Evaluating the Efficacy and Tolerability of Targeted Transcranial Magnetic Stimulation in Youth

NCT03845504

October 27, 2020

1. PURPOSE OF THE STUDY

a. Brief Summary

To evaluate the antidepressant effects of daily active iTBS in adolescents and young adults with moderate to severe depressive symptoms.

b. Objectives

The investigators hope to learn if iTBS is an effective treatment for depressive symptoms in adolescents. This is important knowledge as many adolescents are intolerant to medications or do not want to receive medications for the treatment of depression.

c. Rationale for Research in Humans

Human subjects must be used since the efficacy of the iTBS procedure is being tested in adolescent humans.

2. STUDY PROCEDURES

a. Procedures

Screening

Subjects will undergo medical, psychological and neuropsychological assessments to assure compliance with all inclusion and exclusion criteria. Eligible subjects will receive active iTBS.

TMS Treatment

All treatments and motor threshold determinations will be completed by physicians or other health care providers who have been trained to the process based on the MagVenture User Manual and certified by the department. All processes are consistent with the clinical use of the MagVenture MagPro rTMS research system.

iTBS sessions will occur approximately 2 days after the baseline session with week daily sessions delivered to left DLPFC over 6 weeks. We will start with the currently FDA approved iTBS protocol for adults. Stimulation will be administered using the MagVenture MagPro rTMS Research System at currently FDA approved parameters: 80% of the active motor threshold, 20 cycles of 10 bursts of 3 pulses at 50Hz delivered in 2 second trains with an 8 second inter-train interval. The stimulation will be applied for

3 min delivering a total of 1800 pulses/session. These stimulation sessions will occur daily (week days) for 6 weeks. Resulting in a total of 30 sessions. Motor Threshold (MT) Determination: MT Location and MT Level - The motor threshold location will be determined by visual confirmation of the location on the motor cortex that controls the abductor pollicis brevis (APB) muscle of the thumb. The resting MT level is the minimum power to produce a stimulation response 50% of the time.

Prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable or painful. During the first week of treatment only, in the event that the subject cannot tolerate the treatment at these dose parameters, dose intensity may be titrated downward to 110% of the motor threshold, with all other dose parameters remaining the same.

Heart Rate Variability (HRV)

Participants will have their HRV measured before they receive any stimulation, at the end of each stimulation week and at the end of the six week treatment course. HRV will be measured using ECG electrodes attached to the wrists and an r-wave trigger device (neuroConn, Ilmenau, Germany). HRV will be measured when viewing videos depicting negative emotions (e.g. anger, fear) and when viewing neutral stimuli.

Structural/Functional Brain MRI

Structural MRI comparisons will be acquired for subjects at the Cognitive Neuroscience Institute (CNI) on the Stanford campus. A consistent MRI technician at each study site will be requested for each of the study scans. Each subject will have a baseline scan and a post- treatment scan.

First-level models: We will use a canonical hemodynamic response function (HRF) convolved event-related model with temporal and dispersion derivatives to model the blood oxygen level dependent (BOLD) in the context of a generalized linear model. Temporal and dispersion derivatives will be treated as regressors of no interest. A region of interest (ROI) analysis will be performed using our established methods, to identify BOLD- dependent signal change in the dorsolateral prefrontal cortex, subgenual cingulate, and default mode network nodes (right, left). Beta values for each ROI will be extracted for each subject for regression analyses.

Details regarding neuroimaging:

The subjects will undergo an MRI scan of the brain that will require about 1 hour in the MRI scanner. A structural MRI scan, fMRI scan will be done using a 3T system at Stanford facilities.

During the scan, subjects will lie on the table in the magnet for approximately 30 minutes while the images are acquired. Subjects will wear earplugs to reduce the noise of the scanner. The standard of care regarding incidental findings that will be communicated to

patient is as follows: The investigators for this project are not trained to perform radiological diagnosis, and the scans performed in this study are not optimized to find abnormalities. The investigators and Stanford are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice a finding on a MRI scan that seems abnormal. When this occurs, a radiologist will be consulted as to whether the finding merits further investigation, in which case the principal investigator of the research study being conducted will contact the participant's primary care physician and inform them of the finding. The decision as to whether to proceed with further examination or treatment lies solely with the participant and his/her physician. The investigators, the consulting radiologist, and Stanford are not responsible for any examination or treatment that you undertake based upon these findings. Because the images collected in this study do not comprise a proper clinical MRI series, these images will not be made available for diagnostic purposes. In the event that a potential abnormality on the MRI images is detected by the researchers, the magnet manager, is to be notified immediately to report the potential issue. Films of images are not be provided to the researcher or volunteer scan subject as the images were obtained using a research MRI scan protocol and not from a clinically- ordered MRI scan protocol prescribed by a radiologist at Stanford.

b. Procedures to Minimize Risks

Outcome Assessments

Trained physicians and raters will administer all diagnostic assessments and clinical interviews determining study eligibility during screening. All study staff will be trained on study procedures.

