Augmentation versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders with Treatment Resistant Depression (ASCERTAIN-TRD)

Version 5.0

December 23rd, 2020

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A. TABLE OF CONTENTS

B. List of Tables 4

C. Study Synopsis 5

D. Background and Introduction 6

E. Study Aims 8

F. Study Design 9

F.1. Overview 9

F.2. Methods 9

F.3. Study Design 9

G. Study Population 9

G.1. Number of Subjects 9

G.2. Subject Eligibility 10

G.2.a. Inclusion Criteria 10

G.2.b. Exclusion Criteria 10

G.3. Rationale for the Inclusion/Exclusion Criteria 11

H. Study Assessments – Plan and Methods 11

H.1. Study Conduct 11

H.1.a. Screening Phase 12

H.1.b. Independent Remote Assessment Visit (MGH CTNI) 13

H.1.c. Randomization 14

H.1.d. Baseline Visit (Visit 1) 14

H.1.e. Visits 2-7 14

H.1.f. Early Termination Visit 15

H.1.g. Post-Study Follow-Up 15

H.1.h. Long-term Follow-up 15

H.1.i. Participant Adherence 15

H.1.j. Patient Recruitment 15

H.2. Procedures 16

H.2.a. Laboratory/Diagnostic Procedures ..... **Error! Bookmark not defined.**

H.2.b. STUDY Measures 16

H.2.c. Study Instruments 16

H.2.d. Patient Adherence to Protocol 18

H.3. Discontinued Subjects 18

H.4. Evaluation of Adverse Events (AEs) 18

H.4.a. Definition of AEs 18

H.4.b. Reporting of AEs 19

H.4.c. Pregnancy 19

H.4.d. Disease Progression or Worsening Depression 19

H.4.e. Serious Adverse Events (SAEs) 19
H.4.f. Protocol Violations 19

I. Treatment 21
I.1. Dosing Schedule 21
I.2. Concomitant Therapy 23
I.3. Discontinuation from Study Treatment 23

J. Ethical Considerations 23
J.1. Risk/Benefit Assessment 23
J.1.a. Human Subjects Involvement and Characteristics 23
J.1.b. Potential Risks 23
J.1.c. Safety 23
J.1.d. Confidentiality and Loss of Privacy 24
J.1.e. Planned procedures for protecting against or minimizing potential risks 24
J.2. Clinical Monitoring of Subjects and Management of clinical Deterioration and Emergence of Worsening of Suicidal Ideation 26
J.3. Informed Consent 26
J.4. IRB Review 27
J.5. Potential Benefits to Study Participants and Others 27

K. Data Handling and Record Keeping 27
K.1. Completion of eCRF 27
K.2. Procedure for Corrections 27
K.3. Record Retention 28
K.4. Data Confidentiality 28

L. Monitoring and Oversight 28
L.1. Initiation of Study Sites 28
L.2. PI Monitoring 28
L.3. Periodic Monitoring Visits 28
L.4. Study Closeout Visit 29
L.5. Direct Access to Source Data/Documents 29
L.6. Interim Analysis 29
L.7. Data and Safety Monitoring Board 29

M. Statistical Analysis 31

N. Protocol Signature Page 34

APPENDIX 1 35

B. LIST OF TABLES

TABLE 1– STUDY SCHEDULE 13
TABLE 2– LABORATORY TESTS ..... **ERROR! BOOKMARK NOT DEFINED.**
TABLE 3 - LIST OF EXAMPLES OF PROTOCOL VIOLATIONS 20

C. STUDY SYNOPSIS

Title of Study:	**Augmentation versus Switch: Comparative Effectiveness Research Trial for Antidepressant Incomplete and Non-responders with Treatment Resistant Depression (ASCERTAIN-TRD)**
Objective:	To evaluate the efficacy of aripiprazole augmentation, rTMS augmentation, and switching to venlafaxine XR or duloxetine as treatments for treatment-resistant depression (TRD).
Methodology:	This is a multi-site, randomized, open-label, effectiveness trial comparing three treatment arms for Major Depressive Disorder (MDD) patients with TRD who are currently on ongoing, stable and adequate antidepressant therapy (ADT). Adequate ADT is defined as a therapeutically sufficient dose for a sufficient treatment period, which would be expected to be effective as listed in the MGH Antidepressant Treatment Response Questionnaire (ATRQ). Patients will be randomized in a 1:1:1 fashion to one of three open-label treatment arms: a) aripiprazole augmentation, b) rTMS augmentation, and c) switching to venlafaxine XR or duloxetine.
Number of Patients:	639 Patients
Diagnosis and Main Criteria for Inclusion:	Male and female outpatients (aged 18 to 80 years) who meet DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition) criteria for MDD, have a current depressive episode of at least 12 weeks, and meet all of the following criteria: • Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 20 at screening and at baseline • >1 failed trials and <6 failed trials in the current episode as per the MGH ATRQ • <50% response to current antidepressant treatment (at least 8 weeks at an adequate dose, stable dose for at least 4 weeks) • Good general health • Willing to use birth control if the patient is of child-bearing potential
Visit Schedule:	Screening Visit (Visit 0), Remote Assessment within 7-10 days of Screening Visit, Baseline visit (Visit 1), Post-baseline visits every 7 (+/- 3) days (Visits 2-9) for 8 weeks, followed by monthly online questionnaires for 12 months.
Primary Outcome Measure:	Symptom improvement will be evaluated by assessing changes in the MADRS.
Safety and Tolerability Measures:	Adverse event (AE) recording, Concise Health Risk Tracking (CHRT)- Self-Report, SIBQ.
Statistical Justification:	The sample size was chosen to ensure 80% power to detect an effect size of f=0.12 on the MADRS between the three treatment arms at a two-sided 0.025 significance level. This assumes the randomization of 639 subjects (213 subjects per arm).

D. BACKGROUND AND INTRODUCTION

Major Depressive Disorder (MDD)

MDD is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds. The point prevalence of MDD is relatively high (2.3-3.2% in men; 4.5-9.3% in women) and the lifetime risk for MDD is 7-12% for men and 20-25% for women (Kessler et al., 2003). Depression has detrimental effects on all aspects of social functioning (e.g., self-care, social role, and family life, including household, marital, kinship, and parental roles) (Fergusson et al., 1995; Wiersma, 1996; Paykel, 1999) — costs not traditionally calculated. MDD is a disabling disorder that costs the U.S. over $200 billion per year in direct and indirect costs (Greenberg et al., 2015). Specifically, the annual cost of depression (approximately $210.5 billion in 2010) (Greenberg et al., 2015) includes 45% in direct medical costs (e.g., diagnosis, treatments, and overall cost to the community), 5% in suicide-related mortality costs, and 50% in workplace costs. Depression substantially impairs work productivity, increasing work absence and reducing work performance (Stewart et al., 2003). Depressed workers report significantly more total health-related lost productive time than nondepressed workers (mean 5.6 hours/week versus expected 1.5 hours/week) (Stewart et al., 2003). Depression is also associated with increased health care utilization for general medical conditions (Simon, 2003), and at least a 50% increase in total health services costs (Simon et al., 1995; Unützer et al., 1997). Finally, recovery from depression is associated with lower primary care costs and less missed work time due to illness (Simon et al., 2002).

Limitations of Current Antidepressant Treatments:

To date, all U.S. Food and Drug Administration (FDA)-approved antidepressants used as monotherapies have shown only modest benefits in MDD. In fact, in acute (6-8 week) studies, typically with relatively uncomplicated, non-chronic forms of MDD, response rates (e.g., 50% or greater reduction in depressive symptoms) range between 45% and 55%, and remission rates (e.g., minimal or no depressive symptoms) range between 30% and 35% (Steffens et al., 1997; Anderson, 2000; Anderson, 2001; Entsuah et al., 2001). Similarly, the efficacy of psychotherapy for the treatment of depression has been found to be modest as well, with small effect sizes comparable to those of standard antidepressants (Cuijpers et al., 2010). Although the combination of antidepressants and psychotherapy appears to be somewhat more efficacious than either one approach alone, the efficacy of this combination treatment remains limited (Cuijpers et al., 2009). Clearly, more research is sorely needed to help improve outcomes for millions of patients with MDD worldwide.

