A Randomized, Double-Blinded, Sham-Controlled Trial of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents

NCT01804296

October 10, 2014

A Randomized, Double-Blinded, Sham-Controlled Trial of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents

Regulatory Sponsor and Principal Investigator (Mayo Clinic Site)	Dr. Paul E. Croarkin Assistant Professor of Psychiatry Child and Adolescent Psychiatry Mayo Clinic 200 First Street SW Rochester, MN 55905
Principal Investigator (South Carolina Site)	Dr. Mark S. George Distinguished University Professor Director, Brain Stimulation Laboratory MUSC Director, SC Brain Imaging Center of Excellence Medical University of South Carolina 67 President Street, RM 502N Charleston, SC 29425

Funding Sponsor:	Paul and Betty Woolls Foundation Mayo Clinic - Department of Psychiatry and Psychology University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine, Department of Psychiatry In-kind support from Neuronetics, Inc.
Study Product:	NeuroStar® TMS System in XPLOR® research configuration
Protocol Number: (IRB)	Mayo Clinic IRB# [redacted] MUSC IRB# [redacted]

Initial version: May 10, 2012 Version **(1)**
Revision: August 17, 2012 Version **(2)**
Revision: September 4, 2012 Version **(3)**
Revision: April 8, 2013 Version **(4)**
Revision: July 30, 2013 Version **(5)**
Revision: November 14, 2013 Version **(6)**
Revision: May 16, 2014 Version **(7)**
Revision: October 10, 2014 Version **(8)**

Table of Contents

List of Abbreviations

1H-MRS	Proton Magnetic Resonance Spectroscopy
3T	3 Tesla
AC	Anterior Cingulate
AE	Adverse Event/Adverse Experience
AMI	Autobiographical Memory Interview
CAVLT-2	Children's Auditory Verbal Learning Test version 2
CDRS-R	Childhood Depression Rating Scale – Revised
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CRF	Case Report Form
CRU	Clinical Research Unit
CSF	Cerebrospinal Fluid
C-SSRS	Columbia – Suicide Severity Rating Scale
C-VAS	Computerized Visual Analog Scale
D-KEFS	Delis-Kaplan Executive Function Scale
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECT	Electroconvulsive Therapy
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSR	Health Sciences Research
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intention-to-Treat
K-SADS	Schedule for Affective Disorders and Schizophrenia for School Aged Children – Affective Disorders Supplement
L-DLPFC	Left Dorsolateral Prefrontal Cortex
MCR	Mayo Clinic of Rochester
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
PHI	Protected Health Information
PI	Principal Investigator
MUSC	Medical University of South Carolina
QIDS-A17-SR	Quick Inventory of Depressive Symptoms – Adolescent Version – Self Report
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
TASS	Transcranial magnetic stimulation Adult Safety Screen
UADE	Unanticipated Adverse Device Effect
YMRS	Young Mania Rating Scale

Study Summary

Title	A Randomized, Double-Blinded, Sham-Controlled Trial of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents
Running Title	Adolescent rTMS RCT
IRB Protocol Number	[redacted] (MCR) [redacted] (MUSC)
Phase	Pilot
Methodology	Randomized, sham-controlled, double-blinded; crossover to open-label maintenance treatment (treatment responders) or open-label acute treatment (treatment nonresponders)
Overall Study Duration	60 months
Subject Participation Duration	Phase I (Randomized, Blinded): 6-8 weeks (Active rTMS vs. Sham) Phase II (Non-Randomized, Open-label): Acute Treatment (Arm 1) vs. Maintenance Treatment (Arm 2) Arm 1: 6-8 weeks of open-label acute treatment (for Phase I treatment nonresponders) Arm 2: 12 months of open-label, bi-weekly maintenance treatment (for Phase I treatment responders)
Objectives	1) To evaluate the antidepressant effects of daily, active rTMS (when compared with sham treatment) in adolescents meeting criteria for Major Depressive Disorder, single or recurrent episode (Phase I). 2a) To evaluate the benefit of daily, active, open-label rTMS in Phase I nonresponders (Phase II, Arm 1). 2b) To evaluate the benefits of bi-weekly, active, open-label maintenance rTMS treatment for Phase I responders over the course of 12 months post-acute treatment (Phase II, Arm 2). 3*) To evaluate, by proton magnetic resonance spectroscopy (^{1}H-MRS) at 3 Tesla (3T), neurometabolic biomarkers at the beginning and end of each study phase. 3a. Define regional specificity [anterior cingulate (AC) and left dorsolateral prefrontal cortex (L-DLPFC)] of cerebral metabolites (i.e. glutamate and glutamine) in adolescent depression. 3b. Study whether specific neurochemical resonances are associated with response, remission, and/or maintenance of improvement of clinical depressive symptoms when rTMS is used to treat adolescent depression. *Assessed at MCR site only
Number of Subjects	Phase I: Total of 75 enrolled (38 Active/37 Sham) across both sites (50 at MCR; 25 at MUSC) Phase II: All treatment responders and nonresponders will be offered qualified follow-up treatments based on Phase I outcomes.
Diagnosis and Main Inclusion Criteria	Diagnosis of Major Depressive Disorder, single or recurrent, antidepressant treatment-resistant
Study Device	NeuroStar™ TMS System in XPLOR® research configuration

Duration of Exposure	**Phase I (Randomized, Blinded):** For subjects randomized to the active treatment, stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more comfortable for the participating adolescents. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6-8 weeks of Phase I treatment initiation. **Phase II (Non-Randomized, Open-label):** <u>Acute Treatment (Arm 1)</u>: Subjects who did not achieve adequate clinical response to treatment in Phase I will be offered the opportunity to undergo acute rTMS treatment using the known-active therapy coil in Phase II. The treatment schedule and parameters will be identical to that in Phase I; i.e. daily stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6-8 weeks of Phase II treatment initiation. Therefore, subjects who had been randomized to active treatment during Phase I and subsequently enroll in the Acute Treatment (Arm 1) of Phase II will receive a total of 60 active treatments using stated study parameters within the 12- to 16-week combined timeframes. Subjects who were randomized to sham treatment during Phase I and subsequently enroll in the Acute Treatment (Arm 1) of Phase II will receive a total of 30 active treatments using stated study parameters within the 12- to 16-week combined timeframes. <u>Maintenance Treatment (Arm 2)</u>: Subjects who achieve adequate clinical response to treatment in Phase I will be offered the opportunity to undergo maintenance rTMS treatment using the known-active therapy coil in Phase II. Subjects will receive one treatment every other week for 52 weeks for a total of 26 treatments. Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. Combined duration of exposure for Phase I active/Phase II maintenance subjects would be 56 active treatments over 58 to 60 weeks. Combined duration of exposure for Phase I sham/Phase II maintenance subjects would be 26 active treatments over 58 to 60 weeks.

Reference Therapy	Subjects in Phase I who are randomized to sham treatments will have schedules, systematic assessments, and treatment approaches that are identical to subjects randomized to active treatments. Subjects, treaters, and clinical raters ***will not*** know whether the treatment is active or sham in nature (double-blinded). The sham coil is identical in its appearance to the active coil. Furthermore, Neuronetics, Inc. has created an acoustic matching profile that renders the sensory experience of the treatments virtually indistinguishable to subjects or researchers. The acoustic signal creates a painless percussive sensation that will be felt by the subject and will assist in simulating the active condition.
Concomitant Therapy	*Permitted:* Subjects are expected to be on stable dose pharmacotherapy with one of the antidepressants listed in protocol Section 4.1 (Inclusion Criteria). Any other medication change including initiation, discontinuation, or dose adjustment of medication, needs to be discussed with the site PI and approved before implementation. *Prohibited:* Initiation of medication listed in protocol Section 4.2 (Exclusion Criteria) is not permitted during either phase of the study. Dose adjustment or initiation of permitted medications (Section 4.1 Inclusion Criteria) after enrollment must be approved by the site PI prior to implementation.
Statistical Methodology	Statistical analysis plan for objectives 1, 2a, 2b : Treatment outcomes defined as remission, response, or nonresponse will be assessed using a logistic regression model with independent variables of treatment number (i.e. #10 vs. #20 vs. #30) and gender (male vs. female) will be analyzed at the 0.05 significance level. The primary outcome measures will include the CDRS-R and CGI-I. Statistical analysis plan for objective 3 (data from MCR site only): The hypotheses will be tested using t-tests. Additionally, analyses of covariance will be performed to control for potentially important covariates or confounders, such as age or gender. Non-parametric distribution will be analyzed by non-ANOVA statistics.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations, Mayo Clinic of Rochester (MCR), and the Medical University of South Carolina (MUSC) policies and procedures.

1.1 Background

This research proposal aims to provide the first randomized, double-blinded, sham-controlled study of repetitive transcranial magnetic stimulation (rTMS) in depressed adolescents. This study will be the first to compare active treatment with a placebo (sham) treatment condition in adolescents who have not adequately responded to a course of antidepressant pharmacotherapy. Thus far, rTMS has proved to be a safe treatment approach that has shown early promise as being an effective and well-tolerated treatment option in youth, but it has not yet been tested under the scientific rigor of a double-blinded, sham-controlled trial.

Although the exact mechanism of action remains unknown, rTMS stimulates cortical neurons using pulsed magnetic fields generated by rapidly changing currents in a coil of wire placed on the scalp. By using advanced imaging techniques that analyze the magnetic resonance spectroscopy (MRS) patterns of rTMS response in depressed adolescents, this proposal will serve as a landmark in advancing the scientific understanding of two fields – neurostimulation and the practice of child and adolescent psychiatry. This research proposal will fundamentally change how rTMS is viewed as a treatment intervention in depressed adolescents.

Dr. Croarkin and colleagues have published previous trial data demonstrating the safety and efficacy of open-label rTMS in depressed adolescents. To date, this is the largest known trial in the United States demonstrating the tolerability and therapeutic potential of rTMS in depressed adolescents. [1]

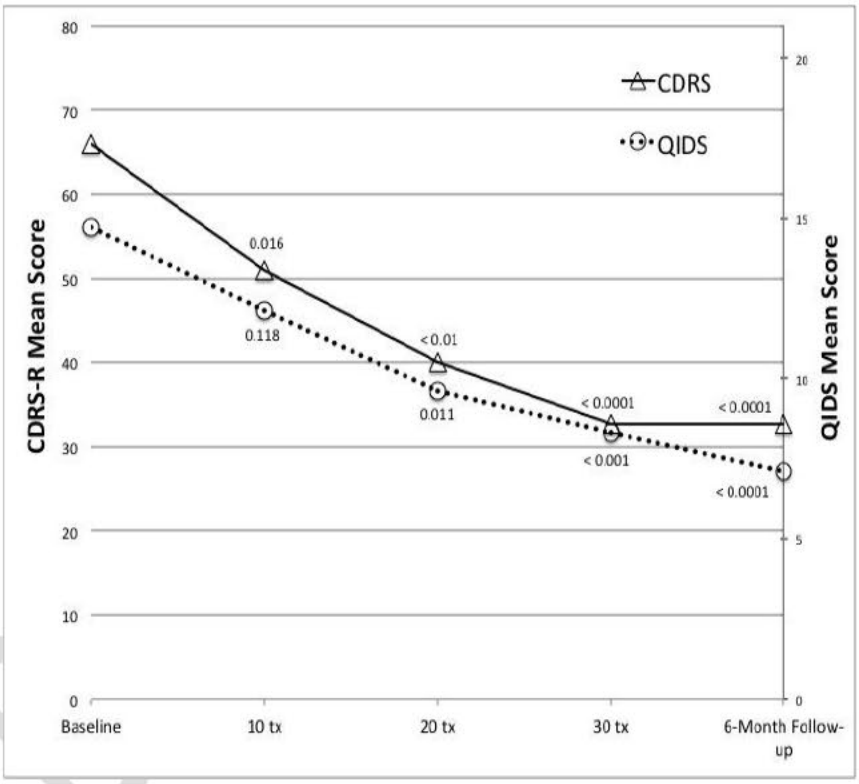
1.2 Investigational Device

The NeuroStar™ XPLOR® TMS Therapy System is a clinical research option for the NeuroStar™ TMS Therapy System that provides features necessary to conduct randomized, controlled trials and other TMS research. The NeuroStar™ 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 for use in the treatment of major depressive disorder in individuals with one prior failed adequate pharmacologic trial (see Appendix J3 for product description and use). The XPLOR® research configuration consists of three coils: a known-active coil identical to the NeuroStar™ TMS System treatment coil and two identical, “blinded” coils. One of the blinded coils provides active treatment identical to the known-active NeuroStar™ TMS system treatment coil; the sham coil provides acoustically indistinguishable (from active) pulses and a gentle percussive sensation that simulates scalp sensations produced during active treatment.

1.3 Clinical Data to Date

The 2011 Wall et al. open-label trial (conducted under IDE number G060269) that treated a total of 7 antidepressant-resistant adolescents demonstrated a robust response rate noted by 5 of 7 subjects achieving remission of depression as rated by the Childhood Depression Rating Scale - Revised (CDRS-R). Furthermore, CDRS-R mean depression severity responses were noted to be significant by treatment #20 with correlated improvement as demonstrated with the self-report Quick Inventory of Depressive Symptoms – Adolescent Version (QIDS-A17-SR) (Figure 1). Placebo response rates in open-label trials of adolescents are a well-known phenomenon. However, the adolescents treated in our initial protocol demonstrated enduring mood improvement 6 months following their final treatment session. Furthermore, 7 of 8 subjects completed the entire treatment course – with 1 dropping out after a total of 5 minutes of treatment due to scalp discomfort and a perceived "lack of improvement".

Figure 1 – CDRS-R and QIDS-A17-SR Response in Depressed Adolescents in an Open-label rTMS Trial (Wall, et al. J Clin Psychiatry, 2011. 72(9): p. 1263-1269



Evidence from the currently proposed study would extend these initial findings and begin to answer questions relating to the neurobiological basis of those who show response or remission of depression with rTMS treatment and those who do not respond.

1.4 Study Rationale and Risk/Benefits

1.4.1 Study Rationale

A large percentage of adolescents suffering from Major Depressive Disorder (MDD) do not adequately benefit from currently-available medications, psychotherapy, and/or social support treatments. In fact, it is estimated that current treatment approaches, considered separately, fail to provide adequate clinical improvement in 40% of adolescents with MDD. Moreover, these treatment approaches produce complete remission in only 30% of adolescent patients. [2-5] Unfortunately, adolescents with persistent symptoms of depression are more likely to experience inpatient psychiatric hospitalization, psychosocial maladjustment, and suicidality. [6] Consequently, they are more likely to receive additional psychopharmacologic agents that generally offer little additional benefit and increase the risk of adverse effects.