Outcome screening will occur after both the Informed Assent/Consent Document and the HIPAA Authorization are signed. Baseline assessments will occur prior to the first iTBS treatment session.

The following outcome assessments will be completed: HAMD/MADRS structured interview, CDRS-R, CGI-S, and QIDS-A17-SR.

Safety Assessments

A physical and complete medical and psychiatric history will be obtained at the screening visit. Subjects will be evaluated clinically for adverse events at each visit. SAEs will be recorded as they occur and reported to the IRB within one business day of notification.

The YMRS will be completed if the interval assessment of spontaneous adverse events indicates the potential occurrence of symptoms of mania or hypomania.

c. Use of Deception in the Study

No deception will be used.

d. Use of Audio and Video Recordings

No audio or video recording to be used.

e. Alternative Procedures or Courses of Treatment

Other treatments are available for the treatment of depression, including Psychotherapy or medications (tricyclic, SSRI, SNRI, antidepressants).

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

When youth become adults, they can receive iTBS through TMS outpatient clinics throughout the peninsula.

g. Study Endpoint

The end of the study is defined as "the last visit of the last patient undergoing the study." The end of study definition is for the entire study. The study is expected to start in spring 2019 and to be completed by the end of 2020. The study may be terminated if the study procedures are not being performed according to GCP, or if recruitment is slow.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

rTMS Therapy System Mechanism of Action

The MagVenture TMS Therapy® System is a computerized electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex. Since TMS therapy produces a time varying magnetic field, its intended effect derives fundamentally from Faraday's Law, which asserts that a time-varying magnetic field produces an electrical current in an adjacent conductive substance. During TMS, the conductive substance of interest is the brain, in particular the region of the cortex that lies beneath the treatment coil.

The electric current induced in this region of the cortex travels in a path orthogonal to the direction of the alternating magnetic field with the point of maximum field strength and greatest current located directly beneath the center of the coil, which is the TMS system component that rests against the patient's head and transmits magnetic pulses to the patient's brain. The induced current is tangential to the scalp at the cortical surface, and diminishes in magnitude with increasing depth.

In the targeted area of the motor cortex, where field strength achieves the stimulation threshold, it is postulated that neuronal depolarization occurs. The peak magnetic field strength achieved with each pulse in the cortex is approximately 0.5 Tesla.

Although the mechanism of action is unknown, it is hypothesized that TMS causes direct neuronal depolarization in brain regions immediately adjacent to the magnetic coil, and

also results in changes in functional activity in areas of the brain that are synaptically connected to the brain regions experiencing direct neuronal depolarization. It is thought that these actions may cause various physiologic changes in the brain which are associated with the symptomatic relief of depression in patients.

Efficacy and Safety of TMS in Major Depression in Adult Patients

The efficacy and safety of TMS in adult patients with major depressive disorder (MDD) who failed to receive satisfactory improvement from prior antidepressant medication was established in two randomized controlled trials (O'Reardon2007; Janicak 2008; George 2010; Li et al., 2012). Clinical efficacy outcomes of the use of TMS in adult patients with major depression in real world clinical practice was demonstrated in a multisite naturalistic study in 42 US centers under conditions of general clinical use (Carpenter, 2012; Janicak2013).

