatial memory, and working memory—baseline, end of treatment, follow-up

(7) Time to Reorientation (as used in the PRIDE Study) [89, 90] - measures reorientation time – after the first three treatments

These assessments will be completed upon participant termination of treatment, including both completion of the treatment course or withdrawal from treatment prior to completion.

The specific cognitive measures included in this battery were selected based on the need for 1) measures of global cognitive function and estimated intellectual ability in statistical models, 2) psychometrically sound cognitive measures, 3) cognitive measures with normative data and alternate forms to minimize confounding demographic and practice effects, and 4) maximizing cognitive measurement while minimizing participant burden.

5.2 Interventions

5.2.1 General Anesthesia: At all sites, treatment with MST or RUL-UB ECT will be provided by trained study psychiatrists and will follow standard protocols. Stimulation will be provided two or three times a week under general anesthesia. Anesthesiologists experienced in ECT will administer general anesthesia using methohexital or etomidate, muscle relaxation using

succinylcholine and mask ventilation with 100% oxygen. For patients with inadequate seizures with methohexital as the induction agent, as determined by the study psychiatrist, the anesthetic agent will be switched to etomidate . Monitoring of blood pressure, oxygen saturation, heart rate and EKG will be conducted throughout the course of the procedures. All medications listed above will be used at doses within labeling.

5.2.2 Determination of Seizure Threshold at the First Session: Following a standard established protocol [91], a study psychiatrist will determine the seizure threshold during the first treatment session. The seizure threshold represents the minimum energy required to achieve a generalized tonic-clonic seizure; it is determined only during the first treatment session and the energy used during subsequent sessions is based on this threshold. Glycopyrrolate IV may be used during seizure titration as subthreshold stimulations with either ECT or MST may result in a marked bradycardia or asystole [92]. Glycopyrrolate will be used at doses within labeling.

5.2.3 Medications for MST or ECT Related Side Effects: 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, 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 should be used as judiciously as possible owing to its potential to prolong reorientation times after treatment. All medications listed above will be used at doses within labeling.

5.2.4 Monitoring and Seizure Adequacy: During all sessions, the seizure quality will be monitored using fronto-mastoid electroencephalography (EEG). Congruent with published criteria, seizures will be considered adequate if they result in generalized tonic-clonic activity $\geq$ 15 seconds of motor tonic-clonic activity [76, 93, 94], which includes the duration of the stimulus[95]. The anaesthetics dosing and MST or ECT parameters will be reviewed and optimized in the event of inadequate seizures.

5.2.5 Treatment Parameters: MST treatments will be administered using the MagPro XP with a twin coil. Stimulation will be delivered over the frontal cortex at the midline position directly over the electrode FZ according to the international 10-20 system[96, 97]. The twin coil produces seizures that are comparable to those produced with ECT[8]. Frontal stimulation is an advancement over previous studies by delivering convulsive stimuli to frontal brain regions[98-100]. The MST determination of seizure threshold will be 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 (Section 5.2.5). During subsequent sessions, one stimulation will be delivered using a train duration that is 4 seconds longer than the train duration at threshold (with a maximum train duration of 10 seconds). For instance, if the threshold train duration is 4 seconds, subsequent stimulations will be delivered with a train duration of 8 seconds.

ECT treatments will be administered using the MECTA spECTrum 5000Q or the MECTA Sigma devices. The ECT determination of seizure threshold and the adjustment of energy at subsequent sessions will be based on a standard published protocol [10]. All participants will receive RUL-UB ECT at six times the seizure threshold. This approach follows the standard of previous ECT trials [9, 76].

If the patient fails to achieve an equal or greater than 25% decrease on the HRSD-24 from baseline following treatment 6, the charge will be increased by approximately 50% for ECT or increased by 200 pulses for MST. After treatment 9, if the patient fails to achieve further response, that is equal to or greater than 25% decrease from the HRSD-24 score after treatment 6, the charge will be again increased another 50% of the initial six times threshold charge for ECT or increased by 200 pulses for MST. After treatment 12, if the patient fails to achieve further response, that is equal or greater than 25% decrease from the score after treatment 9, the charge will be increased again another 50% of the six times threshold charge for ECT or increased by 200 pulses for MST. If at any point the patient is already at maximum stimulation (568.3 mC or 1000 pulses) the treatment continues with the dose unchanged.

If the seizure produced in the session is inadequate, a second stimulation will be 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 (15 sec) duration cutoffs, then the seizure is accepted for that particular treatment.

5.2.6 Adverse Event Analysis and Mitigation Plan

Convulsive therapy is an involved treatment and there are other potential side effects that we anticipate over the course of the trial. This section discusses anticipated adverse events based on a careful review of existing research literature regarding ECT and MST treatment. This review has been further supplemented by subject reports received to date.

The following adverse events 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, memory impairment (e.g., anterograde and retrograde memory loss), prolonged seizures (i.e., seizures > 120 seconds in duration), treatment emergent mania, treatment emergent anxiety and fear, laryngospasm, peripheral nerve palsies, and aspiration, wakening paralysis, IV infiltration, other complications due to anesthesia (e.g., sore throat, headache, shivering), dental injury, lip lacerations and falls.