The current literature on rTMS describes a total of approximately 1,300 adult subjects safely treated with rTMS. Two recent sham-controlled, randomized clinical trials (combined

sample of about 500 patients) using the same device and treatment parameters demonstrated the safety and efficacy of rTMS monotherapy applied to the left dorsolateral prefrontal cortex (L-DLPFC) in depressed adults.[7, 8] By contrast, rTMS has been applied to a much smaller number of adolescent depressed patients. In four separate studies using varying clinical characteristics, devices, and stimulus dosing, significant improvement was demonstrated in 12 of 18 patients with no evidence of significant treatment-related adverse events beyond scalp discomfort, boredom during the treatment, and mild headaches.[1, 9-11] In recent years, rTMS treatment parameters have changed with regard to increased numbers of stimulations per session and the percentage of motor threshold at which the stimulations are applied.

1.4.2 Anticipated Risks

Seizures

Repetitive transcranial magnetic stimulation is generally regarded as safe and without any serious or lasting adverse effects.[12] Inadvertent induction of a seizure is the most concerning potential neurophysiologic safety concern. However, with the adoption and widespread use of recommendations delineating a safe margin for both intertrain intervals and for other relevant rTMS dosing parameters as disseminated in the 1998 safety guideline from the National Institute of Neurological Disorders and Stroke (NINDS) on TMS, the risk for seizures is at or below the rate of occurrence cited in the NeuroStar device labeling (1 in 30,000 treatments) or 1 in 1,000 patients (0.1% of patients).[12] Since this time only one seizure has been reported, and in that particular case the treatment parameters used were not within the NINDS guideline recommendations. This study will comply with NINDS guideline standards for rTMS. It is important to note that there is no evidence that a single seizure, or even a series of induced seizures, makes subsequent seizures more likely in an otherwise non-seizure-prone individual. Nevertheless, it is also true that there are potential psychosocial consequences of a seizure. These include anxiety in the individual about recurring seizures and consequences regarding employment or insurability in the future. If a subject does have a seizure related to this investigation, a letter from the site PI will note that the seizure was produced under experimental conditions, and there is no reason to expect another seizure.

Individuals with a known seizure disorder, history of epilepsy, or intracranial abnormality such as a prior stroke will be excluded from this protocol for safety reasons. This protocol will exclude pregnant women (women of child bearing age will perform a pregnancy test prior to enrollment of each phase). Certain medications may increase the risk of seizure, and adolescents taking these medications will also be excluded from participating in this research. All other well-established safety procedures will be utilized to ensure the safest possible conduct of this study. Dr. Shirlene Sampson will serve as a Mayo Clinic on-site rTMS trial Co-Investigator and mentor for Dr. Croarkin. Dr. Mark George will serve as the MUSC site Principal Investigator with Dr. Edwards acting as MUSC on-site Co-Investigator.

Seizure management plan and precautions to ensure safety of subjects

A resuscitation cart including an Ambu bag and oxygen will be available in the treatment suite. Furthermore, a clinician trained in seizure management will observe all rTMS sessions. All individuals acting as the on-site seizure management clinician will be required to demonstrate this capacity to the regulatory sponsor. In the event of a seizure, the primary en suite clinician will initiate appropriate clinical care as defined within the clinical rTMS practice. In management of seizures, attention must be taken to minimize

the risk of aspiration, and when possible guiding the patient into the left lateral decubitus position is desirable. Because most seizures are brief (typically <60 seconds) and without serious physical sequelae, efforts will be focused on preventing complications of the seizure rather than initiating any specific medication that is not required unless a seizure is prolonged. If a prolonged seizure (>60 seconds) is identified, appropriate response measures will be initiated which may include notifying a hospital-based pediatric rapid response team (Mayo Clinic site), following approved MUSC policies pertaining to medical events in "Non-clinical areas", and/or escorting patient to the nearest emergency department upon stabilization. The patient may be provided lorazepam (or equivalent benzodiazepine available in the resuscitation cart) to abort the seizure. To date, status epilepticus has never been described following rTMS.

If a seizure occurs during the active treatment phase of the study, active treatment as part of the study will be discontinued. Ongoing monitoring of mood and neurocognitive symptoms per the study protocol will be offered.

Any seizure event during the study will be reported as follows:

MUSC will report to the regulatory sponsor (Dr. Croarkin) and reviewing IRB per policy.

The regulatory sponsor and MCR site PI will report to the DSMB, reviewing IRBs, Neuronetics, and FDA as required per agreements, regulations, and policies.

Mood considerations

There is a risk that the rTMS treatment may not be effective for some patients and that their depression may worsen. Concerns for theoretical mood destabilization, including induction of mania or worsening of suicidality, will be carefully considered throughout the course of treatment (at every treatment visit); and subjects, their families, and investigators may elect to discontinue the treatment protocol and withdraw from the study at any point. Furthermore, safety considerations consistent with current standard of care in child and adolescent psychiatric practice will be employed including contacting the primary mental health care provider, referral to on-call child and adolescent psychiatric services, referral to the emergency room, and/or hospitalization if necessary.

Several studies in the adult population and limited studies in the adolescent population have so far demonstrated the feasibility of rTMS to treat depression without any alarming indicators of exacerbation of depression or suicidality. [1, 7, 8, 11] However, pediatric use of antidepressant *pharmacotherapy* has corresponded with warnings about increases in suicidal ideation and behavior in youths and young adults treated with selective serotonin reuptake inhibitors (SSRIs). No compelling data are available to indicate whether the net result of treatment of depressed youths with these compounds is an overall increase or an overall decrease in the hazard of completed suicide; there is limited and inconclusive evidence in each direction.[13-17]

For the purposes of this study, exacerbation of depression will be defined as a CDRS-R score increase of >33% of baseline accompanied by clinician determination of significant clinical deterioration as noted by a clinical global improvement (CGI-I) scale score of ≥6 (much worse or very much worse). Exacerbation of suicidal ideation and behavior will be defined as an increase of the Columbia – Suicide Severity Rating Scale (C-SSRS) suicidal ideation score of ≥ 4 or suicidal behavior including actual suicide attempts, interrupted/aborted attempts, or preparatory acts or behavior.

Suspected treatment-induced mania will be evaluated using the Young Mania Rating Scale (YMRS). A YMRS score of ≥ 20 will prompt administration of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS) - Affective Disorders Supplement, to establish whether the patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) 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-IV-verified mania will be treated as a serious adverse event (SAE) and will also be monitored using the YMRS.

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 adolescent and parent(s) will be told to initiate contact with their study doctor, either Dr. Paul Croarkin (MCR) or Dr. Mark George (MUSC), if they experience any significant mood or behavior changes including suicidal ideation. Principal Investigator contact information is included in each site's consent/assent document. See Appendices H and I for drafts. Furthermore, during the active treatment phases of the protocol, subjects will have clinician interactions 5 days/week where changes of psychological symptoms will be queried (see Tables 4-6 for schedules of assessments). Ongoing monitoring for worsening of depression and emergence of suicidal ideation and/or behaviors will be evaluated using the CDRS-R, C-SSRS, CGI-I, and CGI-S.

Some youth with depression will encounter crises. Most crisis management involves a combination of case management and creative problem solving, which can be accomplished within the framework of the existing treatment. If any treatment-related SAE occurs, including verified treatment-emergent mania, hypomania, exacerbation of depression, and/or worsening of suicidality, the subject, their guardian/parent, and their primary treating physician will be notified of this development, and a discussion as to the most appropriate clinical course of action will occur. This will include an offer to discontinue the rTMS treatment course, withdrawal from the study, and may include the need to seek emergent psychiatric stabilization (including hospitalization).

This protocol will follow the procedures of the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters on Suicidal Behavior.[18] These parameters indicate that subjects should be referred for hospitalization if their condition is unstable as manifested by suicidal ideation with inability to contract for safety, psychosis, current intoxication, mania, rapid cycling, or mixed state. Social factors that may cause the clinician to consider hospitalization include lack of sufficient environmental support and structure to guarantee the child's safety. Subjects and families will be given recommendations for alternative treatment options and will be offered care through the clinic. There are no funds to pay for clinical care outside the parameters of the study or for psychiatric hospitalization of a subject in this study; however, research staff and physicians will be available at all times to evaluate subjects with adverse behavioral consequences and, if necessary, arrange for admission to a local hospital.

Other potential side effects of rTMS that may be experienced *during* treatment

Some patients treated with rTMS have reported experiencing discomfort due to stimulation of the scalp musculature under the site of stimulation. A muscle tension headache may result in some patients that can persist for 1-2 hours post stimulation; however, these headaches typically respond to symptomatic treatment. In fact, recent findings suggest the possibility that chronic headache sufferers had mitigation of headaches during the course of treatment and upon follow-up (Wall, Baruth, Croarkin, et al. Submitted 2012). See Appendix C1 for copy.

Some patients may experience buzzing, tapping, or painful sensations at the treatment site, but this is usually reported to be mild. There is a rare risk of scalp burn (first degree burn similar to a sun burn) from the procedure. Some patients report "twitching" of the facial/scalp muscles around where the coil is located. This sensation may be "annoying" or temporarily uncomfortable but is not considered dangerous.

Treatment plan for other side effects of rTMS experienced *during* treatment
Prophylactic use of acetaminophen or ibuprofen will be recommended to subjects reporting painful sensations at stimulation site or discomfort from facial/scalp muscle twitching. In extreme situations, for subjects reporting pain or discomfort that is severe or intolerable, topical application of lidocaine at the treatment site has been found to be useful and may be used, at the discretion of the site PI, for this study. Additionally, study personnel may decrease the "intensity" of the treatment strength to 80% of MT as necessary. It is common that the scalp discomfort abates following the first 2-3 treatments. Titration to maximum treatment power (not to exceed 120% MT) will occur as tolerated by each subject. Any report of scalp burning sensation by a subject will result in discontinuation of treatment for the day. Treatment would be offered the following day or as tolerated within the study timeframe.

Other potential side effects that may be experienced *following* rTMS treatment
Transient numbness of the face, local pain, headache including migraine, transient dizziness, brief changes in attention and thinking, transient or permanent hearing loss, visual changes, dental pain, and treatment-induced neurocardiogenic syncope (especially in children with predisposition to neurocardiogenic syncope including syncope/presyncope related to noxious stimuli, anxiety, micturition, or posture).

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 patients will be monitored, and appropriate treatment will be recommended including the possibility of stopping rTMS. Any other potential side effects will be managed symptomatically with treatment(s) deemed appropriate by site PI. All symptomatic interventions will be recorded in subject's case file and, if applicable, adverse event CRF.

Treatment with the Neurostar rTMS Stimulation System may involve other risks that are not known at the present time. The long-term effects of rTMS are not known.*

MRI/MRS Human Safety Considerations and Protection of Subjects
As this study only involves three MR scans (Phase I Baseline; End of Phase I/Phase II Baseline; Phase I Follow-Up/End of Phase II), the risk is assessed as minimal. No contrast material or exposure to ionizing radiation will occur for the conduct of this protocol.

The risks for the MRI/MRS scan in this study are no more than would occur while receiving a routine clinical MRI scan. To minimize any potential risks from the scans, the clinician will be required to fill out an MRI Patient Screening Form (Appendix F3) prior to the each scan. Subjects will not be able to take part in the study if they have certain medical devices (e.g. heart pacemakers), aneurysm clips placed on the blood vessels of the brain, or metallic particles in the eye (such as may happen from coming in contact with metal filings). A physician will review the MRI Patient Screening Form to determine if a subject is eligible to participate in this study. Adolescents 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. Subjects will be withdrawn from the study if they cannot complete the MRI-localization procedure. The total scanning time will be approximately 50 minutes per scanning session.

Overall Risk Analysis Statement

It is felt that the potential benefits of this study outweigh the risks. Depressed adolescents who fail to respond to medication are at increased risk for suicide and prolonged disability related to depressed mood during a critical developmental stage. The preliminary data suggest that rTMS has antidepressant effects – in both the adult and the pediatric populations. The risks of rTMS are slight relative to electroconvulsive therapy (ECT), a treatment sometimes used in this population, or pharmaceutical therapy with multiple medications. If rTMS proves to be an effective alternative to ECT and/or combination pharmaceutical therapy, depressed adolescents not responding to medication would have a treatment alternative with fewer side effects and risks. The protocol procedures are felt to be safe, are well within previously established rTMS guidelines, and will be conducted by leaders in the field of rTMS research and administration. Dr. Croarkin and MCR colleagues have the single greatest treatment experience of this modality in depressed adolescents to date. Furthermore, Dr. George is an internationally-recognized expert in the study and use of rTMS in both clinical and research practice.

1.4.3 Potential Benefits

Repetitive transcranial magnetic stimulation is a novel therapy that was cleared by the United States FDA in the autumn of 2008 for the treatment of MDD in adults who fail to achieve satisfactory improvement from one prior adequate antidepressant trial (see Appendix J2 for copy of Approval Letter). It is a promising alternative to treatments such as ECT or pharmacotherapy for patients presenting with treatment-resistant cases of MDD. The rTMS procedure is non-invasive, does not require anesthesia, and may be delivered in an outpatient setting.

2 Study Objectives

2.1 Primary Objective

2.1.1 Phase I

The primary objective of this study is to evaluate the safety and efficacy of rTMS as an adjunctive antidepressant therapy in a prospective, randomized, sham-controlled study in adolescents with MDD who have not responded sufficiently to at least one adequate

antidepressant medication trial. Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more tolerable for the participating adolescents. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6-8 weeks of Phase I treatment initiation.

2.1.2 Phase II, Arm 1

The primary objective of this study is to evaluate the antidepressant benefit of 30 sessions of daily, active, open-label rTMS in Phase I nonresponders. Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more tolerable for the participating adolescents. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session.

2.1.3 Phase II, Arm 2

The primary objective of this study is to evaluate the sustained antidepressant benefit of 26 sessions of biweekly, open-label, active maintenance rTMS treatment for Phase I responders. Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more tolerable for the participating adolescents. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session.

2.2 Secondary Objective (MCR site only)

Secondary objectives of this study are to evaluate, by proton magnetic resonance spectroscopy (^{1}H-MRS) at 3 Tesla (3T), the following neurometabolic biomarkers:

1) Define regional specificity [anterior cingulate (AC) and left dorsolateral prefrontal cortex (L-DLPFC)] of cerebral metabolites (i.e. glutamate and glutamine) in adolescent depression.

2) Study whether specific neurochemical resonances are associated with response or remission of clinical depressive symptoms when rTMS is used to treat adolescent depression.