A randomized controlled trial funded by the National Institute of Mental Health, evaluated the safety and efficacy of TMS using a clinical trial version of the NeuroStar TMS Therapy System in adult patients (N=197, 4 sites) with moderate to severe major depressive disorder and who failed to benefit from 1 through 4 adequate antidepressant medication trials, as defined using the Antidepressant Treatment History Form (ATHF), or who could not tolerate 3 or more antidepressant medications (George 2010). The study evaluated 197 outpatients across 4 sites, ages 21-70 years, most with a recurrent course of major depression (~97%), with the maximum duration of the current episode of depression of ≤3 years. Patients had received a median of 1.6 total prior antidepressant medications at an adequate dose and duration in the current episode or a median of 4 treatment attempts at any dose and duration. The primary outcome measure was remission using the HAMD24 (HAMD24 total score ≤3 or 2 consecutive HAMD24 total scores <10) through 6 weeks of acute treatment. A statistically significant benefit of active TMS as compared to sham treatment for the HAMD24 remission outcome (Active TMS: 13.4% vs Sham TMS: 5.0%, P=0. 0173) was observed in the ITT study population (N=197). An adjusted odds ratio of achieving remission with active TMS was 4.05 (95% confidence interval (CI), 1.28- 12.83) as compared to sham TMS. The baseline to endpoint change score outcome using the HAMD24 also favored active TMS compared to sham treatment (-2.11, 95% CI: -4.30, 0.08; P=0.0588). Baseline to endpoint outcomes for patients treated with active TMS were statistically significant as compared to sham treatment as measured using the MADRS (P=0.0136), CGI-S (P=0.0181) and the patient-rated IDS-SR (P=0.0008). For the categorical endpoints, higher rates of remission were observed for patients receiving active TMS as compared to sham treatment as measured using the MADRS (P=0.0170) and the patient-rated IDS-SR (P=0.1199), and for response (50% improvement from baseline) for all three measures (HAMD24, P=0.0104; MADRS, P=0.0063; IDS-SR, P=0.0145). Standardized effect size estimates for the continuous outcome endpoints range from 0.43 to 0.67, indicating a moderate to large effect size in this patient population.

Efficacy of TMS for the treatment of adolescent depression, for all TMS devices including the NeuroStar TMS Therapy® System, has been reported in two pilot clinical studies and in multiple case reports (Walter 2001; Bloch 2008; Wall 2011). These open-

label studies describe the treatment of 24 patients, ages 10-18. The 2011 Wall et al. open-label trial is the only study that used the NeuroStar TMS Therapy System. This study reported on the treatment of 7 antidepressant-resistant adolescents and demonstrated a robust response rate noted by 5 of 7 subjects achieving remission of depression,as rated using the Childhood Depression Rating Scale – Revised (CDRS-R). Furthermore, CDRS-R mean depression severity scores were significant by treatment 20 as compared to baseline with similar efficacy demonstrated using the patient reported Quick Inventory of Depressive Symptoms – Adolescent Version (QIDS-A17- SR). Placebo effects in open-label trials of adolescents are a well- known phenomenon. However, adolescents demonstrate enduring mood improvement for at least 6 months following their final acute treatment (session 30). Furthermore, 7 of 8 subjects completed the entire treatment course, with 1 patient exiting the study after only 5 minutes of treatment due to scalp discomfort and a perceived lack of improvement.

iTBS has been shown to be more effective at inducing antidepressant responses in adults than traditional rTMS. 3 minutes of iTBS induce equivalent antidepressant responses as 37 minutes of traditional rTMS stimulation (Blumberger et al., 2015) and lower stimulation intensities are required to induce antidepressant responses (Wu, Shahana, Huddleston, Lewis, & Gilbert, 2012).

The shorter stimulation times and the lower stimulation intensities required for iTBS in comparison to traditional rTMS make iTBS potentially advantageous method for adolescents with MDD. Traditional rTMS has been shown to be effective at reducing depressive symptoms in adolescents (Carpenter et al., 2012) but iTBS has not been trialled in adolescents with MDD. Initial trials investigating the safety of iTBS in adolescents have identified iTBS as minimal risk (Hong et al., 2015; Wu et al., 2012).

It is clear that the dorsolateral prefrontal cortex is heavily implicated in the pathophysiology of depression. The left DLPFC is hypoactive in depressed patients and is associated with negative emotional judgment (Grimm et al., 2008). Additionally, the DLPFC is a component of the cognitive control network (CCN) and the modulation of this node appears to modulate the CCN. At least four groups have performed iTBS to the DLPFC in adults and have seen antidepressant effects (Chung et al., 2015; Desmyter et al., 2016; Duprat et al., 2016).