Treatment-Resistant Depression (TRD)

TRD typically refers to the occurrence of an inadequate response following at least two adequate antidepressant treatments among patients suffering from MDD (Rush et al., 2009), with the more traditional view of inadequate response defined as less than 50% symptom improvement (Papakostas and Ionescu, 2015). The findings of the largest clinical trial in MDD to date, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, have shown that approximately two thirds of MDD patients do not achieve remission following an initial adequate trial of antidepressant therapy (Trivedi et al., 2006), suggesting that TRD is highly common in practice. There is substantial mortality and morbidity associated with TRD, and both depression and general medical health care expenditures tend to increase with the degree of TRD (Russell et al., 2004). TRD is associated with poorer clinical outcome, particularly among those who require multiple

antidepressant medications (Fekadu et al., 2009). The scope of this problem is therefore highly significant both in terms of the numbers of affected individuals and the resultant societal and economic burdens. Despite the enormous public health significance of this problem, systematic research on TRD has yielded only limited success (Nierenberg et al., 2007). Again, clearly, more research is needed to help improve outcomes for millions of patients with TRD worldwide.

Switching versus Augmentation: A Critical Evidence Gap in TRD

A particularly critical decision in everyday practice is choosing what to do next when patients with MDD present after antidepressant treatments have failed to produce a clinical response, and a large evidence gap exists with respect to this common clinical scenario (Patkar and Pae, 2013; Bschor and Baethge, 2010; Connoly and Thase, 2011; Rush et al. 2009; Papakostas et al., 2007a; Souery et al., 2006; Fava, 2000; Nelson, 1998). This evidence gap exists despite the completion of the large, multi-center STAR*D study, since most patients in the trial were not assigned at random to augmentation versus switch as very few patients agreed to potentially accept either of these two broad treatment arms (Wisniewski et al., 2007). As clearly stated by the STAR*D study team when referring to augmentation versus switching in STAR*D, "we do not know whether one is preferred over another and for whom switch or augmentation is preferred" (Rush et al., 2009). Since the probability of response and remission of mood disorders decreases with each successive treatment failure (Rush et al., 2006a; Petersen et al., 2005), research is urgently needed to help settle the long standing question of whether there is a difference in efficacy between these two broad treatment strategies. This comparative effectiveness research (CER) proposal aims to address this well-known and critical evidence gap. If there is a clear difference in efficacy, this could potentially lead to the development of a treatment algorithm for patients with TRD aimed at improving outcomes early-on. If not, better accepted, tolerated, and safer treatments should be prioritized.

Choice among Popular, Well-Evidenced Pharmacological Switch and Augmentation Options

There are many augmentation and switch options to choose from for patients with TRD, each of these with varying degrees of evidence (Papakostas, 2009; Papakostas and Ionescu, 2015). As discussed in a recent review on the integrative management of TRD (Carvalho et al., 2014), the authors conclude that two pharmacotherapeutic options have accrued the most evidence for efficacy from well-controlled studies of TRD patients: switching to an antidepressant of a different class and augmenting the antidepressant with atypical antipsychotics. Despite the fact that both augmentation with atypical antipsychotic agents and switching to a different antidepressant class have well-established efficacy, strikingly, there has never been a direct comparison across them (Carvalho et al., 2014); STAR*D was designed before the current evidence on the efficacy of the atypical antipsychotics was made publicly available (and, indeed, before many of the studies had even been designed). Indeed, this evidence gap has been cited many times in the relevant literature describing the advantages and disadvantages of augmentation with atypical antipsychotic agents for TRD (Papakostas, Shelton, and Fava, 2007a; Shelton and Papakostas, 2008; Papakostas and Zarate, 2007; Nelson and Papakostas, 2009). The proposed study will therefore help resolve decisional uncertainty currently facing TRD patients and their clinicians.

Choice Between Well-Evidenced Augmentation Options with Atypical Antipsychotics and rTMS

To date, aside from the atypical antipsychotic agents, repetitive transcranial magnetic stimulation (rTMS) represents the only other modality approved for use in MDD patients who have not responded to antidepressant therapy (O'Reardon et al., 2007; Levkovitz et al., 2015). rTMS has been extensively studied for MDD (29 RCTs; Berlim et al., 2014), as well as in TRD specifically (18 RCTs; Berlim et al., 2014), including as augmentation with an evidence-base greater than for almost any other intervention for TRD save for the atypical antipsychotic agents (21 RCTs; Berlim et al., 2014). The results of a recent meta-analysis showed rTMS to be efficacious in MDD and in TRD, with equivalent efficacy when delivered as monotherapy or augmentation (Brunoni et al., 2009). There is also accumulating evidence for the durability of the antidepressant effect of rTMS in clinical practice (Dunner et al., 2014). Unfortunately, however, TMS has only been compared to switching to venlafaxine in TRD in a small (n=60) underpowered study which yielded inconclusive results (Bares et al., 2009). There has never been a direct comparison between rTMS and augmentation with atypical antipsychotics in TRD. (RQ-1)

Significance

In summary, TRD remains a significant challenge for clinicians and patients alike, and further research is needed to help improve both the standard of care and the outcome for patients with TRD. A particularly critical evidence gap exists with respect to whether pharmacological or non-pharmacological augmentation is superior to antidepressant switch, or vice-versa. An additional evidence gap exists with regards to our limited knowledge as to which, of a number of most commonly used, FDA-approved augmentation versus switch strategies to employ. Our proposal is designed to address these critical evidence gaps by comparing two popular, FDA-approved treatments for patients with TRD, namely augmentation with atypical antipsychotics versus augmentation with repetitive transcranial magnetic stimulation (rTMS), with one of the most popular strategies for TRD: switching to the serotonin-norepinephrine reuptake inhibitors (SNRI) venlafaxine extended release (XR) or duloxetine. These treatments are widely available and commonly used in TRD. They are either generic (i.e. venlafaxine XR, duloxetine, aripiprazole), or covered by Medicare and commercial insurance (rTMS). These are factors that will facilitate their further use and render the data stemming from the study widely applicable and relevant to clinical practice. Hence, our proposed study results have the potential to markedly impact treatment of TRD patients since the data will provide currently unavailable guidance in managing one of the most disabling, common and therapeutically challenging medical conditions and resolve decisional uncertainty currently facing TRD patients and their clinicians.

E. STUDY AIMS

Primary Aim 1: To compare the effectiveness of augmentation of antidepressants with aripiprazole versus switching to venlafaxine XR or duloxetine in MDD patients with TRD.

Primary Aim 2: To compare the effectiveness of augmentation of antidepressants with rTMS versus switching to venlafaxine XR or duloxetine in MDD patients with TRD.

Secondary Aim 1: To compare the impact of the aripiprazole and venlafaxine XR/duloxetionetreatment arms on quality of life in MDD patients with TRD.

Secondary Aim 2: To compare the impact of rTMS and venlafaxine XR/duloxetine treatment arms on quality of life in MDD patients with TRD.

Tertiary Aim 1: To compare the impact of aripiprazole and venlafaxine XR/duloxetine treatment arms on cognition in MDD patients with TRD.

Tertiary Aim 2: To compare the impact of rTMS and venlafaxine XR/duloxetine treatment arms on cognition in MDD patients with TRD.

F. STUDY DESIGN

Regardless of what is stated in the protocol, al visits and procedures with the exception of those related to the administration of rTMS will continue remotely until further notice due to the COVID-19 pandemic.

F.1. OVERVIEW

This is a multi-site, randomized, open-label, effectiveness trial comparing three treatment arms for MDD patients with TRD who are currently on ongoing, stable and adequate antidepressant therapy (ADT). Adequate ADT is defined as a therapeutically sufficient dose for a sufficient treatment period, which would be expected to be effective according to the MGH Antidepressant Treatment Response Questionnaire (ATRQ). Patients will be randomized in a 1:1:1 fashion to one of three treatment arms: a) aripiprazole augmentation, b) rTMS augmentation, and c) switching to venlafaxine XR or duloxetine.

F.2. METHODS

64 eligible subjects will be randomly assigned at MGH in a 1:1:1 fashion to one of three treatment arms: a) aripiprazole augmentation, b) rTMS augmentation, and c) switching to venlafaxine XR or duloxetine. All subjects will be followed for 56 (+/- 3) days (8 weeks) to examine the efficacy of the study treatments. Following their last on-site visit, subjects will be asked to complete monthly questionnaires for 12 months through the PCORI MoodNetwork.

F.3. STUDY DESIGN

The study will consist of a screening period and a randomization period. Patients who meet eligibility during the screening period will be randomized in a 1:1:1 fashion to one of three treatment arms: a) aripiprazole augmentation, b) rTMS augmentation, and c) switching to venlafaxine XR or duloxetine.

G. STUDY POPULATION

G.1. NUMBER OF SUBJECTS

64 subjects will enter the open-label treatment phase of this multicenter study at MGH. This trial will be conducted according to the U.S. FDA guidelines and the Declaration of Helsinki. IRB-approved written informed consent will be obtained from all patients before any protocol-specified procedures are carried out.