To accomplish these goals, the MCR site will utilize ^{1}H-MRS, a valuable, non-invasive method to study in-vivo brain biochemistry. Of the available imaging paradigms, ^{1}H-MRS is uniquely suited to investigate biochemical mechanisms of treatment action that are objectively

measurable and clinically relevant. As there is increasing interest in glutamatergic dysregulation in mood disorders, this project will utilize ^{1}H-MRS at 3T to study specific neurometabolic levels in the primary brain regions associated with major depressive disorder [anterior cingulate (Brodmann's areas 24a/b and 32) and L-DLPFC (Brodmann's 9/46)]. The goal of this aspect of the proposal is to evaluate whether anterior cingulate and prefrontal cortex neurochemicals (such as glutamine), quantified as a cerebrospinal fluid (CSF)-corrected absolute concentration percent change from baseline, are associated with clinical remission of depression when active rTMS is used.

3 Study Design

3.1 General Design

Treatment-site Localization Procedure:
A neuroradiologist at each site will review baseline MRI for potential exclusionary head and brain pathology. This localization procedure is the same procedure utilized preoperatively for neurosurgery – using a frameless stereotactic system (STEALTH– Mayo; Brainsight – MUSC). The optimal site of treatment, L-DLPFC, operationally defined as the gray matter of the superior frontal sulcus and portions of the superior and middle frontal gyri, containing Brodmann's areas 9 and 46. This location will be designated with a fiducial marker, along with clearly marked anatomic landmarks (nasion line, front and back of the ears) will be transferred to a lycra "swim-cap". The treatment site noted on the swim cap will then be translated to the NeuroStar machine using a 2-dimensional coil template that will align the coil precisely over the designated treatment site. Once in place, treatment-site coordinates will be loaded into the device database so that subsequent treatments will be identically located. This process will forego the "guesswork" associated with moving the coil 5 or 6 cm anteriorly to the optimal motor threshold site – also known as the point at which the contralateral abductor pollicis brevis is consistently stimulated.

Phase I (Randomized, Double-Blinded):
Active Treatment
Adolescents randomized to active rTMS treatments will receive therapy using parameters that have been safely and feasibly utilized in adult randomized, controlled trials [7, 8] and the 2011 Wall et al. open-label trial in adolescents.[1] Stimulation will occur at 120% magnetic field intensity relative to the participant's resting motor threshold, at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Titration and a return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more comfortable. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6-8 weeks of treatment initiation.

Sham Treatment
Adolescents randomized to sham treatments will have identical schedules, systematic assessments, and treatment approaches to their active treatment counterparts. Neither the adolescents nor the investigators (clinical raters or treaters) will know whether the treatment is active or sham in nature. The sham coil is identical in its appearance to the active coil. Furthermore, Neuronetics, Inc. has created an acoustic matching profile that renders the "sound" of the treatments virtually indistinguishable to participants or researchers. The acoustic

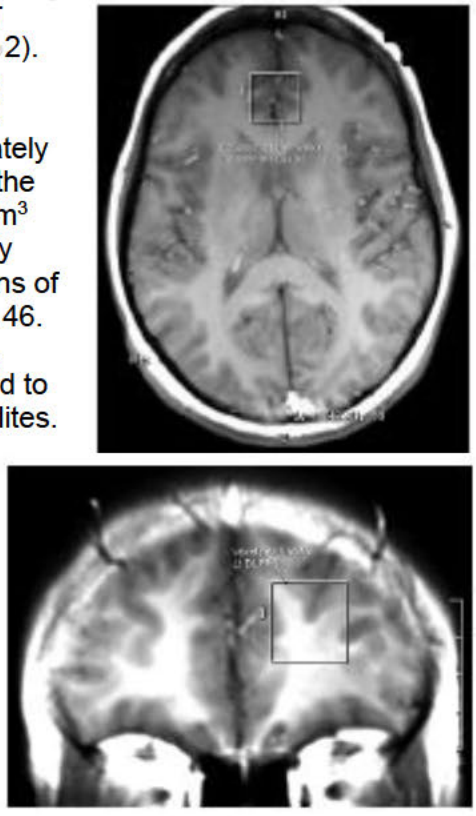
signal creates a painless percussive sensation that will be felt by the subject and will assist in simulating the active condition.

[1]H-MRS methods (MCR site only)

Structural MRI and [1]H-MRS comparisons will be acquired for participants at the MCR site in two sessions lasting approximately 40 minutes each. A General Electric (GE) 3T Discovery MRI scanner running 22.1 software (or greater) and an 8-channel head coil will be used. The scanner is located in the Mayo Clinic - Main Mary Brigh MRI facility that is adjacent to the Generose Psychiatric Hospital (where the rTMS suite is located). A consistent MRS technician will be requested for each of the study scans as directed by Dr. John Port. Each MCR subject will have a baseline scan and additional scans at the completion of each treatment phase or at six months post treatment for subjects not electing to participate in Phase II. The maximum number of scans during the study will be three. Participants who discontinue the study will be offered a scan at the time of treatment withdrawal.

In order to ensure that the voxel location does not significantly change from scan to scan, a systematic approach to reference voxel positioning in all subjects is used. Briefly, an axial cut approximately 1 cm above the genu of the corpus callosum showing a continuous view of the anterior and posterior horns of the lateral ventricles will be chosen as a reference slice (Figure 2). The center of a single 4-cm^3 voxel (2-x-2 cm in-plane resolution by 1 cm thick) of predominantly gray (prefrontal) matter is centered on the frontal interhemispheric fissure. The voxel's posterior margin is placed immediately anterior to the genu of the corpus callosum in an area corresponding to the pregenual AC cortex (Brodmann areas 24a, 24b, and 32). A second 8-cm^3 voxel will be centered in white matter deep to the L-DLPFC, operationally defined as the gray matter of the superior frontal sulcus and large portions of the superior and middle frontal gyri, containing Brodmann's areas 9 and 46. A long echotime (TE=80 ms) standard PRESS sequence (TR=2000 ms, number of acquisitions=128, bandwidth 500 Hz, 4096 points) will be used to measure glutamate and glutamine as well as measure the other metabolites. A second 2D J-averaged MRS sequence (TE=35-195 ms in 16 steps of 10 ms each, TR=2000, number of acquisitions=128, bandwidth 500 Hz, 4096 points) will also be used to optimally measure glutamate in each voxel. All MRS data will be processed using LCModel, a well-accepted, unbiased program for determining metabolite concentrations. A quantitative analysis of brain metabolites will be performed with a focus on the target metabolites. Anatomical image data will be segmented into gray matter, white matter, and CSF using a semiautomated thresholding technique developed internally at MCR (John Port, Cliff Jack, Paul Bao). This segmented anatomical data will be combined with the spectroscopic data to obtain tissue-volume-corrected metabolite concentrations per accepted methods. This generates "absolute" (versus relative to creatine) metabolite concentrations in "institutional units" specific to our scanner and technique. These concentrations will then be used in the statistical analysis. An accepted data standard for healthy controls in these particular voxel locations will be used in the comparison.

Figure 2 – Voxel Placement examples
Top = AC; Bottom = L-DLPFC



Phase II (Non-Randomized, Open-label):

Arm 1: Acute Treatment (Nonresponder Cohort)

Participants who do not meet criteria for response (CGI-I rating of 3 or greater and/or a CDRS-R score of 28 or greater) following Phase I treatment will be offered the opportunity for 30 treatments using the known-active coil. The treatment parameters and methods of assessment will be identical to those in Phase I. The only difference will be that the coil used for Phase II will be active and known to the subject, family, and investigators. See Table 5 for schedule of assessments.

Arm 2: Maintenance Treatment (Responder Cohort)
Subjects who, at the completion of Phase I, meet clinical criteria for treatment response (CGI-I rating of ≤2 **and** CDRS-R score of <28) will be offered the opportunity for 52 weeks of maintenance rTMS treatment. The treatment parameters will be identical to those in Phase I treatment except for the frequency of visits (biweekly) instead of daily. Clinical assessments will be offered monthly throughout the duration of the maintenance phase. One final follow-up assessment will be scheduled for six months post final treatment. See Table 6 for schedule of assessments.

3.2 Primary Study Endpoints

3.2.1 Phase I

Primary outcome screening measures in Phase I will be assessed at 10-treatment intervals which will equate to roughly every other week until the 30th treatment has been completed (see Table 4 for schedule of assessments). These outcome measures will provide an opportunity for mood ratings in the form of self-assessment (QIDS-A17-SR), a semi-structured clinical interview of the adolescent with input from parents (CDRS-R), and a clinical rating by the clinician of illness severity and improvement (CGI-S & I).

Furthermore, from a safety standpoint, suicidality will be carefully monitored on a weekly basis via the C-SSRS. Board certified/board eligible child and adolescent psychiatrists will administer all diagnostic assessments and clinical interviews determining study eligibility. Outcome measures assessing neurocognitive safety [the Children's Auditory Verbal Learning Test version 2 (CAVLT-2) and the Delis-Kaplan Executive Function Scale (D-KEFS)] will occur at baseline and at treatment completion and will be administered by trained psychometrists. These measures will be used in the assessment of any unanticipated change in cognitive function that may have occurred during the course of treatment. Inter-rater reliability exercises will be conducted for the CDRS-R to ensure intra-site and inter-site consistency of depression ratings.

3.2.2 Phase II, Arm 1

The schedule of primary outcome measures for Acute Treatment (Arm 1) of Phase II will be identical to that of Phase I with the exception that the End of Phase I assessments will be used for Phase II Baseline measures. See Table 5 for schedule of assessments.

3.2.3 Phase II, Arm 2

Primary outcome measures for Maintenance Treatment (Arm 2) in Phase II, including QIDS-A17-SR, CDRS-R, CGI-I, and CGI-S, will be assessed monthly. Suicidality will be carefully monitored on a monthly basis or more frequently as needed using the C-SSRS. Neurocognitive safety outcome measures (CAVLT-2 and D-KEFS) will be assessed at the completion of the maintenance treatments and at six-month follow-up. These will be

compared to Phase I Baseline and Phase I Completion assessments. See Table 6 for schedule of assessments.

3.3 Secondary Study Endpoints (MCR site only)

Secondary outcome measures will be collected for MCR subjects at baseline and at treatment completion (see Tables 4-6 for schedules of assessments). Imaging studies with ^{1}H-MRS at 3T will be utilized to study specific neurometabolic levels in the primary brain regions associated with major depressive disorder [AC (Brodmann's areas 24a/b and 32) and dorsolateral prefrontal cortex (Brodmann's 9/46)]. We also propose the investigation of the IC, an area of the brain thought to be related to integration of emotional and somatosensory inputs.[19]

3.4 Primary Safety Endpoints

The primary safety endpoint of this study is freedom from all treatment-related Unexpected Adverse Device Effects (UADEs) during the active treatment course and during the 6-month follow-up period. The definition of UADE is outlined in section 8.1 of the protocol.

3.5 Secondary Safety Endpoints

Secondary safety endpoints for this study include no statistically significant change (i.e. worsening) in cognitive performance as measured by the protocol-defined neurocognitive battery (D-KEFS and CAVLT-2). Neurocognitive assessments will occur at baseline, after the final treatment, and again six months following the final treatment. Measured outcomes at each time point will be compared with baseline scores to calculate change. (Wall, Baruth, Croarkin, et al. Submitted 2012). See Appendix C1 for copy.

4 Subject Selection, Enrollment and Withdrawal

Nearly 1,500 depressed adolescents (ages 13 to 18) are treated annually at Mayo Clinic in Rochester. Another 300-400 depressed adolescents are treated annually at MUSC in South Carolina. Approximately 40% of adolescents will not respond to currently available antidepressant or psychotherapeutic treatment approaches. Thus, annually, nearly 720-760 adolescents within the combined MCR and MUSC treatment areas would be potential rTMS treatment candidates. This protocol will plan to screen approximately 150 depressed adolescents (over three years) to enroll 75 subjects (50 at MCR and 25 at MUSC). Each site will plan to screen 5 adolescents per month for the study, with likely recruitment of 1-2 study subjects per month at each site. All adolescents meeting inclusion and exclusion criteria, as described in protocol Sections 4.1 and 4.2, will be offered participation in the study regardless of gender, race, or ethnicity. A strength of this multicenter collaboration is the ability to provide treatment to a more economically and ethnically diverse demographic population than would occur in the Rochester, MN, region alone.

Based on the most recent census data available (2010), Olmsted County, Minnesota, is primarily comprised of Caucasians (86%) of Non-Hispanic or Latino ethnicity (96%). African Americans and Asians each represent 5% of the total population. Females represent 51% of the population.

The Charleston County area in South Carolina population is primarily comprised of Caucasians (62%) of Non-Hispanic or Latino ethnicity (98%). The minority race population is represented by

African Americans (35%), Asians (1%), Other (1%), and Two or More Races (1%). Females represent 52% of the total population.

Therefore, we anticipate the distribution of gender (given the predominance of adolescent females with MDD), race, and ethnicity of enrolled subjects for the target 75 subjects, to be 25 males and 50 females; 3 Hispanic or Latino and 72 Non-Hispanic or Latino; 59 Caucasian, 11 African American, 3 Asian, 1 Other, and 1 Identified by two or more races. See Table 1.

All adolescents and their guardians will be provided a careful assent and consent discussion prior to enrollment. Since this is a sham-controlled trial, all subjects would need to understand that during Phase I of the trial, they will be randomized to either the active treatment condition or the sham treatment condition. They will also be informed about the opportunity to receive open, active rTMS treatment (during Phase II) if they did not have clinical response during Phase I.