Safety of TMS in adolescent depression:

rTMS and iTBS have been well tolerated in pediatric populations, with reports of mild adverse events that bear only minimal risk to children. Risk from stimulation protocols (e.g. high frequency TMS and theta-burst) in children has been deemed to be similar to that in adults.

b. Findings from Past Animal Experiments

N/A

4. RADIOISOTOPES OR RADIATION MACHINES

N/A

5. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	TMS Magnet (MagVenture)
Description:	Transcranial Magnetic Stimulation
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	Device within FDA specified parameters (iTBS).

b. IDE-Exempt Devices

N/A

6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

N/A

7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

N/A

8. PARTICIPANT POPULATION

a. Planned Enrollment

A total of 30 subjects are expected to enroll at Stanford. All subjects will have single or recurrent depression of moderate or greater symptom severity.

b. Age, Gender, and Ethnic Background

Male and Female Outpatients between the ages of 12-21 yo of any ethnic background will be recruited.

c. Vulnerable Populations

All of the subjects enrolled into this trial are adolescents per the FDA definition. The TMS treatment is being investigated for efficacy and safety in the adolescent population that experiences major depression. TMS is currently FDA approved for the treatment of MDD in adults.

d. Rationale for Exclusion of Certain Populations

Women, minorities, non-English speaking individuals, or children are included in enrollment.

e. Stanford Populations

Stanford laboratory personnel, employees, and/or students will not be specifically sought, they will also not be excluded from participation.

f. Healthy Volunteers

No healthy volunteers.

g. Recruitment Details

We anticipate a majority of the recruitment will also come from the outpatient child psychiatry clinic.

Several resources will be utilized for recruitment of potential subjects including:
from within the clinical and referral practices of the clinical study site

- referrals from other care providers within the treatment communities
- radio advertisements
- invitation letters sent to parents of potentially eligible subjects
- print advertisements, including but not limited to brochures, flyers, Craig's List, and listings in research classifieds
- trial listing with ClinicalTrials.gov
- trial listing on university and clinical study site website
- social media

We will also begin utilizing the Stanford Research Registry (protocol 25422) to recruit 30 study participants. The research registry is a list of individuals who have consented to be contacted by researchers at Stanford and at present includes over 1,000 volunteers.

h. Eligibility Criteria

i. Inclusion Criteria

1) Ages 12-21 years of age;
2) with at least moderate to severe depressive symptoms confirmed by the Children's Depression Rating Scale-Revised (CDRS-R>40);
3) able to commit to protocol schedule and provide Informed consent by a legal guardian and assent by a youth participant;
4) have had at least one prior antidepressant treatment failure with adequate dose and duration.
5) Display low heart rate variability (HRV) at baseline

ii. Exclusion Criteria

1) No prior neurological diagnosis (neurodevelopmental disorders, strokes/traumatic brain injuries, brain tumor, epilepsy);
    - Antecedent seizures
    - Any condition likely to be associated with increased intracranial pressure
    - Space occupying brain lesion
    - of cerebrovascular accident

- Transient ischemic attack within 2 years
- Cerebral aneurysm
- Dementia
- Brain surgery
- Head trauma with loss of consciousness for >5 minutes
- History of stroke
- History and/or family history of epilepsy

2) No contraindications for TMS or MRI e.g. have any implanted metal;
3) Unstable medical conditions

    - Hematological or infectious (e.g., human immunodeficiency virus-HIV) disorders.
    - History of autoimmune, endocrine, viral, or vascular disorder
    - Unstable cardiac disease, uncontrolled hypertension, or sleep apnea
    - Current anticoagulant, immune suppressive, and/or chemotherapy or those who have received any of these therapies within 3 months before enrollment in the study.

4) Acute suicide risk as defined by the investigator
5) Pregnancy, suspected pregnancy or not on birth control if sexually active;
6) Inability to locate and quantify a motor threshold; and
7) Any factor that the PI determines to be reason for exclusion.

i. Screening Procedures

Following the informed consent process, enrolled subjects will begin the study eligibility screening process. Verification of inclusion and exclusion will be completed by the study physician to ensure that the subject is eligible for the study and that it is safe for them to participate.

j. Participation in Multiple Protocols

The consent form clearly asks patients if they are participating in any other research studies. The PI and/or research coordinator will also ask the patient. If patients are currently participating in another protocol, the PI will determine if it is appropriate to continue the participation.

k. Payments to Participants

Participants will be paid $50.00 per MRI scan.

l. Costs to Participants

All procedures are covered by the study. There may be additional costs incurred for the personal time it will take for participants to come to study appointments.

m. Planned Duration of the Study

The estimated duration of the entire study is two years. Screening a participant may take 4-6 hours, and active participation would involve daily iTBS treatments for 6 weeks. Analyses of participant data may take up to 2-3 years.