The TRD subjects (see definition below) will be drawn from an outpatient sample of patients with MDD, diagnosed with the use of the Mini International Neuropsychiatric Interview (MINI), currently on an adequate dose of antidepressant therapy, as defined by the MGH ATRQ, for at least 8 weeks, with the dose being stable for at least 4 weeks. For entry into the study, all inclusion criteria must be met, and none of the exclusion criteria can be met.

G.2. SUBJECT ELIGIBILITY

G.2.a. INCLUSION CRITERIA

A subject will be eligible for inclusion only if all the following criteria are met:

1. women and men ages 18-80,
2. with MDD, of at least 12 weeks duration, according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria confirmed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al, 1998),
3. have a Montgomery-Asberg Depression Rating Scale (MADRS – Montgomery and Asberg, 1979) score of at least 20 at screen and baseline as assessed by site clinicians,
4. meet criteria for TRD during the current major depressive episode documented in the MGH Antidepressant Treatment History Questionnaire (ATRQ) (Chandler et al., 2010), which will be defined as being non-responders (less than 50% of symptom improvement) to two or more depression treatment trials of adequate dose and duration as defined by the MGH ATRQ,
5. are currently on an antidepressant of adequate dose (as defined by the MGH ATRQ) and duration (at least 8 weeks), with the antidepressant dose being stable over the past four weeks, and with documented (in the MGH ATRQ) non-response (less than 50% improvement) to the current antidepressant.
6. Patients who have passed the MGH CTNI remote assessment, with documentation provided to sites by MGH CTNI.

G.2.b. EXCLUSION CRITERIA

A potential participant will NOT be eligible for participation in this study if any of the following criteria are met:

1. pregnant or breastfeeding women, women of childbearing potential who are not using an accepted means of birth control
2. patients who have received treatment with rTMS, atypical antipsychotic agents, electroconvulsive therapy (ECT), or venlafaxine *and* duloxetine during the current episode,
3. patients who express an objection to receiving treatment with rTMS, aripiprazole, or duloxetine and venlafaxine.
4. patients with any history of bipolar disorder or psychosis (diagnosed by MINI),

5. patients with active alcohol or substance abuse disorders within the past 6 months (diagnosed by MINI),

6. patients with suicidal ideation of the degree that, in the opinion of the evaluating clinician, participation in the study would place them at significantly increased risk of suicide,

7. patients with unstable medical issues of such degree that, in the opinion of the evaluating clinician, participation in the study would place them at significant risk of a serious adverse event, or patients with diabetes mellitus, uncontrolled hypertension, abnormalities in thyroid function tests during the past 12 months, or patients with epilepsy, dementia, Parkinson's disease, or Huntington's Disease,

8. patients who have received treatment with vagus nerve stimulation (VNS),

9. patients who have not responded to more than five FDA-approved antidepressant treatment trials of adequate dose and duration during the current episode, or who did not respond to ECT in previous episodes

10. patients on excluded medications (see Appendix 1),

11. patients who have received at least one dose of a monoamine oxidase inhibitor (MAOI) four weeks or less prior, and

12. for patients on concomitant psychotropic agents (anticonvulsants, benzodiazepines, hypnotics, opiates, triiodothyronine (T3), modafinil, psychostimulants, buspirone, melatonin, omega-3 fatty acids, folate, l-methylfolate, s-adenosyl methionine, lithium) not on the same dose for at least four weeks prior to study entry or who do not agree to continue at the same dose during the acute phase of the study.

13. Patients who do not meet safety criteria for TMS: history of seizures, cardiac pacemaker, DBS or VNS, brain aneurism clips or other metallic implants in the intracranial space.

14. Also excluded is an individual who has received any administration of ketamine in the current episode for the treatment of depression.

G.3. Rationale for the Inclusion/Exclusion Criteria

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study are meaningful in support of the research hypotheses. It is imperative that subjects fully meet all eligibility criteria.

H. Study Assessments – Plan and Methods

H.1. Study Conduct

Subjects will be screened for eligibility as detailed above. Study participants will be consented prior to the administration of any procedure. Following the screening period, central rater remote assessment, baseline assessment, and confirmation that all criteria for entry into the study are met, eligible subjects will be randomly assigned in a 1:1:1 fashion to one of three treatment arms: a) aripiprazole augmentation (n=213), b) rTMS augmentation (n=213), and c) switching to venlafaxine XR or duloxetine (n=213).

H.1.a. SCREENING PHASE

The screening period can take up to 28 days. The screening period begins when informed consent is signed. Only study physicians will perform the informed consent procedures. Once patients agree to participate in the study by signing the informed consent document, a full medical and psychiatric history will be taken as outlined in Table 1. Screening evaluations are to be conducted as outlined in the Study Schedule (Table 1). The purpose is to ensure that only appropriate patients are entered into the study. The investigator will determine that the patients meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the patients. Only patients currently on stable antidepressant therapy will be eligible for the study. During screening, investigators must document history during the *current* episode of inadequate response to at least 2 trials of depression treatment of adequate dose and duration, as specified by the MGH ATRQ (Fava and Davidson, 1996; Fava, 2003; Chandler et al, 2010). Patients found to be in potential need of hospitalization due to their degree of suicidal ideation at screening will be referred to the nearest emergency room.

TABLE 1– STUDY SCHEDULE

	V0	Central Rater	V1*	V 2	V 3	V 4	V 5	V 6	V 7 or final visit	Follow-up
Days	-28 to -0	-25 to -3	0	7 (+/-3)	14 (+/-3)	21 (+/-3)	28 (+/-3)	42 (+/-3)	56 (+/-3)	Monthly 12 months
MINI (axis-I only)	X									
MINI (Mood module only)		X								
MGH ATRQ	X	X								
HAMD-AS (central)			X							
CIRS, RLHQ			X							
MADRS (Site)	X		X							
MADRS (Central)		X	X	X	X	X	X	X	X	
SDQ, CGI, MGH-CPFQ, CHRT, SIBQ, WSAS, PAQ			X	X	X	X	X	X	X	SDQ, CPFQ, WSAS Only
Q-LES-Q-SF			X	X	X	X	X	X	X	X
DSST			X						X	
Adverse Events Form			X	X	X	X	X	X	X	
Demographic-Educational Form			X							
rTMS eligibility form	X									
Concomitant Medication List.	X		X	X	X	X	X	X	X	
Treatment preference form			X							

* For patients who refuse a direct switch to venlafaxine/duloxetine and who wish to undergo a taper, the site (v1) MADRS should be completed to confirm baseline severity for eligibility, followed by treatment assignment (randomization). All other v1 study-related measurements should be postponed for the last day of the taper, including the MGH CTNI remote assessment. The date of the last day of the taper (not the day of randomization/treatment assignment) will be used for the purposes of calculating the timing of subsequent study visits.

H.1.b. INDEPENDENT REMOTE ASSESSMENT VISIT (MGH CTNI)

During this visit, eligibility will be confirmed remotely (via telephone) by an MGH clinician at MGH Clinical Trials Network and Institute (CTNI). In order to continue in the study, patients must meet all of the following inclusion criteria and none of the following exclusion criteria as assessed by remote (MGH CTNI) clinicians specifically during this visit. Inclusion criteria: a) patients who meet criteria for current MDD according to the DSM-5 and as assessed by the MINI, b) patients with a MADRS score of at least 20, c) patients who have

experienced less than 50% symptom improvement to their current antidepressant trial, which must be of adequate dose and duration as per the MGH ATRQ, d) patients on an antidepressant of adequate dose (as per MGH ATRQ) and for at least 8 weeks, with stable dose for at least four weeks prior, e) patients who have experienced less than 50% symptom improvement to at least two depression treatment trials of adequate dose and duration (as per the MGH ATRQ) during the current MDD episode.

Exclusion criterion: a) Patients who have experienced less than 50% symptom improvement to more than five FDA-approved antidepressants of adequate dose and duration (as per the MGH ATRQ) during the current MDD episode or to ECT in their lifetime, b) patients who have received ECT, atypical antipsychotic agents, rTMS, or venlafaxine *and* duloxetine during the current episode, or c) patients who have received (VNS) during their lifetime. Patients deemed eligible to continue in the study will be scheduled for a baseline visit.

