

PROTOCOL

Open Label Study of the Efficacy, Durability, Safety and Feasibility of Intermittent Theta Burst Stimulation (iTBS) in Adolescents with Major Depressive Disorder: Effect Duration, Suicidality, and Non-Suicidal Self Injurious Behavior

NCT number NCT04485455
Document Date 12/03/2020

PROTOCOL TEMPLATE: INTERVENTIONAL STUDY

Complete Title: Open Label Study of the Efficacy, Durability, Safety and Feasibility of Intermittent Theta Burst Stimulation (iTBS) in Adolescents with Major Depressive Disorder: Effect Duration, Suicidality, and Non-Suicidal Self Injurious Behavior

Short Title: iTBS for Adolescent Depression

Drug or Device Name(s): MagVenture; Intermittent Theta Burst Stimulation

FDA IND/IDE (if applicable):

Sponsor: Center for Health Innovation

Protocol Date: December 11, 2019

Amendment 1 Date: July 16, 2020

Amendment 2 Date: December 3, 2020

Amendment 3 Date:

Amendment 4 Date:

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Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CDRS-R	Children's Depression Rating Scale Revised
CPR	Cardiopulmonary resuscitation
C-SSRS	Columbia Suicide Severity Rating Scale
cTBS	Continuous Theta Burst Stimulation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders version 5
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
iTBS	Intermittent Theta Burst Stimulation TMS
iTMS	Intermittent Transcranial Magnetic Stimulation
IRB	Institutional Review Board
MDD	Major Depressive Disorder
MMSE	Mini-Mental State Examination
NIH	National Institute of Health
NSSIB	Non-Suicidal Self Injurious Behavior
PHI	Protected Health Information
PTSD	Post-Traumatic Stress Disorder
rTMS	Repetitive Transcranial Magnetic Stimulation
SCID-5	Structured Clinical Interview for DSM-5
SITBI	Self-Injurious Thoughts and Behavior Interview
TBS	Theta Burst Stimulation
TMS	Transcranial Magnetic Stimulation
TMT	Trails Making Test
TMT-B	Trails Making Test part B
TRD	Treatment Resistant Depression
UDS	Urine Drug Screen
UNC	University of North Carolina

Protocol Synopsis

Study Title	Open Label Study of the Efficacy, Durability, Safety and Feasibility of Intermittent Theta Burst Stimulation (iTBS) in Adolescents with Major Depressive Disorder: Effect Duration, Suicidality, and Non-Suicidal Self Injurious Behavior
Funder	Center for Health Innovation Grant- UNC Health
Clinical Phase	Pilot feasibility, open label
Study Rationale	<p>MDD (Major Depressive Disorder) is prevalent in the adolescent population and is associated with significant morbidity and in extreme cases mortality. Current treatment consists of medications, psychotherapy and ECT (Electroconvulsive Therapy), each having its own potential complications and rates of efficacy.</p> <p>An alternative avenue of treatment is TMS (Transcranial Magnetic Stimulation), which has been FDA (Food and Drug Administration) approved in the treatment of adults, with evidence of efficacy and safety in adolescents. Current TMS treatments consist of a high burden of time – 37 minute daily treatments for 30 treatments. A potential solution to this is iTBS (Intermittent Theta Burst Stimulation), which cuts down the treatment time to 3 minutes per day. iTBS has been shown to be effective in adults, is non-inferior to prior FDA approved TMS protocols, and is itself FDA approved for treatment resistant MDD in adults.</p> <p>Our study proposes to investigate the efficacy, durability, safety and feasibility of feasibility of iTBS in adolescents with MDD.</p>
Study Objective(s)	<ul style="list-style-type: none"> To assess the efficacy in reducing depressive symptoms, durability of antidepressant effect, safety of treatment and feasibility of iTBS in 5 adolescents with MDD.
Test Article(s) <i>(If Applicable)</i>	Theta burst transcranial magnetic stimulation will be performed for the treatment of depression in adolescents.
Study Design	Open label, feasibility
Subject Population	Inclusion Criteria
key criteria for Inclusion and Exclusion:	<ol style="list-style-type: none"> Subjects aged 13-17 Major Depressive Disorder (MDD) or Treatment Resistant Depression (TRD) by a score of >17 on Hamilton Depression Rating Scale (HAM-D) and >40 on Children's Depression Rating Scale Revised (CDRS-R) <p>Exclusion Criteria</p> <ol style="list-style-type: none"> Subjects with metallic implants, brain injury, seizure disorder Current or lifetime history of an eating disorder, psychosis, bipolar disorder, substance abuse

	<p>3. Current inpatient psychiatric hospitalization, or current symptoms (including suicide ideation) that would require inpatient hospitalization</p> <p>4. Pregnancy for female subjects</p> <p>5. Any other condition investigators deem may interfere with study participation or safety</p>
Number Of Subjects	5
Study Duration	<p>Participation will last 17 weeks. Treatment will occur 5 days a week for 4 weeks. 3 Follow-up visits will be performed.</p> <p>Study will recruit for 1 year.</p>
Study Phases	(1) <u>Screening</u> : screening for eligibility and obtaining consent
Screening	(2) <u>Intervention</u> : subjects will receive iTBS, 5 days a week for 4 weeks
Study Treatment	(3) <u>Follow up</u> : a follow up visit will be done at 1 week, 4 weeks, and 12 weeks after the last treatment session.
Follow-Up	
Efficacy Evaluations	<p>Evaluations of CDRS-R (Children’s Depressive Rating Scale Revised) and HAM-D (Hamilton Depression rating scale) scores will be used to measure efficacy. MMSE, Trails B, list generation, Columbia Suicide Scale, semi-structured interviews for Non-suicidal Self Injurious Behavior (NSSIB), and medical review will be used to evaluate safety. Assessment of the number and per cent treatments completed and number and percent of subjects who withdraw from treatment will be used to assess feasibility</p>
Pharmacokinetic Evaluations	N/A
Safety Evaluations	<ul style="list-style-type: none"> Evaluations of CDRS-R (Children’s Depressive Rating Scale Revised) and HAM-D (Hamilton Depression rating scale) scores will be used to measure efficacy. MMSE, Trails B, list generation, Columbia Suicide Scale, semi-structured interviews for Non-suicidal Self Injurious Behavior (NSSIB), and medical review will be used to evaluate safety. Assessment of the number and per cent treatments completed and number and percent of subjects who withdraw from treatment will be used to assess feasibility <u>In addition</u>, a medical review of symptoms, vital signs, UDS (Urine Drug Screen), physical exam, and applicable pregnancy test, regular assessment of adverse events and change in pregnancy status will be obtained.
Statistical And Analytic Plan	<p>This is a pilot feasibility study, and it will not be powered to show significance.</p> <ul style="list-style-type: none"> We will compare pre- and post-treatment measures of depression in all subjects with repeated ANOVA measures Cognitive scales and safety assessments Descriptive statistics Pearson’s r coefficient for correlation between Non-suicidal Self Injurious Behavior (NSSIB), depression, and suicidality changes

throughout the study.