9. RISKS

a. Potential Risks

i. Investigational devices

Anticipated Risks

Seizures

Repetitive transcranial magnetic stimulation is generally regarded as safe and without any serious or lasting adverse effects (Wasserman 1998; Rossi 2009). Inadvertent induction of a seizure is the most medically significant potential safety concern. However, there is no known risk of seizure for the above-stated brain stimulation parameters. The motor threshold is reflective of stimulation output necessary to cause neuronal depolarization. Since its first use in 2005, only one case of TBS has resulted in seizure, which occurred for stimulation at >100% resting MT (120% of aMT) and this was continuous TBS not iTBS. This proposed protocol involves iTBS delivered at 80% motor threshold. Finally, the proposed stimulation parameters mirror those used in Stanford IRB-approved iTBS protocols (Protocol Director Williams N; ID 33797, ID 38138), which have received a "minimal risk" designation.
Studies evaluating the safety of iTBS in adolescents have shown it to be minimal risk (Hong et al., 2015; Wu et al., 2012).

Safety Monitoring for Potential Seizure Risk

Safety monitoring for the potential risk of seizure is addressed in several ways in this protocol. All subjects will be assessed during the screening phase for neurologic disease, concurrent medication use, or other clinical factors that may contribute to the risk of seizure. The Transcranial Magnetic Stimulation Adult Safety Screen (TASS) will be used as a screening tool to assure rigorous review of these clinical factors. Stimulation parameters have been selected to optimize the likelihood of clinical efficacy, while maintaining a safety level within the guidelines consistent with the 1998 NINDS workshop recommendations (Wasserman 1998).
All clinical personnel involved in the motor threshold determinations and the iTBS treatment sessions will be familiar with the ISTS Consensus Statement on Managing the Risks of Repetitive Transcranial Magnetic Stimulation, with specific attention to the requirements of medical supervision and first-responder capability in the event of a seizure as outlined in that document. Specifically, all personnel will be familiar with the procedures for subject screening for risk factors prior to treatment, individual risks and potential benefits for specific subjects, appropriate discussion of the risks and potential benefits of study participation as outlined in the informed consent document, the stimulation parameters to be used in this study, monitoring subjects for the potential development of seizures by continuous visual inspection during the course of each treatment session (especially the more subtle signs and symptoms of frontal lobe seizures), and first responder management in the event of a seizure. We will have immediate (i.e., within minutes) availability of more sophisticated medical support, including access to an emergency room, in the event that a seizure is not a self-limited

event, access to antiepileptic medications, and to life support equipment including oxygen, suction, blood pressure monitoring and cardiopulmonary (CPR) equipment.

As stated above, for all subjects who may experience a seizure during the study, the Investigator will provide a letter documenting that the seizure was experimentally produced.

If a seizure occurs during the study, that subject will be discontinued from the study.

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents or chemicals

N/A

iv. Procedures

Structural/Functional Head MRI

As this study only involves MR scans, the risk is assessed as minimal. No contrast material or exposure to ionizing radiation will occur for the conduct of this protocol.

To minimize any potential risks from the scans, the physician will ensure that the subject does not meet any contradictions for an MRI. Subjects who are uncomfortable in enclosed places (claustrophobic) may experience some discomfort. The MRI staff will be in contact with subjects at all times throughout the scanning process, and if necessary the scan can be stopped at any time. The total scanning time will be approximately 60 minutes per scanning session.

Participants may have tattoos or piercings that are magnetic. Because of the electromagnetic pulse, these might feel warm or hot during the treatment.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

The risks to physical well being include those listed above for study intervention (iTBS) and MRI.

vii. Psychological well-being

While completing the self report assessments and the clinical assessments, patients may become upset or frustration may occur.

Participants may not experience an improvement in mood or their mood may worsen over the course of the study.