As noted above, various measures will be implemented to mitigate the risk of side effects. Prior to treatment all MST patients receive an in-depth consultation from an ECT psychiatrist. The purpose of the consultation is to assess illness type and severity, previous treatments and outcomes, relative contraindications, discuss risks and benefits, and capacity to consent to ECT/MST. At consultation, the referring psychiatrist may direct the participant to change, reduce,

or taper off medications that may impact treatment response (ex. anticonvulsant medications) before the participant begins treatment. In addition to the psychiatric consult, all potential subjects receive a pre-MST consultation from the anesthesia service to assess suitability for general anesthesia, medical comorbidities that may impact anesthesia, discuss the risks of general anesthesia, review current medications and suggest any medication changes, and finally, conduct the informed consent for general anesthesia. During all treatment sessions, vital signs (heart rate, BP, O2 saturation, ECG, EEG) are monitored continuously. Patients undergo preoxygenation, anesthesia and muscle relaxation with accepted medications used in ECT practice, bite guard placement, and immmoblization prior to seizure induction. After EEG-confirmed seizure termination and recovery from anesthesia, patients are transferred to a recovery room once vital signs are stable and breathing.

In the event a participant experiences a side effect, several steps are taken to minimize discomfort. Additional medications for symptomatic relief of side effects will be used based on accepted medications used in convulsive therapy practice as outlined in Section 5.2.4. For example, participants reporting moderate to severe headaches during previous treatments may receive an anti-inflammatory medication prior to their next treatment as a means of preventing headaches. Similarly, a participant that experienced nausea or vomiting will be given an intravenous anti-nausea medication to ease symptoms at the next treatment. Participants are also encouraged to take Tylenol for any muscle soreness. Risks of wakening paralysis and post-ictal agitation are mitigated by giving midazolam post-treatment. This is done on a case-by-case basis after careful observation of the patient's reaction to the first treatment. Furthermore, in the event of treatment emergent mania or hypomania, the participant will be discontinued but will be offered treatment with bitemporal ECT which has been shown to act as a mood stabilizer when this occurs.

Please refer to Appendix B (CREST MST Safety Management Plan) for the safety reporting process for this trial, including the mandatory reporting to Health Canada and the U.S. FDA.

5.3 Neurophysiological Indices of Cortical Inhibition in the DLPFC

TMS-EEG will be used to evaluate neurophysiological measures from the DLPFC prior to and after a course of either ECT or MST treatment. TMS will be administered to the left DLPFC using two Magstim-200 stimulators (Magstim Company Ltd., UK) connected via a Bistim module and electrophysiological data will be collected using dedicated hardware and software (Neuroscan, Compumedics, USA). Each TMS session will include the establishment of the individual threshold for stimulation, followed by cortical inhibition paradigms in the DLPFC according to our previously published methods [63]. Identification of the DLPFC will be conducted in a manner that is identical to those during rTMS treatment. Recordings will be acquired through a 64-channel electroencephalography (EEG). Neurophysiological indices from the DLPFC (e.g., N100 and LICI) will be the dependant variables of interest and derived according to previous publications [63, 66]. Prior to study start, the teams at UT Southwestern and UCSD will set up a laboratory with the necessary equipment and materials, and will be trained on the methods of the proposed experiment. A neurophysiology expert from the Temerty Centre at CAMH will be visiting UT Southwestern and UCSD to ensure that the TMS-EEG recordings are compatible between sites.

Variability between sites is low as previous trials between CAMH and Melbourne, Australia have shown comparable measures between these three sites. Neurophysiological data will be collected and coded by experienced raters who will be blind to treatment status. Data analysis will take place at CAMH using semi-automated methods developed and validated by our group.