- *The study may provide important preliminary data for NIH R01 applications.*

**Data And Safety
Monitoring Plan**

PI is responsible for data quality management and ongoing assessment of safety

1.0 BACKGROUND AND RATIONALE

1.1 Introduction

Major depression disorder (MDD) in adolescents is a very common neuropsychiatric disorder. [1] Left untreated, adolescent MDD can severely affect relationships, the ability to participate in extracurricular activities, academics, as well as social functioning.[1,2] In adolescents with MDD left untreated, the condition can affect the cognitive and emotional trajectory towards adulthood. In the worst-case scenario, adolescent MDD can lead to suicide. [1,2]

Current psychiatric treatment options for adolescent MDD include psychotherapy, medications and ECT. [3] While effective, there are limitations for those requiring more rapid stabilization or with limited access to trained therapists in their community. Psychotropic medications for adolescent MDD are typically offered as first line treatment for teens with severe symptoms. [3] Side effects and concern about increased suicidality limit the acceptance of medication by teens and their parents. ECT is effective; however, it is associated with significant adverse effects (anesthesia complications, memory deficits, and headache, nausea and vomiting, memory deficits). The effect of ECT on the developing adolescent brain is unknown, rendering ECT a less desirable treatment choice in this population. [4a] Close to 30-40% of adolescents do not respond to the first round of accepted treatment strategies including antidepressants and psychotherapy. [4b] Of these patients, only half will then respond to a second treatment strategy, including a change in antidepressant. [5] Those that do not respond to two standard treatment regimens may be considered as having “Treatment Resistant Depression (TRD)” [5].

Transcranial Magnetic Stimulation (TMS) is an effective [6-8] and FDA approved treatment for MDD in adults. However, a newer form of TMS — Intermittent Theta burst stimulation (iTBS) — has been developed [9, 10] and was recently FDA approved for MDD in adults [11] after it was shown to be non-inferior to conventional TMS in adults. iTBS sessions are much shorter in duration (3 minutes) than conventional TMS (37 minutes). The brevity of iTBS may allow for increased capacity, decreased cost, decreased treatment burden, and more accessibility of TMS for patients with MDD. [11] There is evidence that conventional TMS is safe and effective in adolescents. [12] Only a very small number of adolescents in just a few studies have been treated with iTBS. [13] Preliminary findings suggest safety and efficacy. [13,14]

It follows that determining whether Intermittent Theta Burst TMS is safe and effective in adolescents is an important question to answer. An open label, uncontrolled trial for the use of iTBS in 5 adolescents from age 13 to <18 with MDD will be performed, based on the relatively novel nature and the current availability of resources.

The rationale behind managing MDD in adolescents with a treatment modality used in adults may be explained by the significant symptoms overlap. The clinical presentation of MDD is similar in adolescents and adults save a few general differences. Both are marked by a low mood or loss of interest in enjoyable activities (anhedonia), along with a number of associated symptoms including a disruption of sleep and appetite, low energy, feelings of guilt, trouble with concentration, and at times suicide ideation. Differences found in the literature include a greater tendency for adolescents who are depressed to have so-called vegetative

symptoms (weight and appetite changes); while in adults, there is a greater tendency to have more concentration problems and anhedonia. [15] Diagnostic criteria also does not show difference between adolescents and adults for Major Depressive Disorder according to the current Diagnostic and Statistical Manual for Mental Disorders (DSM-V) except for clarification that in adolescents irritability can be present instead of or in addition to low mood. [16] Although there may be differences between the etiology of adolescent and adult MDD [15], there is precedence for managing adolescent MDD and adult MDD with similar modalities – various antidepressants such as fluoxetine or sertraline were initially studied in adults and later were studied and FDA approved in adolescents. Indeed, many of the practice parameters for managing adolescent MDD are based on the few large studies in adolescents, but also on adult studies and practical experience. [17]

Adolescence itself is a dynamic period both physiologically and psychologically. Around the start of puberty, there will start to be an increase in myelination in the brain, neural circuitry development, changes in the architecture of the gray and white matter in various regions of the brain, in addition to hormonal and neurotransmitter changes. [18] The onset of puberty depends on various factors including hereditary and environmental factors. [18] There are no differences in the DSM-V diagnostic criteria for MDD between the various stages of puberty, or between the various ages of adolescence. Fluoxetine has been FDA approved for pediatric MDD from age 8 to 17. [19] It is the authors' opinion that a study focusing on age 13 to 17 may serve to keep consistent the psychosocial factors of being in high school.

Although iTBS is FDA approved for TRD in adults, we will not focus exclusively on adolescents with TRD in this study, although they will be included. Optimization of two separate treatment strategies can take up to 3-4 months each, which will lead to prolonged suffering and may worsen the depression. The availability of an alternate and potentially effective treatment method may be welcomed by families. Some adolescents with MDD that are seen in our clinic cannot take part in routine treatment strategies due to logistic or financial reasons or due to the unavailability of resources – it is the goal of the investigators to not be biased against including these patients in the study. Due to the available resources for this study, the relative scarcity of adolescents with TRD may prolong recruitment. As a pilot study, the goal is to eventually perform a larger study, where exploring iTBS' place in the treatment algorithm for adolescents with MDD would be more appropriate.

1.2 Name and Description of Investigational Product or Intervention

TMS is currently an FDA approved treatment for MDD in adults who currently are in a depressive episode and have not responded to, or are unable to tolerate at least two medication trials. [20] Multiple devices have been approved by the FDA to provide TMS for MDD. [21] It is thus the aim of the researchers to study the treatment modality, and not the machine. The specific machine that we will be using is from MagVenture, and the specific model is the MagPro. The MagVenture machine that we intend to use is currently being used in our outpatient clinic to provide treatment. This machine has the capability to provide iTBS. The researchers that will be providing the TMS treatment have been trained in the use of this machine, and have logged multiple patient hours with this specific machine.