H.1.c. RANDOMIZATION

For entry into the study and randomization, all eligibility criteria MUST be met (e.g., all inclusion criteria and no exclusion criteria). Patients who meet eligibility criteria at the baseline visit will be randomized in a 1:1:1 fashion to open-label treatment with one of three treatment arms: a) aripiprazole augmentation, b) rTMS augmentation, and c) switching to venlafaxine XR or duloxetine. All subjects will be followed for up to 56 (+/-3) days post randomization.

Upon determining at the baseline visit (Day 0) that a patient still meets all entry criteria for the study, the patient will be assigned (by study subject number assigned at consent) to the next randomization slot from the randomization list that will have been generated by the study Biostatistician. Randomization will employ variable block sizes.

H.1.d. BASELINE VISIT (VISIT 1)

The patient will first be administered the HAMD-AS and MADRS by the Independent Remote Rater. The patient will then be administered the MADRS, SDQ, CGI-S, SIBQ, MGH CPFQ, adverse events form, DSST, CHRT and Q-LES-Q-SF, WSAS.

Upon completion of all study-related inclusion procedures as listed in the Study Schedule (Table 1), and upon the investigator's confirmation that the patient still meets all study inclusion criteria and none of the exclusion criteria, the patient may be randomized as per procedures outlines in section H.1.c. For patients randomized to receive a study drug, it will be prescribed throughout the study in compliance with the study drug prescribing procedure outlined in section I.1 of this protocol. For patients receiving rTMS, it will be provided in accordance with the guidelines outlined in section I.1 of this protocol.

H.1.e. VISITS 2-7

Post-baseline visits will occur as per Table 1. Upon arrival of subjects to the clinic, a remote (telephone) independent assessment by clinicians blind to treatment assignment will first be conducted by MGH CTNI staff with the goal of obtaining data on clinical outcomes without a bias related to the knowledge of treatment assignments. These remote assessments will occur at the beginning of visits 1-7, and are to be done just before patients are to have their visit with the participating clinical center and just before any other procedures occur (the content of these assessments is detailed in Table 1).

Following the remote assessment, the remaining procedures listed in the Study Schedule (Table 1) should be completed. During these visits, physicians will also prescribe treatment, assessing medication dosages as per clinical practice, adjusting dosages for effectiveness and tolerability as described in the relevant section of this proposal. For patients in the rTMS arm, treatment adjustments will be made by the physician administering rTMS.

H.1.f. Early Termination Visit

Every effort will be made to keep the patient in the study for the full study period. Acceptable reasons for early termination from the randomized clinical trial include the following: 1) request of patient, 2) decision of physician, 3) serious adverse event and 4) protocol violation. In addition, global clinical worsening which will be defined as a CGI-I>6 at any post-baseline visit (visits 2-6) or the development of psychotic symptoms or mania/hypomania will serve as indications for early termination of a study participant from the randomized clinical trial. Patients will be assessed for suicidal ideation at every visit. Subjects who, in the opinion of the assessing clinician have a worsening of suicidal ideation that renders them at increased risk for study participation will be removed from the study and given an appropriate clinical referral. If a patient is terminated from the study before completion, the procedures listed in Table 1 for Visit 7 should be completed.

H.1.g. Post-Study Follow-Up

At the final visit (visit 7 or earlier for patients who discontinue the study prematurely), patients will be instructed to follow-up with their treating clinicians. For patients who, at baseline, do not have one in place, study staff will assist and facilitate setting up an intake appointment with a treating clinician. Patients will also complete self-rated forms as per Table 1 on a monthly basis for a total of 12 months. Completion of the forms will be done online.

H.1.h. Long-term Follow-up

In order to collect longer-term, real-world, naturalistic outcome data for patients who complete the randomized clinical trial, they will be instructed to complete monthly assessments online using our established EDC system. Patients will be prompted to complete the patient-centered outcome questionnaires on a monthly basis for a total of 12 months. A list of patient-rated scales completed per visit is provided in Table 1.

H.1.i. Participant Adherence

Every effort will be made to encourage patients to adhere to the procedures and the assessments involved in study. However, a pill count, an often employed method in clinical trials, will not be employed in this study as we deem it a significant departure from standard clinical practice and would reduce the ecological validity of the trial.

H.1.j. Patient Recruitment

Patients will be recruited through advertisement, as well as clinician referral and self-referral. Self-referred patients will call the study sites and will be screened over the phone by the study coordinators. Those deemed potentially eligible will be scheduled for a screening visit with one of the study physicians.

Participants will also be recruited through physician referral. Each site will recruit participants via referral from primary care and specialty clinics from the communities surrounding their site. Sites will regularly collaborate

on strategies to recruit women and minorities, and sites will employ strategies specific to their local community, in ways that are culturally sensitive and specific to the local minority population. Retention will be enhanced with fair reimbursement (as deemed appropriate by the local IRB) for participants' time.

Assessments and procedures within the study visits will occur as shown in Table 1. A summary description of each data collection instrument is provided later in this section.

H.2. PROCEDURES

H.2.a. STUDY MEASURES

H.2.a.1. OUTCOME MEASURES

Symptom improvement will be evaluated by assessing changes in the primary outcome measure, the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The a-priori-defined key secondary outcome measure for the study will be the short-form version of the quality of life, enjoyment and satisfaction questionnaire – short form (Q-LES-Q-SF; Endicott et al., 1993). The a-priori-defined tertiary outcome measure for the study will be the Massachusetts General Hospital Cognitive and Physical Symptoms Questionnaire (MGH CPFQ, Fava et al. 2009a).

H.2.a.2. SAFETY MEASURES

The presence of any side effect or adverse event will be carefully documented at screen and at every subsequent visit covering events since the last visit. Reasons for premature discontinuation, including intolerable side effects, will be recorded.

H.2.b. STUDY INSTRUMENTS

The following instruments will be administered according to the schedule outlined in Table 1.

H.2.b.1. DIAGNOSTIC AND DEMOGRAPHIC INSTRUMENTS

Mini International Neuropsychiatric Interview (MINI) (Sheehan et al, 1998): The MINI, administered by the clinician, includes modules aimed at diagnosing different Axis I disorders. Questions are asked exactly as written, and each is based on the individual criteria from DSM-5. The mood module is used to diagnose MDD and to rule-out bipolar disorder, psychotic disorders, or active substance use disorders. Only sections pertaining to axis-I disorders will be utilized for this trial.

MGH Antidepressant Treatment Response Questionnaire (ATRQ) (Chandler et al., 2010): This a questionnaire that examines the antidepressant treatment history, using specific anchor points to define the adequacy of both dose and duration of each antidepressant trial, as well as the degree of symptomatic improvement obtained with each trial. This questionnaire, which has been validated (Chandler et al., 2010), will be utilized to define and diagnose the degree of treatment resistance and TRD status in study subjects.

Cumulative Illness Rating Scale (CIRS) (Miller et al., 1992): The CIRS is a clinician-scored instrument designed to provide a metric of overall severity and burden of medical co-morbidity. It will be used to define subgroups based on medical co-morbidity for subgroup analyses (score of 0 or greater than 0).

Hamilton Depression Rating Scale Anxiety Somatization Subscale (HAMD-AS) (Cleary and Guy, 1977): This clinician-administered, six-item subscale will be administered once at baseline, in order to identify patients with anxious depressive subtype (score of 7 or greater) for subgroup analyses.

Reproductive Life-cycle and Hormone Questionnaire (RLHQ) (Freeman et al., 2013) : This is a standard brief questionnaire implemented systematically at baseline in clinical trials for MDD to assess reproductive lifecycle status and the use of exogenous hormones. This study will use Modules 1 and 2 in all women, and add Module 3 (menstrual cycle tracking) in women for whom this questionnaire is appropriate and relevant. It will be used to define subgroups based on reproductive and hormonal status for subgroup analyses (pre-, peri- and post-menopausal- with versus without hormonal therapy).

Demographic and Education form: This form, completed by study participants, will collect key demographic, professional and educational data for the purpose of subgroup analyses (socioeconomic, ethnic, racial or age group based on age 65 and older versus younger).

Treatment Preference form: This subject-completed form, administered only during the randomization visit, will inquire whether subjects have a preference for one of the treatment arms.

Concomitant Medication List: This instrument will collect information on all concomitant medications.

H.2.b.2. EFFICACY MEASURES

Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979): This validated and well established 10-item clinician-rated instrument measures depression severity. It will be administered with a structured interview guide. It is a standard research scale, widely accepted by investigators and regulators. It will be used to assess subject eligibility and, for purposes of allowing us to compare study findings with the broader TRD literature, will be administered during remote assessments as the study primary outcome measure.