5.4. Resting EEG and Multi-Scale Entropy

Ten minutes of resting-state eyes closed EEG data are recorded prior to the start and after a course of ECT or MST treatment. EEG will be through a 64-channel NeuroScan EEG system. Acquired data will be imported into MATLAB (The MathWorks. Inc. Natick, MA, USA) for preprocessing. The open source signal processing functions in EEGLAB toolbox will be used for data import and preprocessing. Multi-scale entropy will be examined across all electrodes using two steps [101]: The *coarse-graining* process and the calculation of the sample entropy (*SampEn*) for each coarse-grained time series. First, for a given time series $\{x_1, x_2, \dots x_N\}$, the multiple coarse-grained time series $\left\{y_1^{(\tau)}, y_2^{(\tau)}, \dots, y_N^{(\tau)}\right\}$ at scale factor τ are calculated by averaging the data points within non-overlapping windows of increasing length τ. Each element of the coarse-grained time series $y_j^{(\tau)}$, will be calculated as $y_j^{(\tau)} = \frac{1}{\tau}\sum_{\mathrm{i}=(\mathrm{j}-1)\tau-1}^{j\tau} x_i$, where τ represents the scale factor and j $\left(1 \leq \mathrm{j} \leq \frac{N}{\tau}\right)$ represents the time index of the element. The length of each coarse-grained time series is M, where M = floor $(\frac{N}{\tau})$. Second, the degree of predictability is measured for each of the multiple coarse-grained time series $\left\{y_1^{(\tau)}, y_2^{(\tau)}, \dots, y_N^{(\tau)}\right\}$ using SampleEn. SampleEn is calculated as $\mathrm{SampleEn}(\mathrm{r}, \mathrm{m}, \mathrm{M}) = -\ln\left(C(m+1)/C(m)\right)$, where C(m) is the total number of pairs of *m* consecutive similar data points, C(m+1) is the total number of pairs of m+1 consecutive similar data points in the multiple coarse-grained time series. SampleEn quantifies the variability by estimating the predictability of amplitude patterns across a time series. Two consecutive data points will be used for data matching (m = 2) and data points will be considered to match if their absolute amplitude difference is less than 0.15% (r = 0. 15) of standard deviation of time series. Multi-scale entropy will be calculated for two 20s continuous epochs according to Farzan et al. and then averaged [102].

5.5 Discontinuation of Treatment Criteria

Participants will be discontinued from the treatment if they cannot continue the study safely based on any of the following criteria:

(1) experience worsening in depression, defined as an increase in HRSD-24 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) withdraw consent

(5) missed seizures (i.e. no induced seizure) on 2 consecutive treatment sessions despite parameter and anaesthesia optimization

(6) non-compliant with treatment schedule (i.e. miss more than two scheduled treatments)

Participants who are non-compliant with the treatment regimen or who experience two missed seizures on two consecutive occasions despite optimization of anesthesia and treatment parameters will not be discontinued from the trial, but will continue to be followed and will complete assessments to the extent possible contingent upon patient agreement consistent with an intention to treat approach.

Patients who are not able to complete the biomarker testing will be able to complete the clinical portion of the trial and will not be excluded.

5.6 Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued from the study if they meet any of the following criteria:
(1) withdraw consent
(2) the Principal Investigator believes that for safety reasons it is in the best interest of the participant to stop participation
(3) are non-compliant with study visits and assessments
(4) participant engages in serious attempt to harm others
(5) emergence of catatonia

5.7 Data Collection and Statistical Considerations

5.7.1 Power Calculations for primary hypotheses

The primary objective of this trial is to assess the efficacy and cognitive adverse effects of RUL-UB ECT and MST in patients with severe depression in a randomized, multi-centre, non-inferiority clinical trial. We will use a combined primary effectiveness endpoint: (1) MST will result in remission rates on the 24-item Hamilton Rating Scale for Depression (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. However, our sample size calculation will be based on non-inferiority trial calculations that are sufficiently large enough to minimize Type II error[103] and are consistent with previous large, multi-centre ECT trials[9]. RUL-UB ECT can achieve remission in about 50% of patients with a treatment resistant form of depression[10]. Non-inferiority trials such as this proposed 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) will yield 80% power to confirm a non-inferior difference in HRSD-24 remission rates of 15% between the two study groups. This sample size would also provide >95% power to detect a minimally important difference $\geq$ 25% (absolute risk difference) change on the AMT total score. The primary analysis will proceed once a minimum of 260 participants achieve a clinically determined adequate trial of treatment. We will define a completer as any participant who has received an adequate trial of RUL-UB-ECT or MST as per the definition used in the literature by Sackeim and colleagues [10] (i.e., 8 treatments or meet remission criteria). The overall rate of dropout in a similar past trial at CAMH was less than 3 percent in those receiving fewer than 8 treatments. As such, the sample size of 260 completers will be attainable. Testing of the cognitive outcome will only proceed if non-inferiority is established on remission. This closed testing procedure will ensure the Type I error probability for these two outcomes does not exceed 0.05.

5.7.2 Data Collection and Management

De-identified data will be stored in a clinical trial management system. Data and statistical management will be contracted to an organization with experience managing academic clinical translational trials.

5.7.3 Data and Safety Monitoring

We will engage in proactive site monitoring through the Office of Clinical Research (OCR) through the National Institutes of Mental Health (NIMH). This service will be provided prior, during and after the study to ensure that Good Clinical Practice is maintained. Representatives from the office will arrange site visits with our team.

The OCR will oversee the creation and maintenance of a data safety monitoring board (DSMB). The DSMB will be comprised of an independent group of researchers and experts based out of the NIMH. Its role will be to monitor patient safety and treatment efficacy data during the conduct of this trial. Members of the group will meet regularly, approximately every six months in order to review safety, study conduct and progress.