TMS treatment for MDD consists of delivering non-invasive, magnetic stimulation to the left prefrontal cortex, where it induces an electrical current, which in turn affects neuronal activity. [22] Repetitive stimulation

patterns of the prefrontal cortex at 10Hz for 40 minutes a day, five days a week, for 4-6 weeks, has been shown to improve depressive symptoms. [20] Theta Burst Stimulation (TBS) is a newer form of TMS. Instead of providing 10HZ stimulation, its stimulation pattern mimics endogenous brain theta rhythms. Studies of this form of stimulation have revealed improved induction of synaptic long-term potentiation, and have shown a benefit over placebo for treating MDD in adults, and have also been shown to be non-inferior to 10Hz TMS for the treatment of MDD in adults. [11]

A non-significant risk determination has been made and a request for this to be reviewed will be sent to the local IRB (Institutional Review Board). A device description will also be sent to the IRB for review. iTBS has also been FDA approved for adults.

iTMS (Intermittent Transcranial Magnetic Stimulation) (sec 12.2) and iTBS (the subject of this investigation) are interchangeable. rTMS (Repetitive transcranial magnetic stimulation) – is a general term that describes how a pulsed magnetic field is applied repeatedly, resulting in an electric current in the cerebral cortex. A TMS device uses a computer to drive an electromagnet to deliver a pulsed magnet field pattern known as the TMS protocol. The first TMS protocol that was FDA approved in 2008 delivered magnetic pulses at 10 cycles per second for 4 seconds followed by 26 seconds rest, repeated 75 times for a total of 3000 pulses delivered over 37.5 minutes. Theta burst stimulation (TBS) describes a new and different TMS protocol recently approved by the FDA in 2019. Theta burst TMS applies stimulation that resembles the endogenous EEG (electroencephalogram) theta rhythms observed in EEG measures of humans. Theta burst TMS protocols can be delivered continuously which is called continuous theta burst stimulation (cTBS), or intermittently which is called intermittent theta burst stimulation (iTBS). Clinical research has demonstrated that iTBS is effective for treatment of depression in adults, whereas cTBS is not effective. The efficacy data of a new iTBS was so impressive that it was FDA approved. This particular TMS protocol delivers the magnetic field in triplet bursts (three stimulations very close together at a frequency of 50 hz very quickly). The triplet bursts are repeated at a rate of 5 Hz for 2 seconds (30 pulses), followed by 8 seconds rest, repeated 20 times for a total of 600 pulses. This new FDA approved iTBS protocol is likely to be effective in adolescents with MDD.

In this study we will investigate the **efficacy and durability** of the effects of iTBS in adolescent depression (see Specific AIM 1 below) by measuring changes in clinical ratings [CDRS-R, HAM-D, and Non-suicidal Self Injurious Behavior (NSSIB) evaluations] before and after 4 weeks of treatment, as well as 12 weeks following treatment. We expect that subjects will show: improvement in symptoms over 20 iTBS sessions as measured by the Children's Depression Rating Scale Revised (CDRS-R), HAM-D and Non-suicidal Self Injurious Behavior (NSSIB) measures, and persistence of this reduction of depressive symptoms through the 12 weeks follow up period of the study. In this study, we will investigate the **safety** of the effects of iTBS in adolescent depression (see Specific Aim 2 below). We will investigate safety of the treatment regimen by assessing suicidality. We expect suicidal thoughts and behavior will reduce with iTBS treatment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) and a psychiatrist's clinical assessment. We also expect that those with NSSIB at the start of the trial will have less after iTBS treatments. We do not expect any change in cognition measured with MMSE, Trails B, and list generation. We will investigate treatment feasibility by assessing treatment completion and withdrawal (See Specific Aim 3 below). We define the feasibility of iTBS will be defined as feasible by as completion of 15/20 (75%) iTBS treatment sessions by all subjects **AND** withdrawal from treatment of no more than one of five subjects (20%) due to intolerable side effects or persistent symptoms of

MDD. Investigation of efficacy, durability, safety as well as feasibility simultaneously is essential in this preliminary study of the use of iTBS in adolescents in order to justify a larger future study.

Non-Clinical and Clinical Study Findings

Potential Risks:

Breach of Confidentiality: Like with all research, there is an unlikely but potential risk of confidentiality being broken. Due the stigma with mental health disorders, if someone were to discover a patient participated in this study, it is possible for them to face embarrassment or discrimination. However, all paper study files will be coded and kept in a locked cabinet, in a locked office, in a secure building at all times. The facility used is routinely used for clinical research as well as routine psychiatric care. Study staff will be the only ones with access to this information unless required by law. Additionally, study staff are trained on confidentiality guidelines for patient healthcare and as research subjects. In allowable circumstances, paper material that are allowed to be destroyed will be shredded by UNC (University of North Carolina) healthcare-grade shredding system. In addition, questionnaires will be done in a private office to protect their identity. Electronic files are stored securely on UNC-provided equipment and complies with all technological security requirements.

Risk of Embarrassment: It is possible that by answering questions during screening and throughout the study that a patient may feel uncomfortable or embarrassed to answer questions. Subjects will be answering these questions in a private office to protect their identity.

Risk of Pain or Discomfort: Some discomfort may temporarily occur during treatment. There may be mild and temporary scalp pain where treatment is administered, in all recorded instances of previous studies, this recovered without intervention and was mild in severity.

Risk of Seizure: This is a very low risk, but more likely to happen if the subject has a history of seizures or central nervous system disorders.

Current side effect statistics below:

iTBS is new for adolescents and kids. So far, however, safety data is extremely similar for that of adults. We looked at current safety data for iTBS used in anyone under 18 years old. The below information summarizes safety data.

- Mild side effects that are brief and resolve on their own without intervention (headaches, local discomfort, pain, tingling, dullness, scalp pain, nausea, loss of appetite, change in hearing, neck stiffness, finger twitching, fatigue, musculoskeletal problems) : 9-12.4 % of participants
- Moderate side effects (headaches, ringing in ears, neurocardiogenic syncope): 1.3%
- Serious side effects (seizures): 0% in kids treated with iTBS in studies performed so far. The risk for seizure increases if someone has central nervous system disorders or a history of epilepsy. In regular Transcranial Magnetic Stimulation (TMS), the risk is .06%

There is no known risk for increasing suicidality by using iTBS. In addition, patients who are imminently suicidal will not be allowed to participate in the study. Appropriate referrals will be made should this happen.

Potential Benefits:

Potential benefits include a reduction in depressive symptoms. This in turn can alleviate other impairments in functioning that are caused by depression; such as better sleep, appetite, socialization, school and work functioning, and overall wellness. This will be measured and tracked through HAM-D and CDRS-R assessments (more information on these assessments in section 5.2)

Additional Follow-up: Patients will continue to be seen by their regular provider and specialist, and may find benefit in working with an additional treatment team for closer follow-up.

Risk /Benefit Assessment

Due to the need to expand treatment for MDD and similarities between the risks and benefits to other treatment options currently available or other clinical studies, it has been determined that the potential benefits outweigh the potential risks.