Table 1 – Population Distribution and Estimated Enrollment Total and by Site

	Olmsted County, MN	**MCR Site Enrollment**	**Charleston County, SC**	**MUSC Site Enrollment**	**Total Study Estimated Enrollment**
Ethnicity					
Hispanic or Latino	4%	2	2%	1	3
Non-Hispanic or Latino	96 %	48	98%	24	72
	100%	**50**	**100%**	**25**	**75**
Race					
Caucasian	86%	43	62%	16	59
African American	5%	2	35%	9	11
Asian	5%	3	1%	0	3
American Indian / Alaska Native	0%	0	0%	0	0
Native Hawaiian / Pacific Islander	0%	0	0%	0	0
Other	2%	1	1%	0	1
Two or More Identified	2%	1	1%	0	1
	100%	**50**	**100%**	**25**	**75**

4.1 Inclusion Criteria

Table 2 – Inclusion Criteria

Inclusion Criteria	Determinant
Diagnosis of unipolar major depressive disorder, in a current major depressive episode, without psychotic features	K-SADS to confirm DSM-IV criteria
Pretreatment CDRS-R Raw score ≥ 40	CDRS-R
Age is at least 12 and less than 22 years	Self-report and review of medical record
Ongoing, stable dose antidepressant therapy for at least 6 weeks prior to active treatment to include the following antidepressants (with dosing range) Celexa (citalopram hydrobromide) – 10 to 60mg Cymbalta (duloxetine) – 40mg to 120mg Desyrel (trazodone HCl) – 12.5mg to 150mg Effexor (venlafaxine HCl) – 37.5mg to 300mg Luvox (fluvoxamine maleate) – 25mg to 200mg Lexapro (escitalopram oxalate) – 10mg to 40mg Paxil (paroxetine HCl) – 10mg to 50mg Pristiq (desvenlafaxine) – 50mg to 100mg Prozac (fluoxetine HCl) – 10mg to 80mg Remeron (mirtazapine) – 7.5mg to 45mg Zoloft (sertraline HCl) – 25mg to 200mg Savella (milnacipran HCl) – 25mg to 200mg	Physician evaluation and review of medical record
Subjects able to attend at least 31 study visits	Subject and family agreement
Willing to provide informed assent (adolescent) and informed consent (family)	Consent/assent discussion

4.2 Exclusion Criteria

Table 3 – Exclusion Criteria

Exclusion Criteria	Determinant
Subjects currently on a stimulant, antipsychotic, bupropion, or a tricyclic antidepressant medication.	Physician evaluation and review of medical record
Active substance use	Urine drug of abuse test (at screening)
Prior rTMS, vagus nerve stimulation (VNS), or ECT	Medical history
Contraindication to MRI	Physician evaluation; medical history; MRI Safety Screening Questionnaire
Contraindication to rTMS (history of neurological disorder such as seizures, increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for >15 minutes, history of stroke, family history of epilepsy, intracardiac lines). Current anticoagulant, immune suppressive, and/or chemotherapy or those who have received any of these therapies within 3 months before enrollment in the study. Unstable medication conditions such as hematological or infectious (e.g., human immunodeficiency virus-HIV) disorders, implanted electronic device, metal in the head, or pregnancy.	Physician evaluation; medical history; MRI; urine pregnancy test (at screening)
History of schizophrenia, schizoaffective disorder, other (non mood disorder) psychosis, depression secondary to a medical condition, mental retardation, substance dependence or abuse within the past year (except nicotine), bipolar disorder, psychotic features in this or previous episodes, amnestic disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder	K-SADS to confirm DSM-IV criteria; Physician Examination and conference with family member/guardian to confirm findings; urine substance abuse survey (at screening)
History of autoimmune, endocrine, viral, or vascular disorder.	Physician evaluation; medical history
Unstable cardiac disease, uncontrolled hypertension, or sleep apnea	Physician evaluation; medical history
Active suicidal intent or plan, or history of attempt within the past 2 months	Physician evaluation
Any other relevant medical, personality, or psychosocial issues specific to the subject that the P.I. determines to be reason for exclusion from the study	Physician evaluation; medical history

4.3 Subject Recruitment, Enrollment and Screening

4.3.1 Subject Recruitment

Several resources will be utilized for recruitment of potential subjects including:

- from within the clinical and referral practices of both Dr. Croarkin (regulatory sponsor and MCR site PI) in Rochester and Dr. George (MUSC site PI) and Dr. Edwards (MUSC site Co-I) in South Carolina
- referrals from other care providers within the treatment communities
- radio advertisements
- invitation letters sent to parents of potentially eligible patients
- print advertisements, including but not limited to brochures, flyers, Craigslist, and listings in research classifieds
- trial listing with ClinicalTrials.gov
- trial listing on SCResearch.org

- trial listing on MCR and MUSC research websites

All advertising materials will be reviewed and approved by appropriate site IRB prior to use.

Potentially interested adolescents and their families may be provided with printed patient educational materials to aid them in making an informed decision regarding their willingness to participate in this study. These include the Mayo Clinic educational materials "Is transcranial magnetic stimulation right for me?" and "Transcranial Magnetic Stimulation (TMS)". (See Appendix L for copies)

4.3.2 Subject Enrollment

At the time of the enrollment visit, potential subjects and their parent(s) will be provided with a written copy of the current IRB-approved informed consent/assent form from the site at which they will be receiving study treatments (Appendices H and I). All adolescents and their guardians will be provided a careful assent and consent discussion prior to enrollment. Due to the nature of a sham-controlled trial, all participants will need to understand that during Phase I of the trial, they will be randomized to either the active treatment condition or the sham treatment condition. They will also be informed about the opportunity to receive open, active rTMS treatment during Phase II if they did not have clinical response during Phase I. For subjects who reach the age of majority (18 years at both sites), written consent will be obtained from the subject at the next visit following their birth date.

4.3.3 Subject Screening

Following the informed consent process, enrolled subjects will begin the study eligibility screening process. The Eligibility Checklist and Verification CRF will be used at both sites to ensure that the subject is eligible for the study and that it is safe for them to participate. See Appendix E for comprehensive list of assessments used during screening to ensure eligibility.

Urine drug sample and, for females, urine pregnancy sample will be collected; subjects will not be initiated on any imaging protocol or rTMS treatment prior to these results becoming available and confirmed as negative for pregnancy and all nonprescribed substances of abuse.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects will be withdrawn from the study immediately if a seizure, DSM-IV-confirmed treatment-induced mania, or other UADE occurs. Subjects will also be withdrawn from the study, at the time of notification of study staff, if at any point they meet any of the exclusionary criteria outlined in protocol Section 4.2.

Subjects enrolled in Maintenance Treatment (Arm 2) in Phase II will be withdrawn from the study if they experience a worsening of their depression. Worsening of depression will be defined as a CDRS-R score increase of >33% of Phase II baseline or a raw CDRS-R score of ≥40, whichever occurs first, accompanied by clinician determination of significant

clinical deterioration as noted by a clinical global improvement (CGI-I) scale score of ≥6 (much worse or very much worse). Worsening of suicidal ideation and behavior will be defined as an increase of the Columbia – Suicide Severity Rating Scale (C-SSRS) suicidal ideation score of ≥ 4 or suicidal behavior including actual suicide attempts, interrupted/aborted attempts, or preparatory acts or behavior. These subjects will be referred to the care of their primary clinician or psychiatric provider. Subjects and families will be given recommendations for alternative treatment options and will be offered care through the clinic. There are no funds to pay for psychiatric hospitalization of a subject in this study; however, research staff and physicians will be available at all times to evaluate subjects with adverse behavioral consequences and, if necessary, arrange for admission to a local hospital.

Subjects may decide to withdraw from the study at any time, for any reason, including inability to tolerate study treatment, lack of improvement of depressive symptoms, or worsening of depressive symptoms. There are no currently-known risks associated with abrupt discontinuation of treatment with rTMS.

Subjects will be encouraged to remain compliant with all prescribed medications and expected study visits. Nonadherence to expected study visits and/or medications will be documented and may result in removal from the study. This will be clearly discussed during the consent/assent process and reinforced throughout the study through regular screening for changes in medications or issues with compliance.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

To enhance the validity of study data, as well as to provide subjects with ongoing monitoring and safety assessments by a qualified professional, subjects who choose to withdraw from the interventional portion of the study will be offered the opportunity to complete mood, cognitive, safety, and imaging assessments as per the study protocol.

5 Study Device

5.1 Description

The NeuroStar 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. It is a non-invasive tool used for the treatment of patients with MDD who have not achieved clinical response from one prior adequate trial of antidepressant pharmacotherapy (see Appendix J3 for detailed product description and use). The NeuroStar TMS Therapy™ System has been FDA-approved for use in adult patients. NeuroStar XPLOR™ is a clinical research option for the NeuroStar TMS Therapy System that provides features necessary to conduct randomized, controlled trials and other TMS research. Active treatment modality is essentially the same for both the NeuroStar TMS Therapy™ System and NeuroStar XPLOR™. See Appendix J4 for description of NeuroStar XPLOR device.

The NeuroStar XPLOR TMS System consists of the following equipment and software:

- Mobile Console (includes processor module, power module, mast, gantry, halo, and display arm)
- System Software; the XPLOR option also includes a dedicated system software

application (software version 1.7.5 or greater) with its own dedicated database of patient/subject treatment history, TrakStar application, and TrakStar database that operates only with the corresponding XPLOR Software, maintaining isolation, security, and data integrity of the research
- Practice Data Management System (PDMS) software
- Therapy Coils; included with the XPLOR option is a set of three TMS coils:
  - a blinded sham or placebo coil; the sham coil is acoustically matched to protect the integrity of the blind,
  - a blinded active coil, and
  - a standard treatment coil that can be used for performing motor threshold level determination or open-label treatment.
- Head Support System (includes laser positioning aid and coil positioning guide)
- Treatment Chair
- Positioning Cushions (to enhance comfort and positioning of the patient in the required posture for the duration of the treatment session)

The NeuroStar TMS System also requires supplies and disposables for each treatment session:
- Head Cushion Liner
- Head Side Pad Liner
- Head Positioning Straps
- Earplugs
- SenStar Treatment Link (a single-use medical device)
- Used SenStar Treatment Link Return Box

5.2 Method for Assigning Subjects to Treatment Groups

Enrolled subjects will be assigned to either the blinded sham coil or the blinded active coil during Phase I of the study using a permuted block randomization method, with the result of the same number of subjects being assigned to both treatment groups. The randomization schedule will be generated by the Mayo Clinic Health Sciences Research (HSR) Biostatistical team. Once generated, the randomization assignment for each subject receiving treatment will be printed on a separate card and sealed in an envelope prepared by the HSR team. These envelopes will be unsealed and subjects will be randomized to the study prior to their first treatment, but not before informed consent/assent has been obtained, they are confirmed to be eligible for the study, and all baseline visit requirements have been fulfilled. In this way, selection bias can be avoided should study staff deduce the nature of the blinded coils. For safety precautions, the full randomization schedule will be sent to the chair of the Data Safety Monitoring Board by the HSR team. In addition, study staff will keep a spreadsheet of the subject number associated with each randomization number, so that the DSMB may unblind a specific subject in the event of a medical emergency.

The XPLOR software has built-in checks that, once a subject has been randomized to a particular coil, will prevent treatment from taking place with the incorrect blinded coil. This safety precaution provides blinding to the staff applying study treatment, staff performing the mood, cognitive, safety, and imaging assessments, and to the subjects – essentially creating a triple-blinded procedure.

5.3 Preparation and Administration of Investigational Device

<u>Motor Threshold Determination Procedure – per NeuroStar User Manual:</u>

1. To determine motor threshold, move the coil down to the patient's head such that the coil is at the vertex and the SenStar tab is aligned above the top of the ear.
2. Move the A/P bar forward until it aligns with the side of the coil.
3. Align the center line on the coil with the 0 degree mark on the coil angle indicator and move back the A/P bar.
4. Once contact and position have been established, ask the subject to enact the hitchhiker position: arm bent 90 degrees at the elbow, fist held loosely, thumb extended outwards.
5. Begin stimulation and focus on any movement of the thumb.
6. Gradually increase the MT level from 0.68 to 1.10 until thumb or concordant finger movement is seen.
7. Once movement is established, begin searching for the motor hotspot. Move the coil around in a grid like pattern, adjusting the MT level as needed. Continue this search until you find a location and power level setting that elicits exactly 5 thumb twitches out of 10 consecutive pulses.
8. Once the motor hotspot has been determined, move the A/P bar forward until it, once again, aligns with the side of the coil.
9. Use the touch screen interface to record the A/P position, Coil Angle, SOA position, and Power Level.
10. Finally, press the Found MT button.

Subjects in Phase I randomized to active treatments will receive treatment parameters that have been safely and feasibly utilized in adult randomized, controlled trials [7, 8] and the 2011 Wall et al. open-label trial in adolescents.[1] Stimulation will occur at a maximum of 120% magnetic field intensity relative to the subject's resting motor threshold (MT), at 10 pulses per second (10 Hz) for 4 seconds, with an intertrain interval of 26 seconds. During the treatment, intensity can be reduced, as needed, to 80% for tolerability. Upward titration with goal of return to maximum intensity (not to exceed 120% MT) will occur as tolerated by each participant. This is not expected to impact treatment response but may make the treatment experience more comfortable for the participating adolescents. Treatment sessions will last for 37.5 minutes (75 trains) to provide a total of 3,000 pulses per treatment session. A total of 30 treatments will be completed within 6-8 weeks of treatment initiation.

Subjects in Phase I randomized to sham treatments will have identical schedules, systematic assessments, and a treatment approach to active treatment. Neither the adolescents nor the investigators will know whether the treatment is active or sham in nature. The sham coil will be identical in its appearance to the active coil. Furthermore, Neuronetics, Inc. has created an acoustic matching profile that renders the "sound" of the treatments virtually indistinguishable to subjects or researchers. The acoustic signal creates a painless percussive sensation that will be felt by the subject and will assist in simulating the active condition.

Subjects in Acute Treatment (Arm 1) of Phase II will receive treatment that is identical in schedule and parameters to that of Phase I with the exception that the known-active therapy coil will be used for all treatments. A total of 30 treatments will be completed within 6-8 weeks.

Subjects in Maintenance Treatment (Arm 2) of Phase II will undergo 52 weeks of maintenance rTMS treatment. The treatment parameters will be identical to those in Phase I except for the frequency of visits (biweekly) instead of daily. Clinical assessments will be offered monthly throughout the duration of the maintenance phase.

5.4 Subject Compliance Monitoring

During Phase I of the trial, subjects will complete 30 treatments within a 6- to 8-week timeframe. This schedule allows for the missing and/or rescheduling of up to 10 treatments over this timeframe. Subjects who are unable to comply with this schedule may be withdrawn from the investigational treatment portion of the study but will be offered ongoing mood, cognitive, safety, and imaging assessments as outlined in the study timeline (Table 4).

During Phase II of the trial, the Non-Responder Cohort from Phase I will receive acute rTMS treatment according to the schedule in Phase I. They will likewise be expected to complete 30 treatments within 6 to 8 weeks (Table 5).

The Responder Cohort from Phase I will receive maintenance treatments in Phase II with a biweekly treatment schedule over the course of 52 weeks (26 treatments). A total of 8 sessions can be missed over the course of 52 weeks (Table 6). More than 8 missed sessions will result in subject withdrawal from the study.

5.5 Prior and Concomitant Therapy

Permitted: Subjects are expected to be on stable dose pharmacotherapy with one of the antidepressants listed in protocol Section 4.1 (Inclusion Criteria). Any other medication change, including initiation, discontinuation, or dose adjustment of medication, needs to be discussed with the site PI and approved before implementation.

Prohibited: Initiation of medication listed in protocol Section 4.2 (Exclusion Criteria) is not permitted during either phase of the study. Dose adjustment or initiation of permitted medications (Section 4.1 Inclusion Criteria) after enrollment must be approved by the site PI prior to implementation.