The main responsibilities of the NIMH DSMB include, but are not limited to the following: review of protocols, consent procedures, consent forms, and safety plans prior to initiation of the study; monitoring of the progress of the study, including recruitment and retention of participants, adverse events, serious adverse events (SAEs), reasons for participant withdrawal, adherence to the timeline of the study, quality of data, and protocol violations; making directives about the continuation, modification, or termination of the study, based on the balance of adverse events and beneficial outcomes. Throughout the study, notification of any Serious Adverse Events (SAEs) as well as any proposed investigator-initiated changes in the protocol will be submitted to the NIMH DSMB. Based on its review of the protocol, the NIMH DSMB will identify the data parameters and format of the information to be regularly reported. The NIMH DSMB may at any time request additional information from the Principal Investigators.

All SAEs and adverse events (AEs will only be reported to the NIMH DSMB annually) will be tabulated and submitted to the central and local IRBs and NIMH DSMB in the triannual DSMB data reports or at the time of continuing review, IRB review of the study, although the NIMH DSMB can determine that more frequent meetings are indicated. Based on review of safety data, the NIMH DSMB will issue directives concerning the conduct of the study. Recommendation/directives made by the DSMB may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed.

5.8 Outcome Analysis

5.8.1 Primary Outcome Analysis

Baseline variables will be summarized for each group by descriptive statistics. As per Senn et al. and Pocock et. al. [104, 105] 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, and only then, will the second stage analysis be carried out. This closed testing procedure ensures that the Type I error will not exceed the nominal alpha of 0.05.

Stage 1 Analysis

The 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 percent remission [106] and 14 percent with antidepressants [107]. The absolute risk difference (difference in proportions) will be calculated along with 90% and 95% confidence intervals, using standard normal approximations. Since intention to treat (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 analysis will be done secondarily. Inverse probability weighted methods will be employed in an attempt to attenuate the bias resulting from the improper sub-group that a PP results in. 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 and multiple imputation approaches will be employed to assess and mitigate the effect of missing data. Multiple Imputation by Chained Equations (MICE) will be used to perform the imputations and the following variables will be used in the missing data model: number of failed antidepressant trials, duration of most recent depressive episode, number of major depressive episodes, benzodiazepine use, age, and presence of the other psychiatric comorbidities, e.g. anxiety, duration of illness, not taking psychiatric medication at baseline, treatment duration, and minority racial status. The number of replications for multiple imputations will be based on the proportion of data that is missing, e.g. 10% missing implies 10 replications. For the inverse probability weighting, weights will be estimated from a logistic regression model (with binary dependent variable: dropout vs not dropout) predicting probability of dropout. In order to have a correctly specified model, most of the baseline variables collected will be included (e.g. demographic and clinical characteristics, HRSD score, SSI score, CGI score, ATHF, BSI score, presence of medical and/or psychiatric comorbidities, etc.). It is only necessary for non-inferiority to be established in the unadjusted analysis described 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. Study site will be included as well as clinical variables known to be associated with remission (see again Senn et al.[105] and Pocock et. al.[104]). 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 depressive episode, number of major depressive episodes, and benzodiazepine use (in lorazepam equivalents). The purpose of the adjusted analysis is to ensure the non-inferiority finding is consistent between an unadjusted analysis and one in which predicators of outcome are controlled for. This consistency 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.

Stage 2 Analysis

In terms of cognitive superiority, we will use the autobiographical memory test (AMT). The binary outcome is defined as a worsening of $\geq$ 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. Secondary analyses will follow a similar approach as in stage 1.

5.8.2 Secondary Outcome Analysis

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. Our sample size calculation of 260 subjects was based on non-inferiority trial calculations that are sufficient to minimize Type II error[103] and are consistent with prior NIMH sponsored ECT trials[27]. RUL-UB-ECT and MST can achieve remission in approximately 60% of TRD patients [28, 92].

5.8.3 Adverse Event Analysis

The analysis of all adverse events will include incidence tables by severity, relationship to treatment and baseline parameters. Adverse event rates will be compared between the study groups:

a. Compare average number of items endorsed on the Columbia ECT Side Effects Schedule between groups after treatment. 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.
b. Compare AE's between groups
    1. Absolute count of AE experienced during treatment course in both groups
    2. Mean headache score for treatment course
    3. Mean nausea score

4. Mean dizziness
5. Mean pain
6. Mean number of treatments with presence of post-ictal confusion or agitation
7. Mean other AE's
8. Absolute count of dropout between groups
9. Absolute count of SAE's between groups

c. Time to reorientation: 1) Compare the average number of participants between ECT and MST who achieved reorientation within a certain time frame across the first three treatments. 2) Compare the proportion of patients who achieve reorientation between the ECT and MST conditions at treatment sessions one, two, and three.

5.8.4 Tertiary Outcome Analysis: Neurophysiological Data

We will investigate the relationship between change in CI and SSI reduction by calculating the area under the receiver operating characteristic (ROC) curve (AUC) as discussed above (Section 1.3.4). ROC analysis is used in medicine to evaluate diagnostic test accuracy. The ROC involves plotting the sensitivity (true positive rate) versus 1-specificity (false positive rate). The ROC AUC predicts performance of the diagnostic test. An AUC of 1 represents perfect prediction with optimal sensitivity and specificity while 0.5 suggests that the diagnostic test is no better than chance at diagnostic prediction. For our purposes, the ROC AUC then corresponds to the change in CI that optimally distinguishes MST and ECT remitters from non-remitters (defined as a zero score on the SSI). Based on our preliminary data described above (Section 1.3.4), we will use change in CI (defined as the LICI TMS-EEG response) to distinguish MST and ECT SSI remitters from non-remitters using a ROC AUC of >0.85 on all frontal electrodes using a false detection rate correction that is applied to all frontal electrodes.