1.5 Relevant Literature and Data

See section 5.2

2.0 STUDY OBJECTIVE

The purpose of the study is to determine the efficacy/durability, the safety, and the feasibility of iTBS in 5 adolescents with MDD.

Specific Aims.

Aim 1. Investigate the efficacy and durability of effects by estimating the magnitudes of pre-regimen vs. post-regimen longitudinal changes in CDRS-R, HAM-D, and NSSIB evaluations.

Hypothesis 1: Adolescents with MDD will show improvement in symptoms over 20 iTBS sessions as measured by the Children's Depression Rating Scale Revised (CDRS-R), HAM-D and NSSIB measures.

Hypothesis 2: Adolescents with MDD will show reduction of depressive symptoms will persists through the 12 week follow up period of the study.

Hypothesis 3: Adolescents with MDD who demonstrate NSSIB at the start of the trial will show reduction in NSSIB after iTBS treatments.

Aim 2. Investigate safety of the treatment regimen by assessing suicidality with the Columbia Suicide Severity Rating Scale (C-SSRS).

Hypothesis 1: Adolescents with MDD will show reduction in suicidal thoughts and behavior with iTBS treatment as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) and a psychiatrist's clinical assessment.

Aim 3. Investigate treatment feasibility by assessing treatment completion and withdrawal.

Hypothesis 1: iTBS will be considered feasible if: a.) 15/20 (75%) iTBS treatment sessions are completed by all subjects, and; b.) no more than one of five subjects (20%) withdraw from iTBS due to intolerable side effects or persistent symptoms of MDD.

3.0 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

Type of design: A pilot study that is an open label, feasibility study. This study will aim to reduce depressive symptoms in adolescents using iTBS and evaluating the safety of methods. This will be an uncontrolled study design.

The study phases are described below:

- **Screening/Baseline:** This will include informed consent, an Intake Assessment (including psychological assessments / questionnaires), medical review with physical exam, vitals, UDS, and pregnancy screening for a total of about 2 hours, and needed collateral. Screening will last up to 1 week prior to scheduling first treatment session in order to allow sufficient time to gather all needed medical information. The entire screening visit itself should last up to 3 hours with patient and caregiver.
- **Intervention/Treatment:** Participants will receive iTBS immediately following screening, should they be determined eligible. Treatment visits will last 20 days, Monday-Friday for approximately 10 minutes each session. Although the actual procedure takes 3 minutes, we estimate close to 5-7 minutes will be required for setting up the treatment and the equipment. Treatment will occur over a 4-week period. Once per week, additional cognitive and safety assessments will be performed. During the last the day of the treatment phase, efficacy and safety scales will be performed also. Subjects will continue to receive routine psychiatric care from their outpatient mental health team, which may consist of a psychiatrist and a therapist.

- **Follow up:** There will be 3 follow up appointments to evaluate long-term efficacy and safety at 1 week, 4 weeks, and 12 weeks since the last treatment session.
- **Unscheduled Visits:** These will be done for any safety concerns and may include any of the assessments listed above. If pregnancy is suspected, another urine pregnancy test will be performed.

3.2 Allocation to Treatment Groups and Blinding (if applicable): N/A

3.3 Study Duration, Enrollment and Number of Subjects

5 subjects are expected to enroll. The total study participation will be over the course of 16-17 weeks, including the 24 study visits. The iTBS treatment itself will last a few minutes, and additional time will be allocated for machine set-up and additional review of symptoms as needed. Once per week during the treatment phase, subjects will also have additional cognitive and safety assessments done for safety monitoring that will last approximately 1 hour.

Given that subjects will need to come in 4 consecutive weeks Monday-Friday for treatments, it is likely one patient will be treated at a time. With the need to enroll and complete all data collection within a year, minus startup time, it is feasible to enroll 5 patients. In addition, iTBS has not been used in patients younger than 16 before, and while there is no safety concern for this, it would make sense from a safety perspective to start with a smaller number of participants. The data used from this study will then be used to pursue larger grant opportunities such as R01 to enroll more subjects that will allow for statistical significance calculations.

3.4 Study Population

Inclusion Criteria:

- A score of greater than 40 on the CDRS-R and 17 on HAM-D.
- Documentation of DSM-V criteria for current MDD or TRD will be required for study entry.
- Patients may be on antidepressant medication at a stable dose or receiving psychotherapy with a licensed provider during the active phase of TMS treatment for 4 weeks.
- Ability to provide consent and take part in questionnaires and scales (i.e.: not currently intellectually disabled).
- The presence of suicidality or NSSIB are not required to enter this study. Although our secondary end-points include suicidality, and we are also exploring NSSIB, and thus this may not lead to many data, the investigators' plan is to use data from this study to justify a larger study where this can be more robustly investigated.

Exclusionary criteria:

- Past or current diagnosis of bipolar disorder, psychosis, seizures or traumatic brain injury.
- Presence of intracranial metallic implants or fragments, which is a contraindication for TMS.

- Lifetime history of (or currently present) epilepsy.
- Current diagnosis of substance abuse, eating disorder, PTSD (Post Traumatic Stress Disorder), or intellectual disability.* Nicotine use disorder will not directly preclude a potential subject from this study. Although chronic nicotine use does effect central nervous system excitability, [23] what would be more confounding to our study would be if there is a sudden change in nicotine use during the treatment phase, as this may affect the motor threshold. Inclusion will however be at the PI's discretion.
- Current imminent suicide ideation or other clinical reasons for inpatient psychiatric hospitalization.
- Currently pregnant. There is currently not adequate data from this population to ensure safety with the scope of this protocol.
- Any reason the investigator determines may cause noncompliance with study rules or is unfit for receiving treatment.
- Currently taking certain medications including antidepressants, stimulants, benzodiazepines, and antipsychotics, antiepileptic (see Appendix A).
- Any positive drug testing from a urine drug test unless medically indicated with a valid prescription.

*Those with marijuana/cannabis positive results may retest later if at that time they do not meet criteria for substance abuse at screening and agree to refrain from use for the duration of study participation. Decision to be made by Investigator discretion.

4.0 STUDY PROCEDURES

Please refer to Appendix B for Time and Event Schedule detailing when study tasks will be performed.

4.1 Screening/Baseline Visit procedures

- Informed consent and assent for study participation will be obtained from the parent/guardian and child respectively
- We will perform a clinical interview and then confirm diagnosis with MINI-KID.
- The following scales will be administered:

Diagnostic:

- A
- A SCID-5 (Structured Clinical Interview for DSM-5) interview will establish diagnosis of major depression and rule out exclusionary psychiatric disorders.