5.6 Packaging and Labeling

The NeuroStar XPLOR system will be clearly labeled with the following warning:

"CAUTION – Investigational Device when used with individuals younger than 18 years of age. Limited by Federal (or United States) law to investigational use"

5.7 Blinding of Study

The blinded TMS coils will arrive from Neuronetics and will be identical in appearance and labeled generically (i.e Coil X and Coil Y). The device will recognize one coil as active and the other coil as sham. Once a participant has been randomized, the device will "link" the participant's treatment with the corresponding coil. The device will remain inactive if the "incorrect" coil is used for a subject, adding an additional safeguard for each participant and the integrity of the study and allow the treaters to remain blinded to the nature of the subject's treatment.

As outlined in protocol Section 5.2, subjects will be randomly assigned to a coil and will receive all treatments during Phase I of the trial using this coil. Neither the subject nor the study staff (including those administering rTMS treatments and those administering mood, cognitive, safety, and imaging assessments) will know whether the subject is receiving active or sham treatment.

In Phase II of the trial, based upon clinical response in Phase I, subjects will be assigned to either Acute Treatment (Arm 1) or Maintenance Treatment (Arm 2). All treatments during phase II will be provided with the known-active coil.

To minimize any source of bias, unblinding of the study will not be done until all subjects have completed both Phase I and Phase II treatments. However, unblinding will occur if the Data and Safety Monitoring Board deems it necessary due to critical, unexpected patient care considerations (such as in the event of a high rate of unexpected serious adverse events).

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

NeuroStar™ XPLOR TMS Systems will be purchased by MCR and MUSC from Neuronetics, Inc. The devices will be delivered to and installed by Neuronetics in the TMS Suites at MCR and at MUSC.

Upon receipt of the NeuroStar and study treatment supplies, an inventory will be performed and a device accountability log completed by designated study staff at each site. The designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies or damaged or unusable devices in a given shipment will be documented in the device accountability log. The MUSC Principal Investigator, Dr. George, will notify the regulatory sponsor, Dr. Croarkin, immediately of any discrepancies or damaged or unusable products. It will be the responsibility of the regulatory sponsor to immediately notify Neuronetics of any discrepancies or damaged or unusable products at either site.

5.8.2 Storage

The NeuroStar device will be housed in the TMS Suites at MCR and MUSC.

The supplies and disposables required for each treatment, as outlined in protocol Section 5.1, will be stored in a supply station separate from clinical stock at each site.

5.8.3 Distribution of Study Device

The NeuroStar XPLOR device will be housed in the TMS suite at the respective study sites. Subjects in Phase I will be randomly assigned to one of the blinded treatment coils at time of enrollment, as outlined in protocol section 5.2. All subjects in Phase II will be treated with the known-active, non-blinded therapy coil. All subjects will receive a treatment positioning cap during the time of their initial imaging scans; they will receive new treatment disposables (protocol section 5.1) from their treatment site at the start of every new treatment. These treatment packs and SenStar shields will be stored in an area that is separate from clinical stock. Regular reconciliation of SenStar shields received from Neuronetics, SenStar shields used during study treatments, and SenStar shields remaining will be performed. This reconciliation of the inventory will be logged in the Device Accountability Log, signed, and dated. Any discrepancies noted will be documented, the site investigator and regulatory sponsor will be notified, and an investigation will be conducted to determine the cause of the discrepancy. Any SenStar shields disposed of for

any reason other than use for the study (i.e., it was found to be defective or to be missing items) will be documented in the Device Accountability Log at the time of disposal.

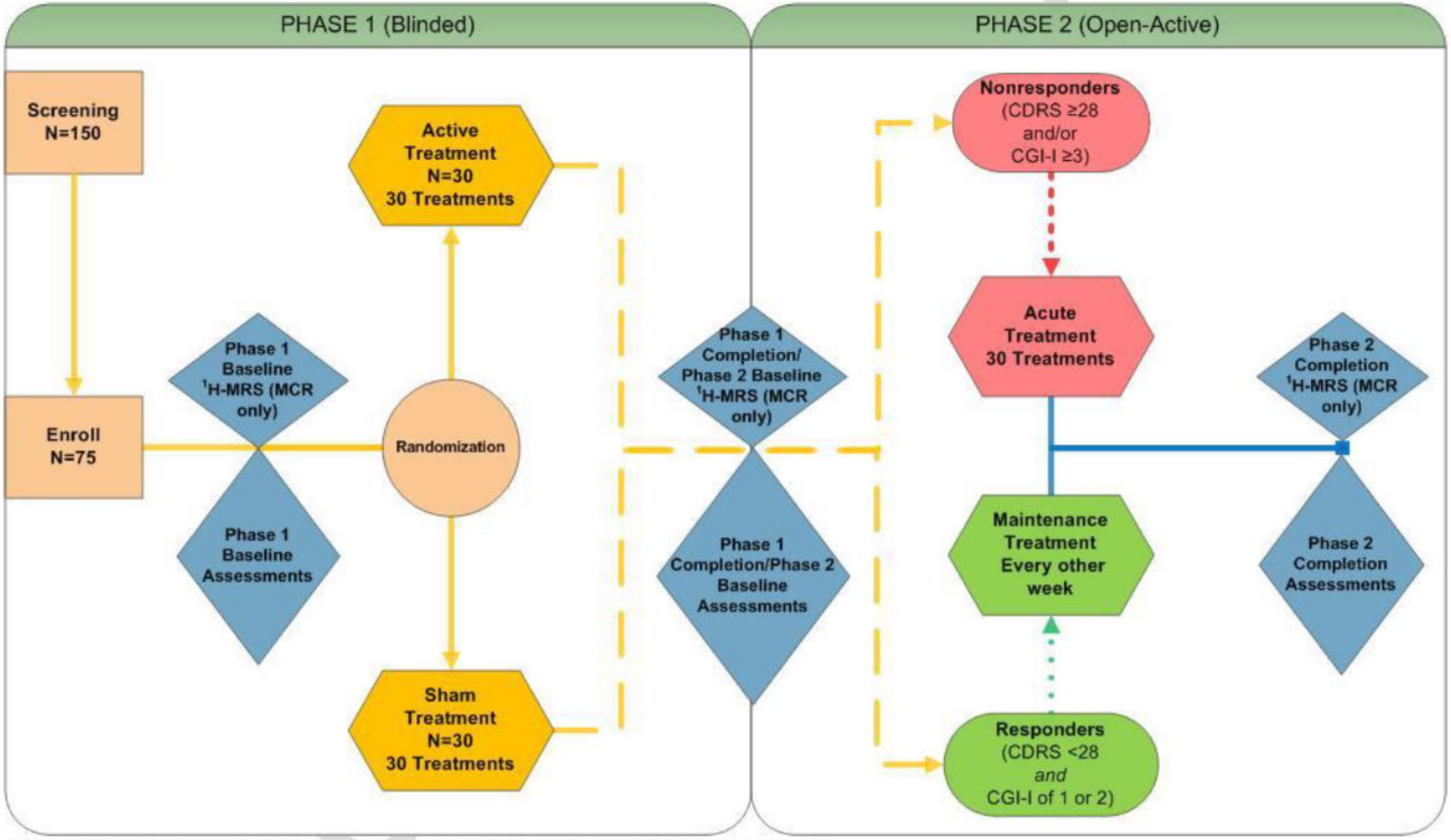
5.8.4 Return or Destruction of Study Device

The NeuroStar devices purchased from Neuronetics, Inc. will remain at the study sites at the completion of the study. Any SenStar shields and treatment packs that are remaining in the inventory at the completion of the study will be packaged and shipped back to Neuronetics.

6 Study Procedures

6.1 Study Overview

Figure 3 – Overview of Two-Phase Study Procedures



See Appendix E for description of mood, safety, and cognitive assessments.

6.2 Phase I – Randomized, Double-Blinded

Study Overview
Adolescents will be screened and enrolled in the study and randomized to either the active treatment or sham treatment group. Neither the subjects nor the investigators will know whether the treatments are active or sham in nature. All subjects will have baseline imaging for neurolocalization of L-DLPFC, mood, safety, and cognitive assessments. Subjects at the MCR site will have baseline magnetic resonance spectroscopy (MRS) at the time of the neurolocalization scan. All subjects will then undergo 30 rTMS treatments at their respective site within the 6- to 8-week timeframe. Mood, safety, and cognitive assessments will be performed at regular intervals throughout the study (Table 4). After the final treatment (i.e. treatment #30 or at early withdrawal), the mood and cognitive assessments will be performed for all subjects. MCR subjects will have MRS scans performed at these time points as well. These assessments may also occur monthly and at 6-month follow-up for those electing to not move on to Phase II treatment opportunities. The treatment and assessment schedules for Phase I are identical for both the active and the sham treatment cohorts. For participants at the MCR site, MRS scans will also occur after the final treatment and again at the 6-month follow-up visit.

Subjects may decline to complete any study assessment or measurement and still remain in the study so long as the assessment or measure in question does not directly impact the ability of study staff to conduct critical study procedures (ex. MRI for treatment localization, measures needed to determine eligibility, etc.) and does not impact the ability of study staff to assess the subject's continued safety (i.e., any of the Safety Assessments).

Table 4 – Phase I Schedule of Assessments (Active and Sham)

	Pretreatment		6-Week Acute Treatment						Follow-Up	
Day(s)	**Screening**	**Baseline**	**Week 1 1-5**	**Week 2 6-10**	**Week 3 11-15**	**Week 4 16-20**	**Week 5 21-25**	**Week 6 26-30**	**Monthly 60, 90, 120, 150, 180**	**Final 210**
Informed Consent	X									
KSADS	X									
Eligibility Checklist and Verification CRF	X									
Medical/Psychiatric History	X									
Urine Pregnancy Test	X									
Urine Drug Test	X									
Pre-TEEQ-P		X								
Pre-TEEQ-A		X								
Post-TEEQ-P								X [g]		
Post-TEEQ-A								X [g]		
Vital Signs [f,g,h,i]		X		X		X		X	X[i]	X
Mood Assessments										
CDRS-R [f,g,h]	X	X		X		X		X	X[i]	X
QIDS-A17-SR [f,g,h]	X	X		X		X		X	X[i]	X
CGI-S [f,g,h]	X	X		X		X		X	X[i]	X
CGI-I [f,g,h]				X		X		X	X[i]	X
Y-MRS [f,g,h]	X	X		X		X		X	X[i]	X
C-VAS [c]			X	X	X	X	X	X		
Cognitive Assessments										
D-KEFS [g]		X						X		X
CAVLT-S [g]		X						X		X
Safety Assessments										
C-SSRS [d,f,g]	X	X	X	X	X	X	X	X	X	X
TASS	X									
Adverse Event Monitoring [e]			X	X	X	X	X	X	X	X
MRI Safety Screening Questionnaire		X						X [g]		X
Imaging Assessments										
MRI localization of L-DLPFC		X								
^{1}H-MRS (MCR site only)		X						X [g]		X
TMS Procedures										
Motor Threshold Determination		X		X [f]		X [f]				
TMS Treatment [a] (5 days/week)			X	X	X	X	X	X		

Phase I Schedule of Assessments Footnotes

a. Subjects are randomized to either the active or sham treatment arm prior to first TMS treatment in Phase I.
b. Motor threshold determination is conducted utilizing the unblinded, known-active treatment coil (Coil C).
c. C-VAS is performed daily pre- and post-treatment.
d. C-SSRS is performed weekly during treatment.
e. Subjects are assessed daily for adverse events during treatment.
e. Assessed at the post-10 and post-20 treatment visit.
f. Assessed at the post-30 treatment visit OR at time of withdrawal for TMS treatment drop-outs.
g. Monthly follow-up assessments may be conducted via telephone
h. Vital signs include height, weight, blood pressure, and heart rate
i. Optional monthly assessments

6.2.1 Consent and Screening Visit

The consent/assent form will be explained in detail to the subjects and their parent(s), and any questions or concerns about the study will be addressed. Written consent/assent will be obtained from both the subject and their parent(s). See Appendices H and I.

The screening process to determine subject eligibility will occur at the respective study sites and will consist of physician evaluation and review of medical record to confirm subject meets other inclusion criteria (Section 4.1) and does not have contraindications to study treatment (Section 4.2). The following assessments will be performed at this visit:

Depression Assessments (estimated 30-45 min):

- K-SADS
- CDRS-R
- QIDS-A17-SR
- CGI-S
- YMRS

Safety Assessments (estimated 20 min):

- C-SSRS
- TASS
- MRI Safety Screen
- urine drug screen
- urine pregnancy screen (for females)

6.2.2 Baseline Visit

Subjects who are found to be eligible are randomized to one of the blinded treatment coils as outlined in protocol Section 5.2. The following assessments will be performed for all subjects:

Mood Assessments (estimated 20-30 min):

- CDRS-R
- QIDS-A17-SR
- CGI-S
- YMRS

Cognitive Assessments (estimated 60 min):

- D-KEFS
- CAVLT-2

Safety Assessments (estimated 10-15 min):

- C-SSRS

Other Assessments (estimated 10 min):

- Pre-TEEQ-P
- Pre-TEEQ-A
- Vital Signs (to include height, weight, blood pressure, and heart rate)

rTMS Procedures (estimated 30-45 min):

- Motor threshold determination

Imaging Assessments
- MRI Safety Screening Questionnaire
- MRI localization of L-DLPFC (estimated 20-30 minutes)
- ^{1}H-MRS (estimated as an additional 20 minutes - MCR site only)

6.2.3 TMS Treatment Days 1-10

rTMS Procedures:
- TMS treatment (37.5 min)

Depression Assessment (estimated 5 min):
- C-VAS (pre and post treatment)

Safety Assessments (estimated 10-15 min):
- C-SSRS (assessed weekly)

6.2.4 Post Treatment 10 Assessment (Performed after Treatment 10 but before Treatment 11)

rTMS Procedures:
- Motor threshold determination

Mood Assessments:
- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I

YMRS

Safety Assessments:
- C-SSRS

Other Assessments (estimated 5 min):
- Vital Signs

6.2.5 TMS Treatment Days 11-20

rTMS Procedures:
- TMS treatment

Depression Assessment:
- C-VAS (pre and post treatment)

Safety Assessment:
- C-SSRS (assessed weekly)

6.2.6 Post Treatment 20 Assessment (Performed after Treatment 20 but before Treatment 21)

rTMS Procedures:
- Motor threshold determination

Depression Assessments:
- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I

YMRS

Safety Assessments:
- C-SSRS

Other Assessments (estimated 5 min):
- Vital Signs

6.2.7 TMS Treatment Days 21-30

rTMS Procedures:
- TMS treatment

Depression Assessment:
- C-VAS (pre and post treatment)

Safety Assessment:
- C-SSRS (assessed weekly)

6.2.8 Post Treatment 30 or Early Withdrawal Assessment (Performed within 5 business days of Treatment 30 or notification of Early Withdrawal)

Mood Assessments:
- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS

Cognitive Assessments:
- D-KEFS
- CAVLT-2

Safety Assessments:
- C-SSRS

Other Assessments (estimated 10 min):
- Post-TEEQ-P
- Post-TEEQ-A
- Vital Signs

Imaging Assessments:

- ^{1}H-MRS (MCR site only)

Subjects will be offered the opportunity to enter into Phase II of the study at completion of this visit by their site's study team. Those choosing to continue to Phase II will follow the treatment schedule outlined in Section 6.3. Those electing not to participate in Phase II will continue with the schedule as outlined below.