Symptoms of depression questionnaire (SDQ) Pedrelli et al., 2014): This 44-item, validated, patient-rated instrument also measures depression severity. It will be used as an additional outcome measure of depressive symptom severity and, along with the MADRS, also to help guide site clinicians and patients when making dosing decisions.

Clinical Global Impressions - Severity (CGI-S) and Improvement (CGI-I) Scales (Guy, 1976): These single-item, clinician-rated scales measure global (mood and any co-morbid psychiatric disorder) severity and improvement. They will be used as an outcome measure of global clinical improvement.

The short-form version of the Quality of Life, Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; Endicott et al., 1993): This 16-item, validated patient-rated instrument is a broad measure of quality of life, and will be used as the a-priori-defined key secondary outcome measure for the study.

The MGH Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al., 2009): This is a brief (7-item), validated self-report inventory to assess rates of significant cognitive symptoms such as memory, attention and executive function difficulties. They will be used as an outcome measure of cognitive functioning.

Digit Symbol Substitution Test (DSST) (Kaplan and Saccuzzo, 2009**):** This instrument will be administered at study sites, and will serve as a measure of global cognitive and executive functioning.

Work and Social Adjustment Scale (WSAS) (Marks, 1986): This self-rated, five item scale is a self-report scale of functional impairment attributable to an identified problem (depression for the purposes of this study).

H.2.b.3. SAFETY AND TOLERABILITY MEASURES

The Concise Health Risk Tracking Scale, Self-Rated Version (CHRT-SR) (Trivedi et al, 2011) The CHRT-SR is a low-burden measure of the spectrum of suicidal ideation that was developed to assess severity and track suicidal events through any treatment. The CHRT-SR will be performed to assess suicidal ideation in this study.

Suicidal Ideation and Behavior Questionnaire (SIBQ): The purpose of this instrument is to ensure clinicians properly assess and document suicidal ideation and behavior as well as any study decisions (study exclusion of subject, filing of a serious adverse event) pertaining to suicidality. It will be completed by site investigators during all visits.

Side-effect form: A clinician-rated simple form will be used to document the onset, course (continued versus resolved), severity (mild, moderate, severe), and causality (whether related or unrelated to treatment) of adverse events. This will serve as a source for comparing tolerability across treatments.

rTMS eligibility form: This form will be administered at screening in order to ensure that patients are eligible (in terms of safety) to be administered rTMS.

H.2.c.4 ADHERENCE MEASURES

Patient Adherence Questionnaire (PAQ): The purpose of this subject-rated instrument is to monitor subject-reported adherence

H.2.c. PATIENT ADHERENCE TO PROTOCOL

Every effort will be made to encourage patients to comply with the procedures and the assessments involved in study. Patients will be compensated for their time, at a rate and frequency determined appropriate by each site IRB and PI. We believe that this level of subject compensation, while non-coercive, facilitates adherence to assessments and procedures that require frequent, inconvenient visits. In addition, the PAQ will be utilized to provide insights into medication adherence.

H.3. DISCONTINUED SUBJECTS

Sites will follow the procedures in Section I.3 for discontinued patients.

H.4. EVALUATION OF ADVERSE EVENTS (AES)

H.4.a. DEFINITION OF AES

Adverse Event

An adverse event is any untoward medical occurrence in a study subject. The reporting period begins when a study subject signs consent and ends at visit 9 or earlier for patients who prematurely discontinue the study.

H.4.b. Reporting of AEs

Adverse events will be recorded using the appropriate form. Patients shall be allowed to contact the investigator or a member of his staff at any time between visits concerning adverse events or worsening of symptoms.

Unanticipated problems involving risks to subjects, including adverse events, will be reported to the overall study PI and to the site IRB.

Serious adverse events, including those spontaneously reported to the site-investigator from the time a signed and dated ICF is obtained until within 30 days after the last dose of study drug or TMS treatment must be reported using the Serious Adverse Event Form.

H.4.c. Pregnancy

If a subject (or subject's partner) becomes pregnant during the study, it must be reported within 24 business hours of the time the investigator becomes aware of the event to the overall study PI, DSMB, and site IRB. Pregnancy in itself is not regarded as an AE unless there is a clinical suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs from the first day of treatment to 30 days following the last treatment given will be followed for gestational outcome.

H.4.d. Disease Progression or Worsening Depression

The development of worsening depression should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

H.4.e. Serious Adverse Events (SAEs)

The EDC platform will provide a mechanism for sites to report SAEs, and for the Site Investigators to sign off on the SAE reports. Reportable (related and/or unexpected) SAEs will be sent to the overall study PI, site IRB, and study DSMB within regulatory timelines.

H.4.e.1. Definition and Reporting of SAEs

The following criteria define an SAE: a) death, b) life-threatening event, c) hospitalization or prolongation of hospitalization, d) persistent or significant disability/incapacity, or e) congenital anomaly/birth defect. The site PI and study PI are in charge of determining if an adverse event represents an SAE. When a SAE is discovered, it will be reported immediately (within 24 hours) to the overall study PI, the chair of the data safety and monitoring board (DSMB), and the site IRBs (same or next business day).

H.4.f. Protocol Violations

A major protocol violation is one which poses 1) a risk to patient safety or 2) a risk to data integrity. In addition, a protocol violation which violates a study participant's rights will also constitute a major protocol violation. These must be reported to the overall study PI, the site IRB and the study DSMB within one business day. Any other protocol violation is defined as a minor protocol violation, and is reported to site IRB on an annual basis. The overall PI is the sole determinant of whether a violation constitutes a minor or major violation. Table 3 includes a list of examples of protocol violations.

TABLE 2 - LIST OF EXAMPLES OF PROTOCOL VIOLATIONS

	Major Protocol Violation	**Minor Protocol Violation**
The list of examples is intended as a guide and is not all-inclusive.		
Definition	A violation that **<u>may</u>:** Impact subject safety, Affect the integrity of study data, and/ or Affect the subject's willingness to participate in the study.	A violation that **<u>does not</u>:** Impact subject safety, Compromise the integrity of study data, and/ or Affect the subject's willingness to participate in the study.
Examples ***(not all-inclusive)***	Failure to obtain informed consent Informed consent obtained by an unauthorized individual Enrollment of a subject who did not meet eligibility criteria for whom a protocol exception was not obtained Performing a study procedure that is not approved by the IRB and/or is not in the protocol Failure to perform a required lab test that, in the opinion of the Investigator, may affect subject safety or data integrity Failure to perform or follow a study procedure that, in the opinion of the Investigator, may affect subject safety or data integrity Failure to follow safety (AE) management plan Failure to report a SAE to the IRB and/or Coordination Center	Implementation of unapproved recruitment procedures Only a photocopy of the signed/ dated consent form is available (the original is missing) Pages are missing from the signed/ dated informed consent form Use of invalid consent form (i.e., without IRB approval or outdated/expired form) Failure to perform or follow an approved study procedure that, in the opinion of the Investigator, **does not** affect subject safety or data integrity Study procedure conducted out of sequence Failure to perform a required lab test Missing lab results Study Visit out of approved window Over-enrollment Enrollment of subjects after IRB approval of the study has expired Failure to submit a continuing review application to the IRB before study expiration

Reporting Requirements	Record the date discovered, date occurred, description of event in the Protocol Deviation Log. Notify the Coordinating Center within 24 business hours.	Record the date discovered, date occurred, description of event in the Protocol Deviation Log. Notify the Coordinating Center

H.4.f.1. Procedure for Non-Compliant Patients

Patients will be scheduled for the period of study participation when they are available for study visits. Patients who miss one visit will be allowed to make up that visit within a window that depends on the visit. Every effort will be made by the site to adhere to the study visit schedule, in order for assessments to be able to be performed at the stipulated time points. Patients who withdraw consent will no longer have data collected for the study. For patient-rated scales only, patients will have the right to not answer any question they deem so and for any reason. This will not constitute a protocol violation.

I. TREATMENT

I.1. DOSING SCHEDULE

Aripiprazole Augmentation: Patients randomized to this treatment arm will be instructed to continue all permitted psychotropics at their current dose throughout the 8-week trial and initiate adjunctive aripiprazole. The starting dose will be 5mg daily. The dose may be reduced to as low as 2mg for tolerability issues (this will be the lowest dose permitted for continuation in the trial). The dose may be adjusted in 2 or 5mg increments. The minimum time per increment will be 7 days. The maximum dose will be set at 15mg daily. For patients who are not on potent cytochrome 2D6 inhibitors (such as paroxetine, fluoxetine, duloxetine) or on potent cytochrome 3A4 inhibitors (such as fluvoxamine and nefazodone) and who are able to tolerate 15mg daily, the maximum dose can be raised to 20mg daily for efficacy. As was performed in registrational studies (Berman et al., 2007 and 2009; Marcus et al., 2008), and to mimic clinical practice, propranolol (10-30mg once or twice daily) and/or benztropine (1-2 mg daily) may also be prescribed for akathisia, if needed. We therefore intend to optimize the dose of aripiprazole.