Efficacy scales to establish a baseline:

- Children's Depression Rating Scale Revised (CDRS-R), a commonly used, highly regarded and validated measure of depression as one of our primary outcome measures.
- Hamilton Depression Rating Scale (HAM-D), one of the most widely used depression rating scales in clinical care and research. This will help measure the primary outcome.

Cognitive / Safety:

- Cognitive assessments will include MMSE, Trails B and List Generation.
- Safety Assessments will include the C-SSRS, semi-structured interview for NSSIB, and a medical review of symptoms including items commonly seen in the literature. [24]
- Medical review for metallic implants, general medical history, and medication review.
- Physical exam including vital signs (temperature, respiratory rate, oxygen saturation, blood pressure, heart rate, weight).
- Neurological exam performed by a trained psychiatrist and has experience providing iTBS. It entails the neurological history for epilepsy, seizures, including febrile seizures in infancy and self-limited isolated seizures in childhood, reason, time course and dose of treatment with anti-epileptic medications, other significant neurological illness that have cause that is infectious (meningitis), metabolic (electrolyte abnormalities), genetic/inherited (syndromes like Downs or 22q deletion syndromes) that are associated with mental illness, dementia and psychosis, any significant delay in cognitive, motor or sensory development. The neurological exam looks at Cranial nerves: I, II, III, IV, V, VI, VII, VIII, IX, X, has a motor exam (strength and symmetry, upper and lower extremity muscle groups), sensory exam (fine touch, pain, temperature, and proprioception), and reflex exam. Cognitive function is also evaluated—Mini Mental Status of Folstein to include alertness, orientation, short/long-term memory, attention, concentration, fund of knowledge.
- Urine pregnancy test for females of childbearing potential
- Urine Drug Screen
- Study team will ask subjects to speak with their regular doctors and have caregivers sign release of information forms if they agree.
- Patients who sign consent for a screening will receive a unique subject ID code. It will be coded as “ERAx” where “xx” represents the number of sequential enrollment “01, 02, etc.” There will be a key that links subject’s identifying information (name, date of birth) and subject ID stored securely with other study materials, that only those with permission have access to on a need-to-know basis.

4.2 Intervention/Treatment procedures (by visits)

- On the first treatment day: Prior to initiation of iTBS administration, the physician will establish 100% of motor threshold. iTBS will then be administered starting at 100% of motor threshold, increasing to 120% of motor threshold while adjusting the coil position to minimize side effects.
- The remaining 19 iTBS treatments: These will be delivered over a four week period, with five treatments delivered weekly by a UNC rTMS-trained physician Monday through Friday.
- General information about the entire treatment phase of study that is not visit specific: Each treatment will follow the iTBS protocols established by MagVenture, Inc. and treatment will be provided at 120% of motor threshold at all 20 treatment visits.
- Patients will undergo CDRS-R, HAM-D, and cognitive assessments once weekly during the treatment phase, starting on their fifth treatment day, and each week from that time point depending on which day of the week they start treatment.
- Patients will be assessed prior to every treatment for side effects or safety-related symptoms, as well as review of concomitant medication.

- Vitals will be taken prior to every treatment administration during all 20 treatment days. Weight will be obtained once per week during the treatment phase. Per investigator discretion, weight may be obtained at additional timepoints during the treatment phase or unscheduled visits to ensure safety of the subject.
- UDS and urine pregnancy tests can be done at any time due to investigator discretion for safety purposes. Pregnancy risk assessment will be documented at every visit for females of childbearing potential.

4.3 Follow- up procedures (by visits)

- At a 1-week post treatment follow-up visit, the CDRS-R, HAM-D, cognitive and safety assessments will be completed (MMSE, List Generation, Trails B, C-SSRS, NSSIB interview). In addition, vitals including weight will be taken, a physical exam performed, and AE and concomitant therapy review will be done.
- At a 4-week post treatment follow-up visit, the CDRS-R, HAM-D, cognitive and safety assessments will be completed (MMSE, List Generation, Trails B, C-SSRS, NSSIB interview). In addition, vitals including weight will be taken, a physical exam performed, and AE and concomitant therapy review will be done.
- At a 12-week post treatment follow-up visit, the CDRS-R, HAM-D, cognitive and safety assessments will be completed (MMSE, List Generation, Trails B, C-SSRS, NSSIB interview). In addition, vitals including weight will be taken, a physical exam performed, and AE and concomitant therapy review will be done. A Patient/Caregiver satisfaction questionnaire will be done to help improve future study designs.

4.4 Unscheduled visits

Any of the assessments used above may be used for an unscheduled visit, depending on the reasons for visit and safety needs. If the participant at any time is experiencing an AE or another reason for safety concern, in which the investigator deems is probably related to the study treatment, an unscheduled visit can be scheduled for a safety review. Appropriate referrals can also be made for ongoing care should a safety concern arise that is not study related.

4.5 Concomitant Medication documentation

Concomitant psychotropic medications will be documented starting 1 month prior to screening and enrollment. In addition, this will be monitored and recorded during every visit in which participant is enrolled in the study. Non-psychotropic medications for other significant medical conditions or birth control will also be monitored. There are a wide variety of medications that can decrease the seizure threshold such as antihistamines, anticholinergics, and cephalosporins among others – there is no absolute contra-indication for TMS when taking these medications in adults. However, the decision to continue treatments will be done at every visit at the PI's discretion of clinical need and risk potential. Monitoring will be done for benzodiazepines, antidepressants, stimulants, and antipsychotics, which would preclude either initiation or continuation of the study. Please see Appendix A for more detailed information.

4.6 Rescue medication administration: N/A

4.7 Subject Completion / Withdrawal procedures

Subjects who complete the study will be reminded of the study team's contact information should they have any questions in the future. Files will be kept under lock and key in a locked office in a secure facility for the

required amount of time according to GCP (Good Clinical Practice) principles and FDA regulations. For those wishing to withdraw from the study early, a termination visit will be scheduled to ensure safety, proper follow up, review adverse effects, and medications. CDRS-R, HAM-D, all cognitive, and safety assessments will be performed for final data capture if the patient agrees.

Patients will be withdrawn by investigators if they miss 20% of planned treatments, for noncompliance, or any other issues the PI determines can cause harm to the patient.

We will not replace discontinued participants. We will use the data we have up until discontinuation.

4.8 Screen failure procedures

Subjects who screen fail will be informed immediately. A copy of their consent form will still go into their electronic medical records (EMR) through EPIC. Any other paper source documents will be stored securely with other enrolled-patient information.