5.8.5 Multi-scale entropy analysis

For this hypothesis, we will follow the analytic methods described in section 5.4. We will investigate the relationship between complexity in course time scales derived through multi-scale entropy and change in the AMT scores in patients with depression. The ROC AUC will correspond to the level of multi-scale entropy at baseline that optimally distinguishes MST and ECT memory performance using a receiver operator area under the curve of >0.85 across all frontal electrodes.

6.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

6.1 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. All patients referred by the general physician or psychiatrist will undergo an extensive consultation with a brain stimulation psychiatrist at each study site. The brain stimulation psychiatrist will determine eligibility for referral to the randomized control trial. They will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided 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. Patients who are referred to the trial will be

seen for eligibility screening by qualified research personnel. Research personnel will also explain the trial in detail prior to obtaining consent. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to completing the initial screening visit and starting the study intervention. Once consent is obtained according to IRB and GCP/Tri-Council guidelines, the research personnel will confirm inclusion/exclusion criteria is met before proceeding with baseline testing. Patients will be informed that they can withdraw participation at any point during the study. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be 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.

6.2 Confidentiality

Procedures designed to maintain confidentially include: (1) formal training sessions for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect subjects' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual subjects. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research coordinator at the time of initial contact will represent subjects during data entry, data transfer, data analysis, or other file management procedures. To facilitate tracking, a password-protected computer file will be maintained containing the identity of subjects, their ID numbers, and information about how they can be reached. This file, however, will contain no clinical data. Only members of the investigative group will have access to secured files or to master lists for subject code numbers and will be well-informed regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project. Such procedures will follow the Institutional Review Board (IRB) policies at all study sites.

6.3 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It 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 comply with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information and FDA Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

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. During and after the study, the researchers will send deidentified information collected from participants to NDA.

6.4 Quality Assurance: Data Management Procedures

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

CAMH has established a service agreement with an academic clinical research organization, the Applied Health Research Centre (AHRC) at St. Michael's Hospital (SMH) in Toronto, Canada. Dr. Kevin Thorpe, Head of Biostatistics at AHRC, will serve as study statistician consulting on the design and implementation of our statistical plan via a collaboration agreement.

The purpose of the service agreement is to engage the services of AHRC to provide a safe and secure electronic data management system, which will facilitate the conduct of this large scale, multi-centre trial. This system is PHIPA compliant and is designed to meet the regulatory requirements of organizations such as Health Canada and the FDA. We will use software called Medidata RAVE (www.mdsol.com) to create the web-based electronic case report forms (eCRF). All study data will be securely stored on local servers at SMH throughout the duration of the study and for up to 10 years after the study is complete. All study subjects will be identified in the database by a unique study ID number. Linkages between the patient name/contact information and the study ID will be retained at the local site and not shared with the study data coordination centre (DCC) or outside the institution. At the end of the study (after all analyses are complete) the DCC will transfer all study datasets over to the study PI (and site data to site PIs.) Data will only be accessible by authorized study site personnel and authorized central DCC personnel. Authorized personnel receive a username and password which is unique, and database access is controlled by the DCC in collaboration with the PI. The SMH data centre infrastructure has several features in place to enhance the security of data, prevent data loss and mitigate downtime. These include: duplicate internet service providers (ISPs), mirror database, web and application servers, replicated firewalls, two data centres (environmentally controlled and monitored with fire retardant systems.) Several additional measures are in place for the protection of study data. These include training of all staff on the use of personal health information in research (Personal Health Information Protection Act), the ongoing creation of a set of SOPs regarding roles, access to the system, security, privacy, data management, and others. Furthermore, with the support of the Privacy Officer of SMH, the RAVE system (hardware, software, and systems and processes) successfully completed a comprehensive Threat Risk Assessment (TRA) conducted by an independent third party consulting firm, to demonstrate that appropriate technical security is in place, and that systems/processes meet current standards.

Study data can only be accessed via application by authorized users or by dedicated database administrators through the database end.