6.2.9 Monthly Post-Study Monitoring (+/- 2 weeks)

Monthly post-treatment monitoring may be conducted in-person (preferred), by telephone, or by videophone. Subjects for whom this scheduled may cause an undue time or travel burden may be given the option to complete abbreviated, safety-only screens for post-treatment months 1-5. If a subject reports a concern during the safety screen, the PI will determine whether they should be scheduled for a follow-up visit (in-person, telephone, or video phone) or whether more immediate action is needed.

Depression Assessments (optional):

- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS

Safety Assessments:

- C-SSRS
- Adverse event monitoring

Other Assessments (estimated 5 min):

- Vital Signs
- Change in medication/therapy monitoring

6.2.10 Six-Month Final Visit (+/- 2 weeks)

Depression Assessments:

- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS

Cognitive Assessments:

- D-KEFS
- CAVLT-2

Safety Assessments:

- C-SSRS
- Adverse event monitoring

Other Assessments (estimated 5 min):

- Vital Signs
- Change in medication/therapy monitoring

Imaging Assessments:

- ^{1}H-MRS (MCR site only)

6.3 Phase II – Non-Randomized, Open-Active

Study Overview

Subjects from Phase I will be offered the opportunity to continue with rTMS treatments in Phase II and assigned to treatment arms according to their clinical outcomes at the completion of Phase I. Adolescents from both the active and sham cohorts who do not meet clinical criteria for response (CDRS-R score ≥28 and/or CGI-1 score ≥3) will be given active treatment (protocol Section 6.3.1). Subjects from both the active and sham cohorts who do meet response criteria (CDRS-R score of <28 and CGI-I score of 1 or 2) will be given maintenance treatment (protocol Section 6.3.2).

6.3.1 Phase II Acute Treatment (Arm 1) – Nonresponder Cohort

Phase I Completion assessments (protocol Section 6.2.8) will be used for Phase II Baseline assessments. A urine drug and pregnancy test will be performed before beginning active treatment for Phase II. Schedule of treatments and assessments will follow that of Phase I (protocol Sections 6.2.3 – 6.2.10) using the known-active coil. See Table 5.

Table 5 – Phase II Acute Treatment (Arm 1)
Schedule of Assessments

		6-Week Acute Treatment						Follow-Up	
Day(s)	**Screening**	**Week 1** **1-5**	**Week 2** **6-10**	**Week 3** **11-15**	**Week 4** **16-20**	**Week 5** **21-25**	**Week 6** **26-30**	**Monthly** **60, 90, 120, 150, 180**	**Final** **210**
Urine Drug Test	X								
Urine Pregnancy Test	X								
Vital Signs [a,f,g,i]			X		X		X	X[i]	X
Mood Assessments									
CDRS-R [a,f,g, h]			X		X		X	X[i]	X
QIDS-A17-SR [a,f,g, h]			X		X		X	X[i]	X
CGI-S [a,f,g, h]			X		X		X	X[i]	X
CGI-I [a,f,g, h]			X		X		X	X[i]	X
Y-MRS [a,f,g, h]			X		X		X	X[i]	X
C-VAS[c]		X	X	X	X	X	X		
Cognitive Assessments									
D-KEFS [a,g]							X		X
CAVLT-S [a,g]							X		X
Safety Assessments									
C-SSRS [a,d, h]		X	X[f]	X	X[f]	X	X[g]	X	X
TASS									
Adverse Event Monitoring [e]		X	X	X	X	X	X	X	X
MRI Safety Screening Questionnaire							X[g]		X
Imaging Assessments									
^{1}H-MRS (MCR site only)							X[g]		X
TMS Procedures									
Motor Threshold Determination [b]			X[f]		X[f]				
TMS Treatment [b] (5 days/week)		X	X	X	X	X	X		

Phase II Acute Treatment Schedule of Assessments Footnotes

a. Post-30 Assessments from Phase I are used for Phase II Baseline.
b. Motor threshold determina ion and all treatments in Phase II are conducted utilizing he unblinded, known-active treatment coil (Coil C).
c. C-VAS is performed daily pre- and post-treatment.
d. C-SSRS is performed weekly during treatment.
e. Subjects are assessed daily for adverse events during treatment.
e. Assessed at the post-10 and post-20 treatment visit.
f. Assessed at the post-30 treatment visit OR at time of withdrawal for TMS treatment drop-outs.
g. Monthly follow-up assessments may be conducted via telephone
h. Vital signs include height, weight, blood pressure, and heart rate
i. Optional monthly assessments

6.3.2 Phase II Maintenance Treatment (Arm 2) – Responder Cohort

Phase I Completion assessments (protocol Section 6.2.8) will be used for Phase II Baseline assessments. A urine drug and pregnancy test will be performed before beginning active treatment for Phase II. Treatments will be administered using the parameters outlined for Phase I utilizing the known-active therapy coil on a biweekly basis for 52 weeks. See Table 6 for schedule of treatments and assessments.

Table 6 – Phase II Maintenance Treatment (Arm 2) Schedule of Assessments

		12-Month Bi-Weekly Maintenance Treatment		Follow-Up
Treatment(s)	**Screening**	**1-25**	**26**	**Six Months**
Urine Drug Test	X			
Urine Pregnancy Test	X			
Vital Signs [a,d,e,f]		X	X	X
Mood Assessments				
CDRS-R [a,d,e]		X	X	X
QIDS-A17-SR [a,d,e]		X	X	X
CGI-S [a,d,e]		X	X	X
CGI-I [a,d,e]		X	X	X
Y-MRS [a,d,e]		X	X	X
C-VAS		X	X	
Cognitive Assessments				
D-KEFS [a,e]			X	X
CAVLT-S [a,e]			X	X
Safety Assessments				
C-SSRS [a,d,e]		X	X	X
TASS				
Adverse Event Monitoring [c]		X	X	X
MRI Safety Screening Questionnaire [a]			X	X
Imaging Assessments				
^{1}H-MRS (MCR site only) [a]			X	X
TMS Procedures				
Motor Threshold Determination [a, b]		X		
TMS Treatment [b] (5 days/week)		X	X	

Phase II Maintenance Treatment Schedule of Assessments Footnotes

a. Post-30 Assessments from Phase I are used for Phase II Baseline.
b. Motor threshold determination and all treatments in Phase II are conducted utilizing the unblinded, known-active treatment coil (Coil C).
c. Assessed at every visit
d. Assessed monthly during maintenance treatment
e. Assessed at final (post-26) treatment OR at time of wi hdrawal.
f. Vital signs include height, weight, blood pressure, and heart rate.

6.3.2.1 Every Other Week Treatment Visits (+/- 3 business days)

rTMS Procedures:
- TMS treatment (bi-weekly)
- Motor threshold determination (monthly)

Depression Assessments (assessed monthly):
- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS
- C-VAS (performed pre- and post-treatment)

Safety Assessments (assessed monthly):
- C-SSRS

Other Assessments (estimated 5 min):
- Vital Signs

6.3.2.2 Post Treatment 26 Visit (Within 5 business days of Last Treatment)

Depression Assessments:
- CDRS-R
- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS

Cognitive Assessments:
- D-KEFS
- CAVLT-2

Safety Assessments:
- C-SSRS

Other Assessments (estimated 5 min):
- Vital Signs

Imaging Assessments:
- MRI Safety Screening Questionnaire
- ^{1}H-MRS (MCR site only)

6.3.2.3 Six-Month Follow-Up Visit (+/- 2 weeks from 6 months post Last Treatment)

Depression Assessments:
- CDRS-R

- QIDS-A17-SR
- CGI-S
- CGI-I
- YMRS

Cognitive Assessments:

- D-KEFS
- CAVLT-2

Safety Assessments:

- C-SSRS
- Adverse event monitoring

Other Assessments (estimated 5 min):

- Vital Signs
- Change in medication/therapy monitoring

Imaging Assessments:

- ^{1}H-MRS (MCR site only)

7 Statistical Plan

7.1 Sample Size Determination

Preliminary data from the 2011 Wall et al. pilot study[1] was used to estimate the sample size needed per treatment group to achieve at least 80% power for detecting a difference between the active and sham treatments using 2 versions of the CDRS-R depression inventory measured at baseline and completion of 30 sessions including: 1) the rate of those responding to treatment based on a CDRS-R and CGI-I finite cutoff score (binary), and 2) the raw change in CDRS-R score from baseline (continuous).

For the binary response we observed a success rate of 71% in our preliminary study. For sample-size purposes we hypothesize a success rate of 65% for rTMS. We further hypothesize a success rate of 25% for the Sham group. Based on these assumptions, we have determined that a total sample-size of N=70 (35 per group) will provide statistical power (two-tailed, alpha=0.05) of 94% to detect a difference between groups.

When the change in CDRS-R was quantified using a continuous variable we observed a mean delta of 33.3 with corresponding standard deviation of 7.3. Under the conservative assumption that the "true" standard deviation of this response is 10.0, we have determined that a total sample-size of N=70 (35 per group) will provide statistical power (two-tailed, alpha=0.05) of 91% to detect a difference between groups of 8.0 units.

Thus a total sample-size of N=35 per group will provide adequate statistical power. Since the primary analysis will be performed using the approach of LOCF, we will not adjust the sample-size to account for attrition. We will however, perform supplementary analyses which are restricted to subjects who complete the study. Under the assumption that the attrition rate is approximately 30% we repeated the power analyses described above using an effective sample-size of N=50 (25 per group). Using these effective sample-sizes, the supplemental

analysis restricted to study completers will have statistical power of 83% to detect the hypothesized difference when change in CDRS-R is quantified as a binary response and statistical power of 80% to detect a difference between groups of 8.0 units when the change in CDRS-R is quantified as a continuous variable.

7.2 Statistical Methods

Descriptive Statistics
Univariate descriptive statistics and frequency distributions will be calculated as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the treatment groups. These analyses will help identify potential confounding variables to be used as covariates in sensitivity analyses. Distributions across subgroups used in randomization will be compared to assess whether the randomization was successful in equalizing distributions of these prognostic variables across treatment groups.

Statistically significant differences on overall comparisons will be explored using multiple pair-wise comparisons of each of the (treatment) groups using Bonferroni correction for multiple comparisons. Mean scores and standard deviation for each group will be calculated. Subsequent multiple comparisons via Tukey's procedure will be set at 0.01 to control Type I error rate.

Primary Hypotheses:
1) Adolescents in Phase I treated with active rTMS at the left dorsolateral prefrontal cortex (L-DLPFC) will have significant mood improvement when compared to sham treatment.

2) Adolescents in Phase II treated with maintenance rTMS at the L-DLPFC will achieve sustained response of the depressive symptoms.

Phase II represents a proof of concept/preliminary study of long-term maintenance for treatment responders (either active or sham in Phase I) and an opportunity for open-active treatment in nonresponders. The inclusion of phase II is ethically necessary to ensure that all pediatric participants are offered an opportunity to receive active treatment if unresponsive in phase I. The analysis of data collected as part of phase II is exploratory and will include primarily descriptive statistics.

Treatment outcomes for both phases will be defined as response (CDRS-R raw score <28 & CGI-I ≤2 & CGI-S ≤2), or nonresponse (CDRS-R raw score ≥28 and CGI-I ≥3) assessed using a logistic regression model with independent variables of treatment number (i.e. #10 vs. #20 vs. #30) and gender (male vs. female) will be analyzed. Assessing potential gender effects will be a secondary analysis. The primary analysis will not adjust for gender. Although we anticipate that more females than males will participate in the study, we assume that the distribution of gender will be similar between treatment arms and have no a priori reason to suspect that the efficacy of treatment will be gender specific.

Serious adverse events will be reported as noted within the application. All adverse events will be summarized according to treatment groups. Given the sample size for the current study, the statistical power for detecting differences between groups is limited. However, we will compare between groups using an exact test.

All statistical tests will be performed at the 0.05 significance level.

Secondary Hypotheses (for MCR site only):
Baseline glutamate, reported as a CSF-corrected absolute concentration and as an overlapping resonance with glutamine, will be significantly higher in both AC and L-DLPFC in depressed adolescents as measured by ^{1}H-MRS at 3T when compared to data derived from previously scanned healthy controls.

In comparison to non-remission subjects, depressed adolescents treated with rTMS who achieve remission (defined as a CDRS-R raw score <28 **and** CGI-I ≤2 **and** CGI-S ≤2 at treatment completion) will exhibit a greater decrease in glutamine, reported as a CSF-corrected absolute concentration percent change (baseline to endpoint) in AC and L-DLPFC as measured by ^{1}H-MRS at 3T.

The hypotheses will be tested using t-tests. Additionally, analyses of covariance will be performed to control for potentially important covariates or confounders, such as age or gender. Non-parametric distribution will be analyzed by non-ANOVA statistics.

7.3 Subject Population(s) for Analysis

The primary analysis will use the intention-to-treat (ITT) population, defined as all patients who started at least one treatment session. Secondary analyses of the primary outcome will examine "completer" and "partially adherent" cohorts. The Completer Cohort will be defined as subjects treated according to the protocol with fewer than 10 rescheduled, missed, or partially completed rTMS sessions ultimately taking part in 30 treatment sessions. The Partially Adherent Cohort will have at least 20 completed or partially completed sessions without reaching the full 30-treatment threshold. Those with less than 20 completed or partially completed rTMS sessions will be analyzed within the intention-to-treat population.

8 Safety and Adverse Events

All Unanticipated Adverse Device Effects (UADEs) and severe, expected adverse events (AEs) at least probably related to the study treatment not meeting the criteria of UADE, including mania, exacerbation of depression, and suicidality will be recorded on the Adverse Event CRF and reported according to severity and the relationship of the AE to rTMS. Records of these events will be maintained and reports submitted to the FDA, regulatory sponsor, and reviewing IRBs according to local IRB policy and regulatory requirements. All other expected clinical adverse events and nonsignificant (not serious) clinical adverse events will be reported to all Principal Investigators on a periodic basis and reported to the appropriate IRB at the time of continuing review and to the FDA at the time of the Annual Report. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

Additionally, all events suspected by the site PI to meet criteria for UADEs or severe, expected AEs at least probably related to the study and all resulting clinical decisions will be reported by telephone to the regulatory sponsor within 24 hours. The regulatory sponsor and MCR site PI will then be responsible for determining the appropriate reporting actions to the DSMB, Neuronetics, and the FDA. If deemed necessary by the regulatory sponsor, a written report will be submitted to the FDA, reviewing IRBs, the DSMB, Neuronetics, and all investigators according to all applicable reporting requirements – under this IDE number - as to the nature of the UADE and clinical course of action/outcome. Moderate and mild AEs at least probably related to the study treatment will be reported to the regulatory sponsor within 3 working days of the incident.