Patients may find the study visits to be inconvenient.

viii. Economic well-being

The cost of patient's time for attending the study visits may be an economic difficulty.

ix. Social well-being

No risk to social well-being is anticipated.

x. Overall evaluation of risk

Medium

b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

Management plan for treatment-emergent mania, exacerbation of depression, and/or suicidality

During the consent process, subjects and families will be educated about the possibility of significant changes in mood, suicidal thinking, and/or behaviors during the treatment. These changes could include emergence of mania, worsening of depression, and/or suicidal thinking and behaviors. Both the subject and parent(s) will be told to initiate contact with their study doctor, if they experience any significant mood or behavior changes including suicidal ideation. Principal Investigator contact information is included in the consent/assent document. Furthermore, during the protocol, subjects will have assessments weekly where changes of psychological symptoms will be queried. Ongoing monitoring for worsening of depression and emergence of suicidal ideation and/or behaviors will be evaluated using the HAMD, C-SSRS, and CGI-S.

Suspected treatment-induced mania will be evaluated using the Young Mania Rating Scale (YMRS). A YMRS score of ≥ 20 will prompt administration of the M.I.N.I./M.I.N.I. KID to determine whether or not the subject meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for mania. A YMRS score of 20 or greater will be considered an adverse event (AE) and will be monitored using the YMRS; the emergence of DSM-5 verified mania will be treated as a serious adverse event (SAE) and will also be monitored using the YMRS.

Exacerbation of depression, suicidality or induction of mania would constitute an SAE and the subject would be discontinued from the study. Subject would then be referred for clinical follow-up outside of the study.

Treatment plan for other side effects of iTBS experienced during treatment: Repositioning of coil and prophylactic use of acetaminophen or ibuprofen will be allowed for subjects reporting sensations at or near the stimulation site which are uncomfortable or painful. During the first week of treatment only.

Treatment plan for other potential side effects experienced following treatment:

Subjects reporting headaches during or following study treatment will be encouraged to take acetaminophen or ibuprofen prior to the daily treatment. To reduce the risk of temporary or permanent hearing loss due to noise emitted from the stimulator, subjects will wear protective ear plugs during treatment. All subjects will be monitored, and appropriate treatment will be recommended including the possibility of stopping iTBS. Any other potential side effects will be managed symptomatically with treatment(s) deemed appropriate by the study site Principal Investigator. All symptomatic interventions will be recorded in the subject's case file and, if applicable, adverse event CRF.

d. Study Conclusion

Subjects may withdraw voluntarily from the study at any time. They may be withdrawn from the study by the Investigator if a subject:

- experiences a seizure,
- experiences a DSM-5-confirmed treatment-induced mania,
- is non-compliant with study procedures

The Investigator may also withdraw a subject if he/she believes that for safety reasons it is in the best interest of the subject to be withdrawn.

Discontinuation information [e.g., date and the reason(s) for discontinuation] must be recorded in the subject's CRF (i.e., Study Completion Form). Subjects who discontinue prematurely should complete the final assessments within 2 days following their last iTBS treatment session.

Subjects withdrawn from the study due to an AE will be followed up for 30 days or until resolution.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

The IRB has oversight for the overall safety of the study. Safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

ii. Person(s) responsible for Data and Safety Monitoring

The protocol director will be responsible for data and safety monitoring for this pilot study.

iii. Safety Reporting

Any SAE, regardless of causal relationship, will be reported immediately to the IRB (within one business day). Compliance with this time requirement is essential so that the IRB may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the IRB after the information is received by the Investigator by faxing a completed serious adverse event form to the fax telephone number listed in Section 1.2 of this protocol and confirming by telephone that the fax was received. The subject should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

iv. Specific triggers or stopping rules

Specific occasions when study treatment may be stopped are explained Section 8.4 in the discussion of Anticipated Risks.
Because of the anticipated low level of adverse events of iTBS, the PD will be charged with reviewing adverse events at least every six months. Serious adverse events will be reviewed on a monthly basis, unless a more urgent review is requested.

v. DSMB Reporting

The outcome of the review will be disseminated to the investigators as appropriate.

vi. Will a board, committee, or safety monitor be responsible for study monitoring?

Yes

f. Risks to Special Populations

iTBS may be a beneficial treatment for adolescents that have not responded well to medication. The risks of iTBS are less great than alternative approaches such as ECT.
All parents or LAR will sign consent for adolescents bw 12-17 yo inclusive. All adolescents bw 12-17yo will also sign assent. These consent and assent procedures are applicable for both the parent and the MRI portion of the study.

10. BENEFITS

It is possible that depression symptoms will improve while receiving the study iTBS.

The study may also benefit other people with MDD by furthering our understanding of the antidepressant effectiveness and safety of iTBS in adolescents and young adults.

11. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.