Repetitive transcranial magnetic stimulation (rTMS): Patients randomized to this treatment arm will be instructed to continue all permitted psychotropics at their current dose throughout the 8-week trial. We will use clinical TMS stimulators with focal figure-of-eight coils. We will start by measuring the patient´s motor threshold (MT), which is a measure of cortical excitability used to standardize the intensity of stimulation across subjects. To do this, the TMS coil is placed over the hand representation of the primary motor cortex (M1) in a rostro-medial 45º angle. Single pulses are applied with an inter-pulse interval (IPI) of at least 5 seconds, to prevent additive neuromodulatory effects. When pulses are applied at supra-threshold intensities, a volley of activity travels through the pyramidal motor pathways and leads to the contraction of the contralateral hand muscle. The intensity of stimulation is sequentially reduced until we reach a point when fewer than 50% of the pulses (usually 3 out of 6 or 5 out of 10) lead to a muscle contraction (identified by visual inspection or electromyographic motor evoked potentials (MEP) with an peak-to-peak amplitude

greater than 50 microV). The lowest TMS intensity that is able to elicit a muscle contraction or MEP 50% of the time is considered the motor threshold (MT), and usually expressed as a percentage of the maximum stimulator output. Once the MT is determined, we will identify the target of stimulation in the left dorsolateral prefrontal cortex (DLPFC) based on individualized coordinates following standardized procedures, and place the TMS coil over the scalp position that corresponds to that cortical target. At that point, the treatment session can begin. We will use the standard FDA-approved protocol of 10Hz stimulation at 120% of the motor threshold intensity and a total of 3000 pulses per session. For patients who are unable to tolerate stimulation at 120% of motor threshold, clinicians administering the treatment will have the flexibility to titrate motor threshold intensity as needed for tolerability. This protocol complies with published safety guidelines (Rossi et al., 2009). Sessions will occur daily Monday through Friday over 5 weeks. After this, there will be a taper period of two weekly sessions during three additional weeks. This is as per the standard FDA-approved protocol (O'Reardon et al., 2007). Further guidance on rTMS treatment is referenced in the relevant MOP for this study. All safety procedures in place at the site rTMS clinic to comply with COVID safety requirements will be adhered to.

Switching to Venlafaxine XR: Patients randomized to this treatment arm will be instructed to continue all permitted psychotropics throughout the 8-week trial, except for their antidepressant(s). They will be instructed to discontinue all antidepressants and initiate venlafaxine that day, as direct switch to serotonergic antidepressants is well tolerated and avoids loss of precious therapeutic time (Montgomery et al., 2014), including to switching to venlafaxine in STAR*D (Rush et al., 2006b). For patients who do not prefer a direct switch, or when clinically indicated otherwise in the opinion of the site investigator, a gradual tapering during the screening period will be permitted as long as a direct switch to venlafaxine is made on the baseline visit from the final antidepressant dose (see table 1 for details). The starting dose of venlafaxine will be 75mg daily. The dose may be reduced to as low as 37.5mg for tolerability issues (this will be the lowest dose permitted for continuation in the trial). The dose can be titrated in 75mg increments. The minimum time per increment is 7 days. The maximum dose will be set at 375mg as per wording in the FDA labeling: "It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225mg per day for Effexor (immediate-release), more severely depressed inpatients in one study of the development program for that product responded to a mean dose of 350mg per day (range of 150 to 375mg per day). Whether or not higher doses of Effexor XR are needed for more severely depressed patients is unknown; however, the experience with Effexor XR doses higher than 225mg per day is very limited." The selection of the dose range, as informed by the FDA label, will reflect real-world clinical practice for TRD patients, who often require higher doses. We therefore intend to optimize the dose of venlafaxine XR.

Switching to Duloxetine:

This treatment option will be made available for patients who have received venlafaxine during the current episode, or for patients who express objections to being treated with venlafaxine or patients for whom treatment with venlafaxine is counter-indicated (i.e. allergies, etc). Patients randomized to this treatment arm will be instructed to continue all permitted psychotropics throughout the 8-week trial, except for their antidepressant(s). They will be instructed to discontinue all antidepressants and initiate duloxetine that day, as direct switch to serotonergic antidepressants is well tolerated and avoids loss of precious therapeutic time (Montgomery et al., 2014; Rush et al., 2006b). For patients who do not prefer a direct switch, or when

clinically indicated otherwise in the opinion of the site investigator, a gradual tapering during the screening period will be permitted (see table 1 for details). The starting dose of duloxetine will be 60mg daily. The dose may be reduced to as low as 30mg for tolerability issues (this will be the lowest dose permitted for continuation in the trial). The dose can be titrated in 30 or 60mg increments. The minimum time per increment is 7 days. The maximum daily dose will be set at 120mg. We therefore intend to optimize the dose of duloxetine.

I.2. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the Concomitant Medication Log for each patient, along with dosage information and start and stop dates. Allowed concomitant medications include any prescription or over-the-counter medication not specifically excluded by the protocol (see Appendix 1), as well as stable, ongoing antidepressant therapy and stable allowed hypnotic therapy. Patients requiring excluded drugs will be discontinued from the study.

I.3. Discontinuation from Study Treatment

Every effort will be made to keep the patient in the study for the full study period. Acceptable reasons for early discontinuation include the following: 1) request of patient, 2) decision of physician, 3) serious adverse event, and 4) protocol violation. In addition, global clinical worsening which will be defined as a CGI-I>6 at any post-baseline visit (visits 2-6) or the development of psychotic symptoms or mania/hypomania will serve as indications for early termination of a study participant from the randomized clinical trial.

J. Ethical Considerations

J.1. Risk/Benefit Assessment

J.1.a. Human Subjects Involvement and Characteristics

This study will randomize a total of 639 individuals, 18-80 years of age, with MDD and TRD. Overall, subjects must be medically stable as defined in the protocol, and we also specifically exclude patients at acute risk for suicide. In addition, we also exclude patients with active substance abuse or dependence, or those with psychosis or bipolar illness. Furthermore, we exclude patients below the age of 18 or over the age of 80 for their safety due to the paucity of safety data for aripiprazole in the excluded populations, and venlafaxine, duloxetine and rTMS in children and adolescents.

J.1.b. Potential Risks

Participants must be capable of understanding the nature of this study, its potential risks, discomforts and benefits. Study physicians will obtain consent after they have fully explained the study purpose and its procedures, and potential participants have demonstrated an understanding of the protocol, willingness to participate, and competency to consent.

J.1.c. Safety

All interventions tested are FDA-approved for MDD, have been extensively studied and employed worldwide, and used according to their labeling and standard clinical practice. Therefore, for patients who are deemed eligible, the risk would be similar to that associated with standard treatment of MDD.

Extensive studies involving the use of venlafaxine XR in MDD have been conducted (Schmitt et al., 2009; Papakostas et al., Papakostas et al., 2007b). The FDA label (http://labeling.pfizer.com/showlabeling.aspx?ID=100) for venlafaxine, citing nausea, dry mouth, dizziness, insomnia, somnolence, sweating, and fatigue as the most common side-effects. There is also a dose-dependent risk of elevation of blood pressure, notably at doses above 300mg daily (Thase, 1998), as well as FDA warnings on 1) risk of serotonin syndrome when combined with serotonergic agents, 2) risk of increase in bleeding time when combined with anticoagulants, and 3) risk of induction of mania and hypomania.

Extensive studies involving the use of duloxetine in MDD have also been conducted (Thase et al, 2007). The FDA label (http://pi.lilly.com/us/cymbalta-pi.pdf), cites nausea, headache, dry mouth, somnolence, and fatigue as the most common side-effects. There are also FDA warnings on 1) risk of serotonin syndrome when combined with serotonergic agents, 2) risk of increase in bleeding time when combined with anticoagulants, and 3) risk of induction of mania and hypomania.