To date, Dr. Croarkin (a practicing, board-certified child and adolescent psychiatrist) and the staff at MCR have conducted the largest known open-label rTMS trial of treatment-resistant depression. Furthermore, Dr. George is a world expert in brain stimulation and depression, and is the editor-in-chief of a new journal he launched with Elsevier in 2008 called *Brain Stimulation: Basic, Translation and Clinical Research in Neuromodulation*. The NIH and other funding agencies have continuously funded him since his fellowships. He has received both a NARSAD Young Investigator and Independent Investigator Award to pursue TMS research in depression. He has received numerous international awards including the NARSAD Klerman Award (2000), NARSAD Falcone Award (2008), and the Lifetime Achievement Award (2007) given by the World Federation of Societies of Biological Psychiatry (WFSBP). In 2009, US News and World Report named him one of 14 'medical pioneers who are not holding back'. He is on several editorial review boards and NIH study sections, has published over 300 scientific articles or book chapters, has eight patents, and has written or edited six books. As such, there is confidence in the ability to safely conduct both phases of this multisite rTMS trial and detect important clinical changes (along with the above-mentioned operationalized safety criteria) in this population of depressed adolescents.

8.1 Definitions

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problems or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Effect (Event)
Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

> **Severity Ratings: Mild (grade 1)** – a transient AE easily tolerated by the patient. **Moderate (grade 2)** – an AE that causes the patient discomfort and interrupts the subject's usual activities, but does not interfere with function. **Severe (grade 3)** – an AE that causes considerable interference with the patient's usual activities.
>
> **Relationship to Treatment: Definite** – AE is related. **Probable** – AE has a strong temporal relationship and another etiology is less likely. **Possible** – AE has a strong temporal relationship but an alternative etiology is likely. **Not Related** – AE is due to underlying or concurrent illness or drug effect.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event related to the device that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery

should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event or UADE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event they become aware of that occurs at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The regulatory sponsor should also be notified if the local investigator should become aware of the development of problems, cancer, or a congenital anomaly in a subsequently conceived offspring of a subject who has participated in this study.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Mayo Clinic-Specific Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets ***all*** of the following three criteria:

- Serious: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality;4 and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) Unanticipated problems or events are those that are not already described as potential risks in the protocol, consent/assent document, the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

- Related: A problem or event is "related" if it is possibly related to the research procedures.

MUSC-Specific Definitions

Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)
An Unanticipated Problem is an event refers to any incident, experience or outcome that:

1. is **unexpected** (in terms of nature, severity or frequency) given: (a) the research procedures described in the protocol-related documents , such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. is **related or possibly related** to a subject's participation in the research; and
3. suggests that the research **places the research subjects or others at a greater risk** of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Adverse Event Reporting Period
For this study, the treatment follow-up period is defined as six months following the last administration of rTMS.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and UADEs and severe, expected AEs at least probably related to the study treatment will also be recorded on the Adverse Event CRF. All clearly related signs, symptoms, and abnormal diagnostic laboratory or procedure results will be recorded in the source document.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group or suspected causal relationship to the investigational device will be recorded in the subjects' case history. For all adverse effects, sufficient information will be pursued and/or obtained as to permit an adequate assessment of the casual relationship between the adverse effect and the investigational device. The clinical course of each event will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events at least probably related to study treatment that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least probably related to the study treatment or study participation will be recorded and reported immediately upon learning of such event(s).

8.3 Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study subject and if required complete the Adverse Event CRF. All events suspected by the site PI to meet criteria for a UADE or severe, expected adverse event at least probably related to the study treatment, including those that might occur at MUSC, will be reported to the regulatory sponsor within 24 hours from time of event. The regulatory sponsor will evaluate the event and determine the necessary follow-up and reporting required. All events suspected by the site PI to meet criteria for moderate or mild, expected adverse

events at least probably related to the study treatment will be reported to the regulatory sponsor within 3 working days from time of event.

The regulatory sponsor will promptly review documented adverse events from both sites and determine whether they meet criteria for a UADE. If necessary the regulatory sponsor will report the results of such to the FDA within 10 working days. Thereafter the regulatory sponsor will submit additional reports concerning the effect as requested.

The site Principal Investigator(s) or designated study staff will be responsible for reporting to their IRB, within institutional guidelines, only those UADEs originating at their site. UADEs originating at other site(s) will be reported at the time of continuing review.

8.3.1 Sponsor and Investigator Reporting, Notifying Reviewing IRBs

The site investigators will report to their reviewing IRB according to local policy and procedure.

MCR Site
The regulatory sponsor or designated study staff will report to the Mayo Clinic IRB any UPIRTSOs originating at MCR (see Section 8.1 for definition of UPIRTSO) according to Mayo Clinic IRB policy and procedures. Non-UPIRTSOs occurring at MCR and any adverse events occurring at other site(s) will be reported to the Mayo Clinic IRB at the time of continuing review, according to the Mayo Clinic IRB policy and procedures.

For any adverse event occurring at MCR, study staff will firstly follow procedures to protect the study subject. The regulatory sponsor will assess and determine if the problem or event meets *all three* criteria for a UPIRTSO and whether any modifications to the study protocol are necessary. If the problem or event *does* meet criteria for a UPIRTSO, the Mayo Clinic IRB will be notified within five working days of knowledge of the problem or event. The regulatory sponsor will also include a corrective action plan or justification as to why a plan is not needed. If necessary, a protocol modification will be submitted to Mayo Clinic IRB. If a protocol modification is deemed necessary, the regulatory sponsor will notify the FDA, DSMB, and the MUSC site PI within five working days. Site investigators will be responsible for ensuring that no participants are enrolled at either site until such modifications have been approved by the respective IRBs. All UPIRTSOs occurring at MCR will be reported to MUSC at the time of FDA and Mayo Clinic IRB reporting. All MCR Non-UPIRTSOs will be reported to MUSC at least yearly or earlier upon request.

MUSC Site
The MUSC PI or designated study staff will report to the MUSC IRB any Unanticipated Problems (see Section 8.1 for definition of Unanticipated Problem) originating at MUSC according to MUSC IRB policy and procedures. Events or effects that do not meet the definition of Unanticipated Problems will be reported to the MUSC IRB at the time of continuing review.

For any adverse event occurring at MUSC, study staff will firstly follow procedures to protect the study subject. The site PI will then assess the severity and relatedness of the study treatment to the event and notify the regulatory sponsor as follows. For events suspected to meet criteria for a UADE (see section 8.1) or a severe, expected AE at least probably related to the study treatment, the regulatory sponsor will be notified within 24 hours of learning of the event. For suspected moderate or mild, expected AEs, the

regulatory sponsor will be notified as soon as possible but in no event more than three working days of the event. The regulatory sponsor will then be responsible for assessing the event and determining the subsequent follow-up and reporting requirements.

If a protocol modification is deemed necessary by the MUSC IRB, the site PI or designated study staff will notify the regulatory sponsor within five working days. The regulatory sponsor will be responsible for submitting these modifications to the FDA, Neuronetics, the DSMB, and Mayo Clinic IRB. No participants will be enrolled at either site until such modifications have been approved by the respective IRBs.

8.3.2 Regulatory Sponsor Reporting: Notifying the FDA

The regulatory sponsor will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats, and regulations.

The regulatory sponsor will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators. The completed FDA Form 3500A will be submitted to the FDA no later than 10 working days after the regulatory sponsor first receives notice of the UADE.

If the results of the regulatory sponsor's follow-up evaluation show that an adverse effect that was initially determined to not constitute a UADE does in fact meet the requirements for reporting, the regulatory sponsor will submit a completed FDA Form 3500A no later than 10 working days after the determination was made.

For each submitted FDA Form 3500A, the regulatory sponsor will identify all previously-submitted reports that addressed a similar adverse effect experience and will provide an analysis of the significance of the newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the regulatory sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process
Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A. The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Deviations from the investigational plan.
An investigator shall notify the regulatory sponsor and reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given after the emergency occurred within reporting timeframe outlined by the site IRB. Except in such an emergency, prior approval from the

regulatory sponsor is required for changes in or deviations from a plan. In addition, if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.4 Unblinding Procedures (Breaking the Blind)

While the safety of the subject always comes first, it is still important to seriously consider if unblinding the study therapy is necessary to ensure a subject's safety. In the event of a serious adverse device effect, the investigator will carefully assess whether breaking the blind will critically affect how a subject is treated in response to the adverse effect and whether this knowledge outweighs the implications to the scientific soundness of the study. In the case of most serious adverse effects, treatment would be discontinued and symptoms treated symptomatically irrespective of the knowledge of whether the treatment received was active or sham in nature. In these instances, having this information would not significantly alter the treatment of the adverse effect(s).

As an additional safeguard against bias, the DSMB has been charged with making the final recommendations for breaking the study blind. If the DSMB recommends unmasking the study, Neuronetics, Inc. will be contacted and the key to active or sham treatment will be obtained. Notation regarding the nature of the treatment the subject had been receiving will be documented in the subject's source document.

If the decision to break the blind is made immediately upon learning of the adverse event, this information will be reported to the FDA and reviewing IRB at the time of initial adverse event reporting. If the unblinding occurs after the initial reporting, the FDA will be notified of the action within ten working days from the time of breaking the blind. The reviewing IRB will be notified according to their reporting guidelines if the decision is made to break the study blind after the initial reporting.

If unblinding occurs at one site, the other site WILL NOT be given the randomization key unless directed to do so by the FDA; Neuroentics, Inc.; reviewing IRB; or the DSMB.

8.5 Stopping Rules

Specific occasions when study treatment may be stopped are explained in the discussion of risk management (section 1.4.2).

Because of the anticipated low level of adverse events of rTMS, the DSMB will be charged with reviewing adverse events every six months. Serious adverse events will be reviewed on a monthly basis, unless a more urgent review is requested. Only under extreme circumstances or if it were determined that a high level of side effects was due to rTMS, would the DSMB be charged with breaking the study mask.

8.6 Medical Monitoring

The regulatory sponsor has oversight for the overall safety of the study. This 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.

8.6.1 Internal Data and Safety Monitoring Board

A Data and Safety Monitoring Board will be assembled to oversee the safety of the study, patients, and the scientific validity and integrity of data collected as part of the study. This DSMB will include members representing both sites and will consist of at least one non-study, Board-certified psychiatrist and at least one non-study, pediatric neuropsychologist. The DSMB will meet bi-annually to review any adverse events related to the study, ensure that appropriate actions were taken by study staff, the event resolved, and the proper agencies notified. If deemed necessary, the DSMB will make recommendations for changes to the study protocol to ensure the continued safety of study subjects and integrity of study data collected. All serious adverse events will be reviewed monthly or sooner upon request. In the event of an SAE, this DSMB has also been charged with making the final decision regarding breaking the study blind. Whenever possible, the DSMB will work directly with Neuronetics and the subject's clinical physician without involving the study physicians in order to prevent study bias.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the source data recorded on the source documents.

9.3 Case Report Forms

An eligibility form will be completed for each subject enrolled into the clinical study. As needed, an adverse event worksheet will be completed for study subjects experiencing AEs. The site investigator or designated study staff will review, approve, and sign/date each completed CRF; the signature serving as attestation that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. See Appendices F and G for draft CRFs.

Data will be captured at each participating site by qualified study staff who will perform primary data collection from source-document reviews to electronic case report forms (eCRF) via Medidata Rave, the information technology endorsed by Mayo Clinic's Clinical Trial Management System (CTMS) as described in Appendix O. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained. Data will be entered for this study utilizing one or a combination of the following methods:

1. Data may be captured electronically, without use of paper.
2. Data may be transcribed from the Electronic Medical Record (EMR-an electronic source that must be available for review) into an EDC system, without use of paper.
3. Data may be captured on paper (considered source documentation) and transcribed into the EDC system, BUT paper documentation must be retained and available for review.

Data Management

Study sites will transcribe subject source data into eCRFs using Medidata Rave. The Medidata Rave system is compliant with 21 CFR (Code of Federal Regulations) Part 11 FDA (Food and Drug Administration) requirements. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection and security. Data will be transmitted via the internet from investigational sites to a central hosting site, utilizing state-of-the-art encryption mechanisms to ensure security and confidentiality.

Details of the study treatments including treatment parameters, such as percent of MT for each treatment, will be retained within the TMS device by the TrakStar software. In addition, a daily summary of the treatment will be created and stored in the subject's source document.

Case files will be created for each subject where completed visit CRFs will be stored. Any adverse event CRFs will also be stored in the case file.

Data Processing

Study site(s) will transcribe or directly enter subject source data into eCRFs using Medidata Rave at the time of or as soon as possible after the subject visit. All completed eCRFs will be reviewed by the study coordinator at regular intervals as the study progresses.

At the conclusion of the study or earlier upon request, all treatment data stored by the TrakStar software at MUSC will be transmitted to the regulatory sponsor for inclusion in data analysis.

Data Security and Confidentiality

Database and Web servers will be secured through controlled physical access. For security reasons, and in compliance with regulatory guidelines of Medidata Rave, system access is granted to the user who owns the sign on identification and password in use. Access codes are non-transferrable. Site personnel who have not undergone training may not access the study eCRF's until appropriate training is completed and documented. The eCRF data elements do

not reside on the users work station; they are transmitted to a secure central database (host site) as forms are completed or updated. Protocol-specified source documents (e.g. hospital discharge summaries, operative/procedural reports) will be retrieved as necessary. Copies of all study-related documentation will be retained at the site.

Case files will be located in a secured area. All case files will be stored in a locked storage cabinet and/or closet, with close monitoring and tracking of key access. As a second line of security, the cabinet and/or closet will located in an area that is only accessible by electronic key card access and/or admittance by desk personnel. Visit data collected and, if applicable, adverse event CRFs will be de-identified and subjects will be referred to using only their assigned study subject identifier. Information stored in the source documents will be safe-guarded according to institutional guidelines.