4.9 Qualifications of study team

The study team has Human Subject Protection and Good Clinical Practice training. The two psychiatrists on the team have been actively providing iTBS to adults for years. Questionnaires used in the study have been used by study team members in previous work both research and non-research related. Regarding NSSIB evaluations, study team received training from the psychology department by a Ph.D. and his graduate student who have studied NSSIB for years. The main study team (study coordinator and 2 M.D.'s) have been working together on multi-phase sponsor clinical trials for several years and have been trained in consent, questionnaires, and have clinical experience in diagnosing, intervention, and safety monitoring. The psychology department has also been invested in clinical research for years. Recruitment, questionnaires, and consent will be done by two M.D. psychiatrists and study coordinator. Confirmation of diagnosis, eligibility, physical and neurological exams, study intervention, and safety monitoring will be done by the two psychiatrists.

5.0 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Safety Evaluation

- **Variables that will be abstracted from medical charts:** General medical health and stability (current), concomitant medications, medical history, and diagnosis will be used to help determine patient eligibility.
- **Baseline evaluation:** Baseline will be done at screening while eligibility is determined. SCID-5, CDRS-R, HAM-D, MMSE, Trails B, List Generation, a semi-structured interview, and C-SSRS will be used for diagnosis of depression and baseline cognitive functioning.
 - SCID-5 – This is a structured interview to evaluate psychiatric diagnosis in children and adolescents. Interrater reliability ranges from .78-1 depending on the diagnosis. [23] This is a descriptive, yes/ no, diagnostic assessment that will only be used at screening.

- UDS and urine pregnancy tests for childbearing-capable participants will be performed at screening for eligibility purposes. Investigators will only repeat these tests as a discretionary basis if there is concern for pregnancy or unauthorized drug use that can cause the participant potential harm in conjunction with study participation.

- **How measurements will be taken:** Assessments will be done by a trained study staff in a private setting to ensure patient comfort and ability to answer questions. Various questionnaires will be used to measure baseline and efficacy, as listed above in section 5.1. These will be done at screening, and the end of each treatment week (4 times total during treatment phase), and again at each of the 3 follow-ups.

- **Rating scales, tests, psychological tools, laboratory evaluations, etc.** Assessments are described in section 5.2.

- **Safety evaluations** include vitals being monitored and a physical exam. Vitals will be monitored every visit. UDS and urine pregnancy test will be done at screening and any other time the investigator deems suspicion it is necessary for safety purposes. A physical exam will be done at screening and all follow up visits. Concomitant medication tracking and AE review will be done at every visit. Attention will also be placed on any change in medications or doses. Psychiatrists will evaluate safety through medical review of symptoms at each study visit and monitor treatment sessions. Additional questionnaires for safety and cognitive evaluation once per week during the treatment phase. Please see Appendix B for detailed information.

- **Columbia-Suicide Severity Rating Scale (C-SSRS)** – C-SSRS is a tool widely used in clinical settings to assess suicidality. A large problem before the scale’s existence was a lack of uniformity among assessing suicidality. C-SSRS was created to address this measuring four different constructs. These constructs are severity of ideation, intensity of ideation, behavior subscale, and lethality subscale. C-SSRS is endorsed and recommended by multiple health and mental health related organizations. C-SSRS is an effective assessment tool for clinical and research environments. [25] This is a descriptive and yes/no assessment.

- **Cognitive assessments:**

Mini-Mental Status Exam (MMSE): MMSE is a tool used to assess cognitive function. It consists of 30 items assessing orientation to time, orientation to place, attention and calculation, registration, recall, language, repetition, and complex commands. While used primarily for assessment of dementia in older adults, MMSE is useful in assessing and screening intellectual disabilities in children and adolescents. Preliminary studies found and concluded that MMSE could be used as a tool to assess cognitive function of children ages 4 and older. [26] This is a scored assessment.

Trail Making Test Part B (TMT-B): TMT (Trails Making Test) is another tool used to assess cognitive function. The test consists of two parts. Part A consists of connecting the dots together in sequential order based on numbers (1,2,3...). Part B consists of the same idea but uses and alternates both letters and numbers (1,A,2,B,3,C...) with the goal of connecting the dots in sequential order. TMT has a number of studies that supports its effectiveness and depicts its ability to differentiate between children with achievement deficits and learning disabilities from their normally developing peers. Trails B has been found to be more sensitive to these differences than Trails A. [27] This is a scored assessment.

List Generation: This assessment determines the ability for one to recall as many items as possible in a given category. This study will utilize “animal names”, where subjects are to recall at least 14 animals with a 60 second period. This is a scored assessment.

5.2 Efficacy Evaluation

Children’s Depression Rating Scale Revised (CDRS-R) – This is one of the most commonly used assessment tools for pediatrics when identifying depression. It assesses symptom severity and can be administered filtered or unfiltered (in context of mood disorder or not). [28] It is a semi structured interview scale. 17 items are scored, with 3 of these 17 being made from observation versus verbal response [28]. This will evaluate overall wellness to determine efficacy of treatment, measuring sleep, appetite, socialization, school/work functioning, and overall wellness. This is a scaled and scored assessment and is filtered.

Hamilton Depression Rating Scale (HAM-D) – This is the most widely used tool to evaluate depression. Interrater reliability is high at 0.97-0.98. It is easily administered and measures severity of depression. It is considered the “gold standard” when assessing depression. There are 21 items to score however only the first 17 are actually totaled, each question has a scaled answer. [29] The HAM-D used in this protocol is the same tool used for routine clinical services in the Department of Psychiatry at UNC. This will also evaluate overall wellness to determine efficacy of treatment, measuring sleep, appetite, socialization, school/work functioning, and overall wellness. This is a scaled and scored assessment.

SITBI (Self-Injurious Thoughts and Behaviors Interview) short form & semi structured interview – Self-injurious thoughts and behaviors, lifetime and past month will be assessed using the Self-Injurious Thoughts and Behaviors Interview (SITBI) short form, a clinician-administered interview (3-10 min) that assesses the presence, frequency, severity, age-of-onset, and other characteristics of a broad range of self-injurious thoughts and behaviors. The SITBI has strong convergent validity, inter-rater reliability ($K = .90$), and test–retest reliability ($K = .70$). [30] It is a comprehensive assessment that is recommended for use in clinical and research settings. [30] This is a descriptive, yes/no assessment.

Other: Patient/Caregiver Satisfaction questionnaire: This is an original, brief questionnaire using scaled and open ended questions that is self-reported. This will gather information on what the participants found helpful and what could be improved for future studies. This questionnaire was created in collaboration and upon request of the funding source Center for Health Innovation.

5.3 Pharmacokinetic Evaluation: N/A

6.0 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

Differences in CDRS-R and HAM-D scores will be divided by the standard deviation for effect size (which will not be scaled for statistical significance given the sample size). Descriptive statistics and repeated ANOVA will be used to evaluate efficacy. Tolerability will be evaluated examining safety and adverse events at every study visit. Given the novelty and duration of treatment, it is more likely 5 patients will be able to participate and provide enough data for future research that is funded to expand sample size.