Extensive studies involving the use of aripiprazole in MDD have also been conducted (Berman et al., 2007 and 2009; Marcus et al., 2008). The FDA label (http://packageinserts.bms.com/pi/pi_abilify.pdf), citing akathisia, restlessness, fatigue, somnolence, and insomnia as the most common side-effects. Risk for cerebrovascular adverse events in elderly patients with dementia-related psychosis, metabolic abnormalities, weight-gain is also a statement applied across all agents in the class (atypical antipsychotics), although mean weight-gain difference versus placebo in MDD augmentation studies appears to be quite low (1.35 Kg), while changes in serum glucose levels (Nelson et al., 2009) or hemoglobin A1c levels (Fava et al., 2009) with aripiprazole augmentation did not differ from those with placebo in registrational studies. Other rare but serious adverse events include neuroleptic malignant syndrome (NMS), and tardive dyskinesia (TD). Unlike some other agents in the class, QTc, prolactin (Nelson et al., 2009), and serum lipid level changes with aripiprazole augmentation do not differ from those seen with placebo in registrational studies (Fava et al., 2009b).

rTMS is one of the most frequently studied interventions in TRD (Berlim et al., 2014). rTMS administration is not painful, although the subject may feel twitching of the scalp muscles or a tapping sensation under the coil during stimulation. It is possible that subjects may experience mild, brief headaches during rTMS that are caused by immobilization of head during administration time and/or by stimulation of the scalp muscles by TMS. rTMS at high frequencies has the extremely rare potential to induce a seizure (approximately 8 reported cases since the FDA approval in 2008, out of hundreds of thousands of treatments). No one has ever developed epilepsy as a consequence of TMS. There are no known or foreseeable long-term risks associated with TMS.

J.1.d. Confidentiality and Loss of Privacy

The risk of loss of privacy is judged to be low. However, patients will be asked to provide personal identifying information at each site, and there is a very rare risk of breach of confidentiality.

J.1.e. Planned procedures for protecting against or minimizing potential risks

Breach of confidentiality: Risk of breach of confidentiality will be minimized by the following measures: 1) personal identifying information (i.e. name on informed consent, data of birth) will be recorded on a paper source, will be cross-referenced with a de-identified subject number, and will be stored in a separate binder and this binder will be locked in a file cabinet. De-identified data will then be coded and entered into

password-protected databases on password-protected and encrypted computers in locked offices. Data will be shared and analyzed in a de-identified manner only. For the PCORI MoodNetwork portion of the study, only de-identified information will be entered.

Risks not specific to tested interventions: We exclude patients with a degree of suicidal ideation that study participating would place them at increased risk for an SAE. We also exclude patients with active substance abuse or dependence, or those with psychosis or bipolar illness because these interventions have not been proved to be relatively safe, effective, or well tolerated in these patient groups. We exclude patients below the age of 18 or over the age of 80 because of the relative paucity of safety data for the use of these treatments in these age groups. For patients eligible, close monitoring of patients throughout the study will ensure that adverse effects from treatment, exacerbation of symptoms, or emergence of suicidality, mania or psychosis will be promptly recognized so that patients can be treated appropriately following study discontinuation. All patients will be instructed on how to contact study clinicians in the case of an emergency. They will also be instructed on how to contact emergency mental health services serving their clinic which provide emergent psychiatry care on a 24hour/day basis.

Venlafaxine or duloxetine treatment: In order to minimize the risk of blood pressure elevation, all patients with poorly controlled hypertension will be excluded. In addition, patients with unstable medical illness specifically deemed at risk for study participation (including unstable cardiovascular or cerebrovascular illness) will be excluded for their protection. In order to minimize the risk of serotonin syndrome, 1) we are choosing to study venlafaxine/duloxetine as monotherapy, 2) patients cannot be switched from an MAOI, and 3) the use of certain high-risk agents such as tramadol is not allowed (see Appendix 1). However, because this is intended to be a study reflecting real-world patients it was decided against excluding other agents with lower risk (i.e. lithium and buspirone) since these are sometimes used in MDD. In order to minimize the risk of bleeding, warfarin is not allowed (see Appendix 1). However, because this is intended to be a study reflecting real-world patients, it was decided against excluding NSAIDs and antiplatelet agents since these are commonly used. Finally, patients with bipolar I or II disorder will be excluded (see venlafaxine and duloxetine FDA label warning on the induction of mania or hypomania) with verification from MGH CTNI remote raters.

Aripiprazole treatment: In order to minimize the risk of akathisia, we have permitted the use of pharmacologic remedies by clinicians (benztropine and propranolol). Patients with psychotic symptoms will be excluded from the trial and, thus, there will be no risk of exposure of elderly patients with psychotic symptoms to aripiprazole. The atypical antipsychotic agents differ with respect to their potential for metabolic (weight gain, dyslipidemia, glucose dysregulation) and endocrine (i.e. prolactin elevating) adverse events. Aripiprazole was chosen for this proposed trial due to its favorable metabolic and endocrine profile compared to the other atypicals. Nevertheless, patients with diabetes mellitus will be excluded. As with all antipsychotic agents, treatment with aripiprazole may result in the emergence of extrapyramidal symptoms (EPS). Two very rare EPS that may occur with the use of aripiprazole include neuroleptic malignant syndrome (NMS), and tardive dyskinesia (TD). NMS is a serious, potentially life-threatening disorder that includes symptoms such as fever, tight muscles, and changes in blood pressure and heart rate. Patients who develop symptoms of NMS will be evaluated and treated immediately by appropriate consulting physicians. Their participation on the study will be terminated. TD is a syndrome of potentially irreversible, abnormal, involuntary movements of the tongue,

jaw, body, arms and legs. There is no known treatment for tardive dyskinesia, although the symptoms may lessen or disappear completely if the antipsychotic medication is stopped.

rTMS treatment: To minimize the risk for seizure, we will 1) exclude patients with epilepsy, 2) setting TMS parameters according to those set according to the international rTMS safety consensus (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), and 3) selecting superficial rTMS (figure of 8 coil) as opposed to deep rTMS (H-shaped coil). In the unlikely event that a suspected seizure would occur, it would happen during the treatment session under the supervision of the treatment team. The seizure stops as soon as TMS is stopped, and the TMS clinical service safety plan is activated, including transfer of the subject with ambulance to local ER for a medical and neurological evaluation. If needed, headaches can be treated by mild over-the-counter analgesics that are available to study participants. Finally, all safety procedures in place at the site rTMS clinic to comply with COVID safety requirements will be adhered to.

J.2. Clinical Monitoring of Subjects and Management of clinical Deterioration and Emergence of Worsening of Suicidal Ideation

All patients will receive monitoring for clinical deterioration, support, attention, and reassurance in the context of a therapeutic alliance. Close monitoring by a trained psychiatrist is beneficial for individuals with mood disorders. If patients are in need of more intensive psychiatric treatment at any time during the course of the trial, study personnel will assist in needed evaluation and referral to appropriate treatment settings. Subjects will be carefully monitored regarding depressive and other psychiatric symptoms. Patients will be assessed for suicidal ideation at every visit. Subjects who, in the opinion of the assessing clinician have a worsening of suicidal ideation that renders them at increased risk for study participation will be removed from the study and given an appropriate clinical referral.

Every third week, the site PI will review any **new** (not previously reviewed by PI) scales that could pertain to patient safety for all active patients at the site. These will include: 1) the SIBQ (which monitors for suicidal ideation), and 2) the CGI-I (which monitors for clinical deterioration).

J.3. Informed Consent

All subjects will receive the consent form for the study as well as the Human Subject's Bill of Rights. First, patients interested in the study will be given a copy of the informed consent form at least 12 hours in advance, so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. If they continue to be interested, they will discuss with the investigator the details of the research study using the informed consent document as a guide. This discussion should include all the required elements of informed consent, e.g., the purpose of the research, the procedures to be followed, the risks and discomforts as well as potential benefits associated with participation, and alternative procedures or treatments, if any, to the study procedures or treatments. Subjects will always be given the opportunity to ask questions and have them answered by the investigator and, whenever possible, to consult with friends/family and/or their physicians. Once they have read the consent document and their questions are answered, if they agree to participate in the research, they sign and date the informed consent document. Patients will sign informed consent and only then will any study-related procedures be conducted. To remove any undue pressure on patients referred to the study

from a study investigator who happens to be their personal clinician, such interested patients will first have an opportunity to inquire about the study from a research assistant and obtain a copy of the consent form in advance. In addition, when presenting for screening, they can only be screened and followed during the study (if eligible) from an investigator who is different than their personal clinician.

J.4. IRB Review

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the IRB for the protocol, consent form, patient recruitment materials/process (e.g., advertisements), and any other written information to be provided to patients.

J.5. Potential Benefits to Study Participants and Others

Potential benefits of the research to participants and others: This study will potentially help individuals with TRD. It may provide relief of depressive symptoms for some patients who enroll.