Data Quality Assurance/Data Clarification Process

The CTMS Medidata Rave database will have consistency checks programmed into the system to inform investigators of potential data issues as the data entry progresses. The exception log for entries will be reviewed by the study coordinator/monitor to identify potential training and/or data integrity issues. If data integrity issues are suspected, the study coordinator/monitor will perform site monitoring, including review of the eCRFs with verification to the source documentation. During monitoring visits, the site will make their computer and/or high speed internet access available to the study coordinator/monitor so that he or she may verify the data entries with the source documentation.

Site monitoring visits to both sites will be used to verify accuracy of source documents.

9.4 Records Retention

The site PIs will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Records will be retained per regulations and local site policy.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored by the Office of Research Regulatory Support at MCR according to the monitoring plan described in Appendix M.

10.2 Auditing and Inspecting

The site investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The site investigators will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

Although this study is considered more than minimal risk to children, rTMS treatments offer a potential direct benefit for the individual subject. In addition, the schedule of mood assessments and daily assessment during the interventional portion of the study for any adverse events has been developed for the purpose of monitoring the subject's well-being.

This protocol and any amendments will be submitted to a properly constituted local IRB, in agreement with local legal prescriptions, for formal approval of the study at each participating site. The decision of the IRB concerning the conduct of the study at MUSC will be documented in writing to the regulatory sponsor before commencement of this study.

All families and subjects for this study will be provided a consent/assent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent/assent form will be submitted with the protocol for review and approval by the site IRB for the study. The formal consent of a subject, using the approved IRB consent/assent form, must be obtained before that subject undergoes any study procedure. This form must be signed and dated by the subject, the subject's legally-authorized representative, and the individual obtaining informed consent/assent.

12 Study Finances

12.1 Funding Source

Mayo Clinic infrastructure and study personnel are funded through the Paul and Betty Woolls Foundation and Mayo Clinic Department of Psychiatry and Psychology.

MUSC infrastructure and study personnel are funded through the Department of Psychiatry departmental research funds allocated to the Brain Stimulation Laboratory for the sole purpose of conducting research such as this Adolescent Study.

In-kind donation of SenStar Shields and treatment disposables for both sites from Neuronetics, Inc.

13 References

1. Wall, C.A., et al., *Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: A prospective, open pilot study.* Journal of Clinical Psychiatry, 2011. **72**(9): p. 1263-1269.
2. March, J.S., et al., *The Treatment for Adolescents with Depression Study (TADS): Long-term effectiveness and safety outcomes.* Archives of General Psychiatry, 2007. **64**(10): p. 1132-1144.
3. March, J.S., *Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial.* Journal of the American Medical Association, 2004. **292**(7): p. 807-820.
4. Brent, D., et al., *Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial.* JAMA - Journal of the American Medical Association, 2008. **299**(8): p. 901-913.
5. Walkup, J.T., *Treatment of depressed adolescents.* American Journal of Psychiatry, 2010. **167**(7): p. 734-737.
6. Croarkin, P.E., et al., *The emerging role for repetitive transcranial magnetic stimulation in optimizing the treatment of adolescent depression.* Journal of ECT, 2010. **26**(4): p. 323-329.
7. George, M.S., et al., *Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial.* Archives of General Psychiatry, 2010. **67**(5): p. 507-516.
8. O'Reardon, J.P., et al., *Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial.* Biological psychiatry, 2007. **62**(11): p. 1208-1216.
9. Walter, G., et al., *Transcranial magnetic stimulation in young persons: a review of known cases.* Journal of child and adolescent psychopharmacology, 2001. **11**(1): p. 69-75.
10. Loo, C., T. McFarquhar, and G. Walter, *Transcranial magnetic stimulation in adolescent depression.* Australas Psychiatry, 2006. **14**(1): p. 81-5.
11. Bloch, Y., et al., *Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: An open-label study.* Journal of ECT, 2008. **24**(2): p. 156-159.
12. Wassermann, E.M., *Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996.* Electroencephalography and clinical neurophysiology, 1998. **108**(1): p. 1-16.
13. Gibbons, R.D., et al., *Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents.* The American journal of psychiatry, 2007. **164**(9): p. 1356-63.
14. Libby, A.M., et al., *Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs.* The American journal of psychiatry, 2007. **164**(6): p. 884-91.
15. Cheung, A., et al., *Pediatric prescribing practices and the FDA Black-box warning on antidepressants.* Journal of developmental and behavioral pediatrics : JDBP, 2008. **29**(3): p. 213-5.
16. Rappaport, N., et al., *Treating pediatric depression in primary care: coping with the patients' blue mood and the FDA's black box.* The Journal of pediatrics, 2006. **148**(5): p. 567-8.

17. Maalouf, F.T. and D.A. Brent, *Pharmacotherapy and psychotherapy of pediatric depression.* Expert opinion on pharmacotherapy, 2010. **11**(13): p. 2129-40.
18. *Practice parameter for the assessment and treatment of children and adolescents with suicidal behavior. American Academy of Child and Adolescent Psychiatry.* Journal of the American Academy of Child and Adolescent Psychiatry, 2001. **40**(7 Suppl): p. 24S-51S.
19. Craig, A.D., *The sentient self.* Brain structure & function, 2010. **214**(5-6): p. 563-77.

14 Appendices

A: Regulatory Sponsor Supporting Documents
- A1: Curriculum Vitae
- A2: Biosketch
- A3: Signed Investigator Agreement

B: MUSC site PI Supporting Documents
- B1: Curriculum Vitae
- B2: Biosketch
- B3: Signed Investigator Agreement

C: Referenced Materials
- C1: Unpublished Articles
- C2: Published Articles

D: Study Protocol

E: Study Assessments

F: Mayo Clinic Draft CRFs

G: MUSC Draft CRFs

H: Mayo Clinic Draft Consent/Assent Documents

I: MUSC Draft Consent/Assent Documents

J: Device Information
- J1: Neuronetics, Inc., Cross-Reference Letter
- J2: NeuroStar TMS System FDA Approval Letter
- J3: NeuroStar TMS Therapy System User Manual
- J4: NeuroStar XPLOR Overview

K: Safety Alert Notice(s)
- K1: Neuronetics Safety Alert Notice 4-26-2011
- K2: Redacted MDA 3-10-2011
- K3: Redacted MDA 3-28-2011

L: Patient Education
- L1: TMS Information Sheet – “Is transcranial magnetic stimulation right for me?”
- L2: TMS Information Booklet – “Transcranial Magnetic Stimulation (TMS)”

M: Study Monitoring Plan

N: Data Safety and Monitoring Board

O: Clinical Trial Management Systems (CTMS)

Appendix E – Description of Study Assessments

Description of Mood Assessments:

- *Schedule for Affective Disorders and Schizophrenia for School Aged Children – Affective Disorders Supplement (K-SADS)* – a semi-structured diagnostic tool designed to assess psychopathology in children and adolescents according to DSM IV criteria
- *Children's Depression Rating Scale, Revised (CDRS-R)* – a validated, 17-item, semi-structured clinician rating tool to assess severity of depression with parents providing input into 14 of the items.
- *Quick Inventory of Depressive Symptoms* – Adolescent version (QIDS-A17-SR) – a 17-item, self-report instrument.
- *Clinical Global Impression – Severity & Improvement (CGI-S & CGI-I)* – standardized clinician assessments rating illness severity and change over time.
- *Young Mania Rating Scale (YMRS)* – an 11-item questionnaire used to assess severity of manic symptoms
- *Computerized Visual Analog Scale (C-VAS)* – a self-entered, computerized interactive graphical visual analog scale that sequentially measures a variety of mood, anxiety, irritability and suicidality variables.

Description of Cognitive and Safety Assessments:

- *The Delis-Kaplan Executive Function Scale (D-KEFS)* - measures flexibility of thinking on a visual motor task and a verbal fluency test to measure fluent productivity in verbal domain.
- *The Children's Auditory Verbal Learning Test version 2 (CAVLT-2)* - measures auditory verbal learning and memory.
- *Columbia - Suicide Severity Rating Scale (C-SSRS) – Short Form* – is a semistructured instrument that elicits information about recent suicidal behavior, attempts and ideation, as well as the potential method employed, medical lethality, precipitants and surrounding circumstances.
- *Keel Transcranial Magnetic Stimulation Adult Safety Screen questionnaire (TASS)* – complements history-taking in identifying potential safety problems related to TMS.
- *MRI Safety Screening Questionnaire* – safety questionnaire that complements history-taking in identifying contraindications to MRI scanning

Description of Experimental Assessments:

- *Pre-Treatment Expectations and Experience Questionnaire – Parent (Pre-TEEQ-P)* – documents parents' initial expectations of trial outcomes and study personnel as well as outcomes of previous treatments.
- *Pre-Treatment Expectations and Experience Questionnaire – Adolescent (Pre-TEEQ-A)* – documents subject's initial expectations of trial outcomes and study personnel as well as outcomes of previous treatments.

- *Post-Treatment Expectations and Experience Questionnaire – Parent (Post-TEEQ-P)* – documents parents' final impressions of the trial and study personnel, including whether they felt their child received the real treatment or sham treatment.

- *Post-Treatment Expectations and Experience Questionnaire – Adolescent (Pre-TEEQ-A)* – documents subject's final impressions of trial and study personnel, including whether they felt they received the real treatment or sham treatment.

Appendix M – Study Monitoring Plan

Study: *A Randomized, Double-Blinded, Sham-Controlled Trial of Repetitive Transcranial Magnetic Stimulation in Depressed Adolescents*

IDE Sponsor
Dr. Paul E. Croarkin
Mayo Clinic, Rochester, MN

Study Site Locations

1. Mayo Clinic: Rochester, MN
   Site Principal Investigator: Dr. Paul E. Croarkin

2. Medical University of South Carolina (MUSC): Charleston, SC
   Site Principal Investigator: Dr. Mark S. George

This study will be monitored according to the monitoring plan described in this document. Each site investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor is given access to all study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.) as required, and has adequate space to conduct the visit.

The investigator will permit access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

Independent monitoring for protocol and IDE compliance will be conducted by Mayo Clinic Office of Research Regulatory Support (ORRS) staff, following standard operating procedures and guidelines for the ORRS department at Mayo Clinic, Rochester. It is anticipated this monitoring will be conducted through a combination of in-person and teleconference visits.

Address of Monitor:

[redacted]

Schedule: Each investigation site will be monitored according to the following schedule:

- A site initiation visit with participants from both sites will be conducted at MUSC during which in-service and protocol specific training will be conducted and regulatory requirements will be presented and discussed. The plan is to schedule this to occur after FDA approval of MUSC as a study site and prior to first subject enrollment at the site
- Routine monitoring visits will be conducted at each site during the active enrollment period of the study as well as the remaining period of time during which study procedures are being conducted with subjects. The first visit will be scheduled after approximately 1 – 2 subjects have been enrolled, and subsequent visits scheduled thereafter based on enrollment, prior findings or other determined need.

- A final visit may be scheduled at, or near study close-out for each site (this may be via teleconference for MUSC site, depending when the last in-person monitoring visit was conducted).

Monitoring Activities: Activities conducted during the routine monitoring visit include, but are not limited to, the following review of regulatory and subject files:

- Subject files are reviewed to verify that:
  - ✓ the subject exists
  - ✓ informed consent and/or assent (as applicable) was obtained before undergoing any research related procedures
  - ✓ enrolled subjects meet inclusion and exclusion eligibility criteria
  - ✓ deviations and adverse events are being properly recorded and reported
  - ✓ device accountability process is traceable and being properly followed.
  - ✓ subject files are being maintained in an organized fashion and updated in a timely manner

- Case Report Forms will be evaluated for:
  - ✓ completeness
  - ✓ legibility
  - ✓ logicalness
  - ✓ accuracy by verification to source documents

- Evaluate compliance to the protocol, regulations and good clinical practices
- Review records to verify proper reporting by MUSC site to the regulatory sponsor
- Verification of proper maintenance of the regulatory binder or file
- Evaluate continued protection of the subject's rights, safety and welfare
- Verify proper maintenance of IDE documentation

Appendix O – Clinical Trial Management Systems (CTMS)

CTMS is the Mayo Clinic Research Committee-endorsed institutional resource for clinical data management. CTMS is a robust institutional effort initiated in 2010 to address emerging changes within the data and statistical coordinating centers affiliated with NCI-funded cooperative groups. In 2010, NCI selected Medidata Rave® [redacted] as the required data collection tool for all cooperative studies. To capitalize on Mayo Clinic and the NCI's investment in Medidata Rave®, Mayo Clinic formalized a three-tier data management infrastructure with the Medidata Rave® product as the premier system.

Medidata Rave® is a product for multi-center clinical trials conducted under 21 CFR Part 11 requirements. This web-based system provides ease of use coupled with an integrated randomization module (Medidata Balance™), custom reporting, robust data validation routines, and straightforward integration with SAS.

- *Electronic Data Capture*: Medidata Rave® allows for data collection in multisite studies. During the course of the data entry into Medidata Rave®, the system provides real-time within-case report form (CRF) and inter-CRF data consistency verification. Medidata Rave® is flexible in nature so that all data can be entered even if "required" fields and or other consistency checks requirements are not satisfied. The system uses an internal "flagging" or "query" system to distinguish the valid from the invalid data thereby ensuring compliance with the FDA guidance document "Computerized Systems Used in Clinical Trials." All data discrepancy issues are tracked and audited by the system to ensure the highest quality data is available for analysis and study reporting.

  Contained within the CTMS initiative at Mayo Clinic is a diverse set of administrative and technical personnel to support the development and implementation of clinical trials in Medidata Rave®. While the time necessary to program Rave's electronic case report forms (eCRFs) has been directly budgeted, the CTMS initiative supports protocol independent activities such as software/server maintenance, data standards, institutional system integrations, SAS data, and training of study personnel through institutional resources.

  The dedicated VPN connection between Mayo Clinic and Medidata provides the conduit for data connectivity. Clinical trial data hosted in Medidata is accessible when needed for SAS using the SAS On Demand Connection, in combination with Mayo Clinic's SAS Pipeline program, which creates a common and direct combination of the metadata (labels, formats, etc.) and data (raw values) into SAS datasets on a scheduled (nightly) basis. This process removes the need to separately label and format the entire clinical trial database separately in SAS.

- *Medidata Balance™*: Randomization encounters challenges in complex multisite clinical studies in which random assignment to study drug must be completed prior to the baseline visit and a subject can fail to attend the baseline visit or be deemed ineligible for the study based on the final inclusion/exclusion criteria assessed at the baseline visit. It is possible that some individuals will not receive active treatment after treatment assignment has been established. Medidata Balance™ uses a novel multidimensional dynamic allocation algorithm minimizing imbalances across multiple dimensions including overall study, sites, factors and cross-factor strata. It is also highly flexible with extensive weighting and can be applied to most randomization scenarios including

unbalanced designs. The algorithm in Medidata Balance™ represents a novel multidimensional dynamic allocation algorithm for treatment assignments.