6.2 Secondary Endpoint

- To evaluate the reduction of suicidality in adolescents with MDD: This will be done with descriptive and repeated measures ANOVA.
- To assess durability of antidepressant effect: This will be done with descriptive and repeated measures ANOVA.
- To evaluate the change in Non-suicidal Self Injurious Behavior (NSSIB): This will be evaluated with descriptive statistics.
- Evaluation of adverse events will be performed at every visit and documented according to GCP guidelines. Appropriate follow up and referrals will be made as needed.

6.3 Statistical Methods

- **Baseline Data:** CDRS-R, HAM-D, and other cognitive and safety assessments will be used at screening to capture baseline data.
- **Efficacy Analysis:** As this is an uncontrolled study design, the investigators understand that any change in scores or observed improvement in symptoms may not be necessarily attributable to the treatment received. Thus, efficacy analysis will be described in this context. The investigators feel that a larger study would be indicated which may be sham controlled. Repeated measures ANOVA will be used to compare depression rating scores from each of the treatment weeks compared to baseline, as well as comparing scores between follow up visits and baseline and end of treatment weeks. Pearson's r coefficient will be used to determine correlation between, CSSR-S scores, and primary endpoints (CDRS-R & HAM-D). Descriptive statistics to identify if NSSIB is present since the subject's last visit at baseline, during the interventional period and follow ups, will be used. It is worth noting that use of ANOVA analysis has been recommended by a biostatistician, but due to a small sample size, longitudinal data will not have adequate statistical power. In addition, confidence intervals will be large and results will be uninformative regarding statistical power. This uncertainty may contribute to a future study sample size that is still too small for statistical power, but a larger sample size than this protocol.
- **Pharmacokinetic Analysis:** N/A
- **Safety Analysis:** Measurement of safety is a continuous process starting with screening. Medical review of symptoms occurs at every visit. In addition, should safety concerns related to study treatment occur, additional unscheduled safety visits can be performed. Additional assessments are done weekly during the 4-week treatment phase.
- **Personnel:** Study coordinator will complete data entry into RedCap system and oversee data management. The Principle Investigator will do oversight. A TraCS biostatistician (Dr. Feng-Chang Lin) will complete data analysis and computations and will work with the study team throughout the duration of study activities and completion.

- **Missing Data and Protocol Violations:** Data will be collected in multiple formats – on paper and later electronically. Paper data will include various scales and assessments. There will be two members of the investigation team during assessments and scale administration, which can assist with looking over the data. Paper documents will be labeled without any personal health information or other sensitive identifying information outside of the study team. These documents will be stored in a locked cabinet in a locked office. If there is any missing data, we will refer to the stored paper documents. If data continues to be missing, we are planning to mitigate selection bias by remarking clearly in our results and discussion that consideration must be given to this fact. Any protocol violations will be assessed by the Principal Investigator, will be submitted to the IRB, and a discussion will be had on how to proceed with the study.
- **Other:** For any missing data, rationale and documentation will be provided in the database (RedCap) and source documentation.

6.4 Sample Size and Rationale

This is a pilot study to measure the efficacy, duration, safety and feasibility iTBS in 5 adolescents with MDD. It will not be powered to show significance. The study may provide important preliminary data for NIH (National Institute of Health) R01 applications. In addition, safety and tolerability will be documented for all 5 subjects to support the expansion of recruitment for future research. The sample size was determined by several factors. This is a novel study treatment for adolescents, thus using smaller sample size will help evaluate safety and feasibility in a safe manner. In addition, realistic logistical factors were considered: there is time commitment of treatment required, our patient pool at our clinic, and realistic ability to enroll and complete the study in a year's given time. We expect to have 5-10 patients consented, accounting for potential screen failures. We also have parents calling our clinic asking for TMS/ iTBS treatment but insurance will not cover it, so we are confident we will be able to successfully recruit. All statistical estimates of population parameters will be tabulated along with corresponding confidence intervals.

6.5 Interim Analysis

No interim analysis will be planned for this study. However, should serious or significant AE's (Adverse Events) become prevalent and at investigator discretion with a causality of likely or very likely related to iTBS, the study will be stopped for safety reasons.

7.0 STUDY INTERVENTION (Device or Other Intervention)

- **Description:** Subjects will receive intermittent theta burst TMS, consisting of a 50 Hz triplet burst at 5 Hz for 2 seconds per train, with an inter-train interval of 200ms, followed by 8 seconds rest, for 600 total pulses per treatment.
- **Receipt/Storage:** The machine used for the study is routinely used for regular care at a UNC outpatient clinic and is regularly maintained and calibrated.
- **Packaging/Labeling:** N/A
- **Dosing:** Patients will be treated at 120% of resting Motor Threshold as determined by standard methods. The treatment will be provided at UNC's outpatient clinic where TMS is routinely provided. TMS Treatment will be provided daily Monday-Friday for 4 weeks, for a total of 20 sessions.
- **Drug Return/Destruction:** N/A
- **Drug Accountability:** N/A

The TMS apparatus consists of the following, the description and use of which is found in the device description.

- Treatment Coil
- Motor Threshold Coil
- TMS stimulator
- Chair with positioning arm

8.0 STUDY INTERVENTION ADMINISTRATION

Treatment compliance and Adherence: A medication review will be performed prior to each treatment administration for treatment compliance. If 20% of planned sessions are missed, contraindicated medications are used, or there is worsening or lack of benefit, investigators can remove subject from the study. A trained study clinician will do administration of treatment.

9.0 SAFETY MANAGEMENT

- **Our protocol includes multiple safety assessments, which include the MMSE, Trails B, list generation, C-SSCR. In addition, we will be performing a review of systems during each visit, which will include the common adverse effects seen in the literature as described in the side-effects section. [12,24]**
- **Hearing: All subjects will be provided ear plugs to be used during the sessions.**
- **Adverse Event/Serious Adverse Event monitoring procedures:** Serious and non-serious AE's will be monitored and documented at every visit. Additional referrals or follow up will be provided on an as-needed basis. See Appendix C for a copy of the UNC template AE log used for documentation.
- **Adverse Event/Serious Adverse Event reporting procedures:** UNC policy will be followed for reporting of serious and non-serious adverse events. If the event is unexpected and related or possibly related to treatment and serious or suggests new/ increased risk, this will be reported to the IRB. Reports of AE's will be made within 24 hours of investigators discovering the reportable event.
- **Medical Emergency procedures:** In the rare event of a medical emergency, the investigators performing iTBS are medically trained to handle the situation. In addition, the location of the study will operate in proximity to UNC emergency department, and 911 can be called for assistance. Investigators and study coordinator are Basic Life Support and CPR (Cardiopulmonary resuscitation) certified.
- **Data Safety Monitoring Plan:** Adverse events will be continuously monitored by investigators and assessed for severity, risk to benefit ratio, causality from study treatment. Study will be stopped if suspected pattern of lack of efficacy or additional risk of harm vs. benefit emerges.