7.0 ADDITIONAL CONSIDERATIONS

7.1.1 Study Initiation Timeline

In order to ensure that the protocol milestones are met in a timely manner, the initial funded period of six months (Aug 1, 17 – Feb 1, 18) has been designated for trial set-up and organization. This includes the following:

1) Obtaining regulatory approvals from FDA in the United States and Health Canada in Canada
2) Obtaining institutional review board approvals at CAMH and UTSW
3) Preparation of electronic case report forms to facilitate data management and data collection
4) Building study SOPs and Manual of Procedures (MOPs)
5) Conducting the hiring process at CAMH and UTSW.
6) Receipt, certification and installation of the MST devices as per each institution's procedures
7) Dr. Daskalakis has a scheduled visit to UTSW in January 2018 for a review of the facility and to the meet the ECT service staff
8) Investigators' Meeting planned for January 2018 at CAMH to conduct training, review study procedures and ensure standardization across both sites
9) CAMH to send staff to UTSW for further neurophysiology training later in January, as part of the neurophysiology lab set-up
10) Site initiation visits are planned for February/March 2018
11) Addition of UCSD as a third site in March 2022
12) Proposed study start at UCSD in Summer 2022

7.1.2 Study Timeline

The study timeline is as follows:

Duration of Project Funding: August 1, 2017 – April 30, 2022
Duration of enrollment: March 1, 2018 – March 30, 2022

Projected annual enrollment at CAMH and UTSW:
August 1, 2017 – April 30, 2018 (Year 1): First six months are devoted to study start-up: August 1, 2017 – January 31, 2018. By end of year 1 (April 30, 2018), 8% of total target recruitment is expected.

May 1, 2018 – April 30, 2019 (Year 2): Enrollment to continue with 2 -3 people enrolled per site per month. By end of year 2 (April 30, 2019), 26% of total target recruitment is expected.

May 1, 2019 – April 30, 2020 (Year 3): Enrollment to continue with 3 people enrolled per site per month. By end of year 3 (April 30, 2020), 52% of total target recruitment is expected.

May 1, 2020 – April 30, 2021 (Year 4): Enrollment to continue with 3 people enrolled per site per month. By end of year 4 (April 30, 2021), 77% of total target recruitment is expected.

May 1, 2021 – April 30, 2022 (Year 5): Enrollment to continue with 3 people enrolled per site per month. By March 2022, 100% of total target recruitment is expected.

Data analysis/queries: This will be ongoing through the trial from Year 2 to Year 5.

8.0 REMOTE AND MODIFIED STUDY DELIVERY (COVID-19)

This section of the protocol details the CREST-MST study procedures and how they will be modified, including remote delivery of study assessments. This section will serve as a guide for study and site specific operating procedures. Participants and research personnel will wear appropriate PPE based on institutional guidelines at the time during any procedures that are completed in person.

8.1 Informed Consent Process

Informed consent will be collected according to institutional guidelines to ensure participant and study team safety. At CAMH, consent will be done in person with added precautions. At UTSW and UCSD, consent will be completed remotely or in person depending on current directives.

8.1.1 CAMH – Informed Consent

Participants will be consented in person by appropriately trained and qualified CAMH research personnel who do not have an existing clinical relationship with the participant. Participant informed consent will be obtained for initial and ongoing participation.

Informed consent will be obtained prior to sending teleconferencing/videoconferencing information (such as links or access information) to participants and prior to the start of any remote session.

Participants must come into the hospital for blood work/ECG and an anesthesia consult as part of the clinical process for receiving treatment and confirmation of study eligibility. The research personnel will obtain consent when the participant is onsite for one of those appointments. The participant will be sent the Informed Consent Form (via email) ahead of that appointment so that they can read it ahead of time in order to minimize contact between the research personnel and the participant.

8.1.2 UTSW – Informed Consent

Participants will be given the option of face to face informed consent (if they are already attending UTSW for an ECT consult visit), or via remote consent if they have adequate access to technology. In both instances, the informed consent discussion will be conducted as usual, although if consent is remote this will occur in a telehealth visit. The Informed Consent Form (ICF) will then be signed either in person, or using a DocuSign format, ensuring a secure consenting process which is compliant with all FDA requirements.

8.1.3 UCSD – Informed Consent

Participants will be given the option of face to face informed consent conducted at the beginning of the screening visit, or via remote consent if they have adequate access to technology. In both instances, the informed consent discussion will be conducted as usual, although if consent is remote this will occur in a telehealth visit. The Informed Consent Form (ICF) will then be signed either in person, or using a DocuSign format, ensuring a secure consenting process which is compliant with all FDA requirements. The participant will be sent the Informed Consent Form (via email) ahead of their consent appointment so that they can read it ahead of time, and to minimize contact between the research personnel and the participant in the case of in-person consenting.

8.2 Study Assessments

All assessments listed in the protocol under Section 5.1.5 will be completed remotely via telemedicine. This includes assessments administered at screening, baseline, during treatment (e.g. post Tx 3, 6, 9, 12, 15, 18), post-acute treatment and 6-month follow-up visits (see updated Table 1: Schedule of Events in Appendix A).

Videoconferencing is preferred, as some of our assessments require scoring based on behavioral observation. If the participant has no access to videoconferencing during treatment, the procedures will be completed via telephone. Screening, baseline, post-acute treatment, and 6-month follow-up will only be completed by video. Both videoconferencing and telephone calls will not be recorded, however, we will use screen capture to for the image and clock drawing in the MoCA without capturing the participants face.

Due to certain limitations around the delivery of remote data collection, there will be certain assessments that cannot be covered virtually or will require an element of modification (i.e., self-report questionnaires and the MoCA) Clinical and cognitive measures are detailed below:

8.2.1 Clinical Assessment Battery

The following clinical rater-administered assessments will be completed virtually via videoconferencing: 1) Mini-International Neuropsychiatric Interview (M.I.N.I.), 2) Hamilton Rating Scale for Depression-24 (HRSD-24), 3) Scale for Suicidal Ideation (SSI), 4) Young Mania Rating Scale (YMRS), 5) Columbia ECT Subjective Side Effects Schedule, 6) the Clinical Global Impression Scale (CGI), 7) Demographics Form, 8) Medical History Form, 9) TMS Adult Safety Screen (TASS), and 10) Antidepressant Treatment History Form (ATHF).

The following self-report questionnaires will be completed virtually via videoconferencing or telephone call: 1) Brief Symptom Inventory (BSI) and 2) Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). For self-report questionnaires, the study personnel will complete the questionnaires by either reading the questions and answers verbatim to the participant and documenting their answers, or by virtually sharing their screen so that the participant can read the questions and provide the answers.

We are able to deliver the entire clinical assessment battery remotely via video call and this will be the medium of choice. If however participants do not have access to a camera, we will offer assessments via telephone during the acute treatment phase. In the case of telephone assessments during the acute treatment phase, we are unable to complete two items on the HRSD-24 which pertain to visual assessment of psychomotor retardation and agitation (Items 8 and 9). We will therefore plan to score these items as "0", and will approach the assessments in the same fashion as the PRIDE study, which similarly used a telephone method of delivery for the HRSD-24[108, 109]. We will also be unable to assess appearance (Item 10) in the YMRS via telephone consult. We will plan to score this item as "0", and as the YMRS is not a primary outcome this will have minimal impact on overall data integrity. In addition, the clinical rater will document that all of the above items could not be assessed for tracking purposes.

There is robust evidence around the effective delivery of virtual clinical measures [110, 111], and with the oversight and training provided by our clinical assessment lead, we are confident that data integrity will not suffer due to the remote collection of these assessments. In-person and remote assessments will be included as factors in the data analysis to confirm this. Raters will receive training on both in-person and virtual assessment administration. The clinical lead will be available throughout the study to provide ongoing support as needed.

8.2.2 Cognitive Assessment Battery

The following cognitive assessments will be completed virtually via video: 1) Montreal Cognitive Assessment (MoCA), 2) Autobiographical Memory Test (AMT), 3) Delis Kaplan Executive Function System (DKEFS) Verbal Fluency Test, 4) California Verbal Learning Test-3 (CVLT-3), 5) Delis Kaplan Executive Function System (DKEFS) Color Word Interference Test, and 6) Test of Premorbid Function. In order to complete the visuospatial/executive section of the MoCA, participants will draw the image and clock on a pen and paper and show the rater via video to score them. It will be documented that this is how the score was determined. The remaining cognitive assessments, which cannot be administered virtually, will not be done. These assessments include the DKEFS Tower Test, and National Institute of Health (NIH) Toolbox Picture Sequence Memory Test, Flanker Inhibitory Control and Attention Test, and List Sorting Working Memory Tests.

There is robust evidence around the reliable and effective delivery of neurocognitive measures by virtual methods including video and telephone [112, 113], and with the oversight and training of our cognitive lead, we are confident that data integrity will not suffer due to the remote collection of these assessments. Raters will review the assessments with the cognitive lead, conduct practice sessions with them and other research staff, and review scoring with the

cognitive lead. The cognitive lead will be in communication as needed with raters across all study sites to address questions that may arise.

8.3 Risks of Virtual Assessments

Some participants may report worsening of symptoms or suicidal ideation that may pose a safety risk during virtual assessments. In addition, some participants may report adverse events that may require further investigation due to safety reasons.

In such cases, the trained study personnel will follow existing safety escalation policies by contacting the Study Investigator or delegate immediately. The Study Investigator or delegate will then contact the participant for follow-up. If a participant reports feeling unsafe due to suicidal thoughts or requires medical attention, study personnel will advise to contact 911 or go to the nearest Emergency Room. The participants address and access to necessary communications technology (i.e., landline or mobile device) will be confirmed at the beginning of the call as part of the safety protocol. If a participant unexpectedly drops off a virtual session they will be called immediately to ensure there is no safety concern. Additionally, participants will be asked to provide an emergency contact in case of an emergency or an inability to contact them after they unexpectedly drop off a virtual session.

All adverse events will be assessed and reported accordingly.

8.4 Data Integrity Risks

As we are not able to administer the full neuropsychological battery remotely, this will result in loss of data for some participants. This will be documented and taken into account when analyzing study data. Cognitive assessments will prioritize the collection of the primary outcome measures. This will ensure should there be any assessment fatigue or technological issues it will not affect the collection of primary neurocognitive outcomes (i.e. the AMT).