10.0 DATA COLLECTION AND MANAGEMENT

10.1 Monitoring Plan: The PI will monitor response rate and adverse events reporting to the UNC IRB.

10.2 Case report forms: Data will be collected on paper source documents and stored according to GCP guidelines (more specifically listed below section 10.3). Data analysis will be performed by a biostatistician from TraCS. Data will be collected on paper source, stored in a secure closet where study staff only have access to, in a locked office, in a secure building where badges are needed to enter off-hours. This building

location is routinely used for clinical research and clinical care (Medical Wings behind the hospital). A biostatistician has been engaged and we have budgeted for TraCS services to help us with data analysis. Data will be manually entered into REDCap. Data analysis will be completed by a biostatistician.

10.3 How confidentiality will be maintained: Data will be collected on paper source and coded with a subject number. All data and confidential PHI (Protected Health Information) will be locked in a secure cabinet/ closet in a secure office in a secure building routinely used for research and clinical purposes. UNC badges and keys will be needed to access study material by study staff only and those authorized per local and federal regulation. In addition, verbal communication will be done privately behind closed doors as routine care is normally provided. EPIC secure in-basket system will also be used by study staff to communicate privately while maintaining confidentiality.

10.4 Data Quality: Source documents will outline which data to be collected and the Principle Investigator will oversee verification of data entry. Study coordinator and investigators will do metrics that can be verified in medical records (demographics). Data that is missing will have documentation as to why it is missing. Scores of assessments used will be collected and entered into the database to measure each aim. Scores will be verified by at least two study personnel.

11.0 RECRUITMENT STRATEGY

5 outpatients will be recruited through either referrals of local psychiatric clinics, including UNC's outpatient psychiatry clinic. Additionally, advertisements will be used to recruit patients who may not have routine treatment at UNC or have a provider referring them.

12.0 CONSENT PROCESS

12.1 Procedure that will be used to obtain informed consent/HIPAA authorization and assent: Parental consent, assent, and HIPAA (Health Insurance Portability and Accountability Act) authorization will be used. A consent checklist/documentation form will be used to ensure all aspects of informed consent are properly obtained.

12.2 Who will obtain consent/assent: Consent will be performed by a study member, licensed clinician experienced in iTBS treatment in order to answer all questions regarding safety, risks, and benefits of study treatment. A study coordinator will also plan to be present to document the consenting process. Paper consent, assent, and HIPAA forms will be obtained and copies will be provided to the subjects as well as placed in medical records. Original copies will be placed in the study record with subject's source documents (subject binders).

12.3 Where consent /assent process will take place: Consent and assent will take place in a private room for confidentiality purposes. The space utilized for this is routinely used for research purposes at UNC.

12.4 How investigator will assure that subjects comprehend the nature of the study, procedures, the risks and benefits: Patients and parents/guardians will be encouraged to ask any questions about the study procedures, and confirm that both parties understand requirements for participating, risks, and benefits. Participants will be reminded that participation is always voluntary and encouraged to do their own research on the topic and discuss with friends/ family as needed.

13.0 PLANS FOR PUBLICATION

We intend to publish the results as a letter to the editor in a peer reviewed medical journal.

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15.0 APPENDIX

Appendix A: PROHIBITED MEDICATION LIST

Antidepressants	Tricyclic antidepressants are not allowed 7 days prior to screening. Investigator discretion for all antidepressants
Benzodiazepines	Not allowed 7 days prior to screening
Stimulants	Investigator discretion, may need to be stopped 7 days prior to study treatment.
Antipsychotics	Investigator discretion, may need to be stopped 7 days prior to study treatment.
Antiepileptic	Not allowed if taken for Central Nervous Disorder (such as epilepsy or to lower seizure threshold).

Appendix B: TIME AND EVENT SCHEDULE

Time and Event Schedule	Screening	Weeks 1-4 Treatment*g					Follow up**		
Study tasks	V1 (1 wk period)	V2b ; V7, V12, V17	V3, V8, V13, V1813, V18	V4, V9, V14, V19	V5, V10, V15, V20	V6, V11, V16, V21	V22 ^c	V23 ^d	V24 ^d
Informed consent***	x								
CDRS-R***	x					x	x	x	x
HAM D ***	x					x	x	x	x
SCID-5***	x								
MSSE	x					x	x	x	x
Trails B	x					x	x	x	x
List Generation	x					x	x	x	x
NSSIB interview & SITBI	x					x	x	x	x
C-SSRS	x					x	x	x	x
UDS ^a	x								
Urine pregnancy test ^a	x								
Vitals (HR, RR, O ² , BP, temp, weight ^h)	x ^h	x	x	x	x	x ^h	x ^h	x ^h	x ^h
Physical exam ***	x						x	x	x
AE review ^h ***	x	x	x	x	x	x	x	x	x
Medication review ***	x	x	x	x	x	x	x	x	x
Satisfaction Questionnaire									x
Neurological exam***	x								
iTBS ^f ***		x	x	x	x	x			

Footnotes

a: Can be done anytime at investigator discretion for safety purposes, predose on any treatment day.

b: Treatment should start by the following business day, within 7 days of screening.

c: 1 week after last treatment.

d: 4 weeks after last treatment.

e: 12 weeks after last treatment.

f: First day of treatment will determine motor threshold

g: Will include change in pregnancy status (OHRE SOP 4801, re: verbal assessments for treatments w/o known teratogenic effects)

h. Weight also collected as planned timepoint – per investigator discretion can also be obtained at any time during participation

*: To be done Monday-Friday, can start any day of the week.

**: +/- 3 days

***: M.D. must be present and/or perform tasks.

APPENDIX C: ADVERSE EVENT LOG

ADVERSE EVENT Make a separate entry for:	✓ if AE meets definition of serious*	Grade / Intensity	Start Date	End Date	Relationship to study intervention	Was Action Taken? (Circle One) Yes/No	Action(s) Taken^:	Outcome:	PI Initials / Date
<ul style="list-style-type: none"> ➤ All new adverse events ➤ All AEs with increased severity ➤ All AEs with changes in study drug relationship ➤ All medical conditions present at study drug initiation which have worsened 		Asymptomatic Mild Moderate Severe			Related Possibly Not Likely Not Related			Recovered Not Recovered Recovered w/Sequelae Fatal Unknown	