There is no risk to participants for not completing the remaining assessments; however, should a concern arise, the site Principal Investigator (PI) or delegate will be notified immediately and will follow-up with the participant.

8.5 Additional Research Procedures in CREST

Neurophysiology will only be offered to participants if non-essential research is deemed safe to conduct by hospital directives. If permitted, these sessions will be conducted in the safest possible manner as detailed below.

8.5.1 Neurophysiology

The TMS-EEG testing session requires close contact between the RA and participant. Added risks of being in a close contact environment for an extended period of time will be discussed with the participant at consent.

The neurophysiology lab and all equipment will be sanitized and wiped down with virox/disinfectant prior to and after each session. The participant will be screened for COVID-19

symptoms at the hospital entrance and will only be permitted to undergo the session with no symptoms. The participant will be provided with and asked to wear a face mask for the duration of the session and to sanitize their hands at the outset. The TMS-EEG technicians will wear a mask, face shield, and gloves throughout the session to protect themselves and the participant.

The session will begin with placing the cap as per usual procedures followed by a measurement of resting state EEG. During resting state, the technician will stay in the room but keep a safe distance between themselves and the participant. The technician will continue to check in with the participant throughout the session. After the resting state EEG is complete, a second TMS technician wearing PPE may enter the room to assist in the remainder of the biomarker collection. Once the session is complete, the participant will be provided with a hair cover for their commute home to minimize use of hospital facilities. The cap will be thoroughly washed and the room disinfected after each use.

8.6 Convulsive Therapy during COVID-19

A number of processes have been put in place which align with the suggestions from the International Society for ECT and Neurostimulation (ISEN) to protect staff and patients while delivering ECT as an essential service during the pandemic. We will follow local IPAC guidelines around safe delivery of ECT in the context of the COVID-19 pandemic.

8.6.1 Missed Treatments due to COVID-19

If a participant has to miss treatments because they fail the daily COVID-19 symptom screening and are not allowed to receive treatment that will not count towards having to discontinue from study treatment per section 5.5/5.6. It will be at the discretion of the investigators if a participant needs to discontinue treatment during the trial should the participant continue to fail the daily symptom screen.

8.7 Time to Reorientation

In the context of more restrictive guidelines around the safe delivery of ECT in hospital settings, it may not always be possible to obtain the time to reorientation measures for participants. This is not a primary outcome measure and will have no adverse effect on other data collected during treatment. As part of our modified procedures, this will become an optional study measure. If deemed safe according to hospital directives, this measure will be re-integrated after implementing precautions to minimize contact and mitigate risks of transmission for both patients and research personnel.

8.8 Treatment Guess Form

With the more restricted guidelines around personnel in the ECT recovery suite, it may not always be possible for blinded study personnel to administer the treatment guess form to participants directly after their first treatment. If this is the case, a blinded study team member will later follow-up the same day with the participant via phone call and administer the treatment guess form. In this situation, the team member will not complete the research team treatment guess form for themselves as they have not had in-person contact with the participant. The lack of

treatment guess completion for the blinded study team member will not have any effect on data collected in the study, however it is important to collect the treatment guess measure from the participant.

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Appendix A

Table 1. Schedule of Events

Clinical and Cognitive Assessments*	**Can be done remotely Y/N**	Screening	Baseline		Acute Phase (Weeks 1 – 7*)	Post Acute Phase	6 Month Follow-up
			V1	V2	After every 3 (or 4) treatments		
MINI	**Y**	X					
Demographics Form	**Y**	X					
Medical History Form	**Y**	X					
TASS	**Y**	X					
HRSD-24	**Y**	X			X	X	X
ATHF	**Y**		X				
SSI	**Y**		X		X	X	X
BSI	**Y**		X		X	X	X
CGI	**Y**		X (CGI-S)			X (CGI-I)	X
Q-LES-Q	**Y**		X			X	X
YMRS	**Y**		X		X	X	
Columbia ECT Side effects Schedule	**Y**		X		X	X	X
Concomitant Meds	**Y**	X	X		X	X	X
Time to Reorientation	**N**				X (After Tx 1 -3)		
TOPF	**Y**			X			
MoCA	**Y**			X		X	X
DKEFS Verbal	**Y**			X		X	X
DKEFS Color Word Interference	**Y**			X		X	X
DKEFS Tower Test	**N**			X		X	X
CVLT-3	**Y**			X		X	X
AMT	**Y**			X		X	X
NIH Toolbox: Flanker Test	**N**			X		X	X
NIH Toolbox: Picture Sequence Test	**N**			X		X	X

NIH Toolbox: Sorting Working Memory	**N**			X		X	X
TMS/EEG	**N**			X		X	
Lab Work** (bloodwork, urine screen)	**N**	X					
ECG**	**N**	X					
*This timeline is based on a participant who attends treatment three times per week. However, it is possible that it may take longer to complete the acute phase if treatment is received two times per week at any point throughout the treatment course.							
**These procedures will be ordered and completed as per standard clinical practice. The results will be available for screening purposes and will be reviewed by the study doctor and anesthesiologist prior to treatment start.							