Risks to subjects relative to the anticipated benefits to research participants and others: The treatments have been selected with consideration of safety in mind (all FDA approved). The risks of participation in the study are therefore judged to be small, and adequate protections are in place to monitor the medical wellbeing of participants. In contrast, the morbidity and mortality associated with TRD risks are well known to be very high, given the long-term disability associated with MDD.

The study may benefit other people with depression and their families and communities, by furthering our understanding of the antidepressant effectiveness of our three selected interventions.

Risks to subjects in relation to the importance of the knowledge that reasonably may be expected to result: The aforementioned data suggest that risks to subjects are minimal. Little data exist to guide treatment in resistant depression. In practice, such patients often wind-up receiving combinations of multiple medications, many with little evidence in support. In addition, the relative effectiveness, patient acceptance, and tolerability of three of the most popular and studied interventions as illustrated in this proposal is unknown due to lack of a direct comparison. The present study is designed to meet this evidence gap – by conducting that direct comparison.

K. Data Handling and Record Keeping

K.1. Completion of eCRF

All Investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.

K.2. Procedure for Corrections

An EDC system will be built for the study. The EDC system will include eCRFs designed to capture study information, which are completed by trained site staff. Specific details of the procedures for Data

Management are found in the Data Management Plan and details regarding the EDC system training process can be found in the Study MOP.

K.3. Record Retention

The Investigator must retain case report forms, and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, and at least for 10 years.

If the Investigator withdraws from the study (e.g., relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB).

K.4. Data Confidentiality

Potential risks to data confidentiality will be mitigated by requirements for the de-identification of all study data and by security protocols for all data capture systems. All users of the EDC system will be tracked and provided access in a secure fashion following established SOPs for this process.

As with all research data, information gathered by the study will be used only for aggregate analysis; it will not be released with any information that identifies research participants. The data managers, statistician, Investigator, and Sponsor do not have access to the identities of patients. That information is retained only at the clinical centers. Uses and risks related to data collection will be outlined in the informed consent and reviewed with the subjects.

L. Monitoring and Oversight

L.1. Initiation of Study Sites

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following: IRB approval has been obtained and documented prior to subject screening, the Investigators and study personnel are appropriately trained and clearly understand the study, the Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

L.2. PI Monitoring

Every three weeks, the site PI will review all new (not previously reviewed by PI) CRF data forms for accuracy and completion to ensure the validity and integrity of the data.

L.3. Periodic Monitoring Visits

Qualified MGH clinical monitors or qualified contract monitors representing MGH CTNI will conduct investigational site monitoring visits to ensure that all Investigators conduct the study in compliance with the protocol and applicable regulations. The site will receive notification prior to each monitoring visit during the course of the study. It is expected that the Investigator and/or sub-Investigator and other appropriately trained study staff are available on the day of the visit in case any questions might arise.

Periodic monitoring visits will be made in accordance with the approved monitoring plan at all active study sites throughout the clinical study to assure that the Investigator obligations are fulfilled and all applicable

regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the IRB, and the Investigator is executing all agreed activities.

MGH CTNI retains the right to remove either the investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements.

On one or more occasions, the study site may be inspected or audited by the MGH CTNI representative or a third party. The Investigator will be informed in advance of this visit.

L.4. Study Closeout Visit

Upon completion of the clinical study (when all subjects at the site have completed follow up visits, all data has been entered in the EDC system and cleaned, all queries resolved, and final electronic signatures have been obtained), a study closeout visit will be performed. Any unused study materials and equipment will be collected and returned to MGH CTNI. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and ensuring that the Investigator will notify the local IRB regarding study closeout.

L.5. Direct Access to Source Data/Documents

Subcontracts with study sites will specify that MGH CTNI or its representatives will have direct access to source data and documents for study monitoring. Additionally, PCORI and the site IRBs may review source data following appropriate guidelines for this process.

L.6. Interim Analysis

No interim analysis is planned for this study.

L.7. Data and Safety Monitoring Board

For this multi-site study of marketed interventions for MDD, monitoring of safety will be performed by the overall study-PIs (Drs. Papakostas, Fava, and Trivedi) in conjunction with the site PIs, and reviewed during conference calls with the coordinating center which will occur every three weeks. Any serious or unexpected adverse events, or any other unanticipated problems involving risks to subjects or others, will be formally reported during these calls. In addition, a Data and Safety Monitoring Board (DSMB) will monitor all sites and serve as a reporting body to PCORI as well as the respective IRBs.

Data and Safety Monitoring: A Data and Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected. To support this purpose, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety

of study subjects, and perform periodic review of the completeness and validity of data to be used for analyses of safety and tolerability. The DSMB will also ensure subject privacy and research data confidentiality.

Membership of the DSMB: To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of any significant career and financial interests with the investigators. The DSMB will consist of four members with experience in conducting clinical trials for psychiatric or neurobehavioral disorders, experience in clinical pharmacology and toxicology, and a thorough knowledge of clinical trial ethics and human subject protection issues. At least three members of the board will be physicians and at least one will be a biostatistician.

Functional Organization of the DSMB: One individual will serve as chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communications among the DSMB members pertaining to the review of serious adverse events (SAEs) will occur within a week of receiving a new SAE report. Reporting and communication regarding other matters will occur on an annual basis for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

Monitoring of Safety Data by the DSMB:

Treatment Reporting: Safety information for this study will be reported to the DSMB categorized by treatment arm.

Range of Safety Reporting to the DSMB: It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, protocol violations, as well as reasons for drop-out.

Serious Adverse Events: Expedited review will occur for all events meeting the definition of an SAE. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study drug. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the overall PI, site IRB and DSMB within 1 business day of the identification of any SAE, followed by a full report within 10 working days.

Non-Serious Adverse Events: Annually, the DSMB will be provided with summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Detailed data on individual non-serious adverse events are not expected to be needed for this review.

Other Safety-Related Reports: Annually throughout the course of the study, the DSMB will also receive summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase, as well as protocol deviations.

Study Stopping Rules: If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Monitoring of Data Quality: The DSMB will receive a report on data quality and completeness on an annual basis. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

M. STATISTICAL ANALYSIS

A detailed Statistical Analysis Plan (SAP) will be developed for the study before the database is locked.

A priori Specific Plans for Data Analysis of Major Aims: Demographic and clinical variables will be compared at baseline to evaluate the effectiveness of the randomization. Variables which differ between groups by an amount large enough to be considered clinically meaningful will be included as covariates in all analyses. Analyses will be conducted using SAS V9.4. All analyses will be modified intent-to-treat, where all patients with post-baseline data will be included. All tests will be two-sided. Because two different augmentation arms will each be compared with switching, we will use a Bonferroni corrected alpha of 0.05/2=0.025 where appropriate.

Primary Aim 1: To compare the effectiveness of augmentation of antidepressants with aripiprazole versus switching to venlafaxine XR/duloxetine in MDD patients with TRD.

The model described below will be applied to the following outcomes: SDQ, MADRS, and Q-LES-Q-SF, with MADRS serving as the study primary outcome measure and Q-LES-Q-SF as the a-priori-defined key secondary outcome measure. A mixed-effects models with repeated measures (MMRM) that includes data from all patients with any post-baseline data will be conducted with treatment group (augment versus switch) as the between-subjects factor, time (visits 1-7) as the within-subjects factor, and a group by time interaction term. The baseline measurement of the dependent variable will be included as a covariate. For all linear MMRM, the assumption of linearity will be examined by reference to a graph of change-over-time for each subject and also by testing if the goodness of fit of the model can be significantly increased by inclusion of a time-squared term or by the transformation ln(week+1). The assumptions of normality and homogeneity of variance and the presence of outliers will be examined by reference to the distribution of model residuals. If the assumption of normality is not satisfied, transformation of the outcome measure or non-parametric methods will be considered. We will investigate the use of transforming time using ln(visit+1) because this transformation of time is useful when the trajectory of response takes on a “fishhook” shape (Gibbons, Hedeker et al. 1993), in which there is very rapid change in the time immediately after start of treatment, then relatively slow changes thereafter. The log transformation expands the early time scale and contracts the later time scale creating a more linear response trajectory. Determination of a significant treatment effect will be based on the model treatment group effect or treatment group by time interaction. We will present effect sizes, in addition to the significance level of the effects in the model. We will consider the semi-partial

eta squared and number needed to treat (NNT) as measures of effect size. SAS Proc Mixed will be used to perform the analysis.

Primary Aim 2: To compare the effectiveness of augmentation of antidepressants with rTMS versus switching to venlafaxine XR/duloxetine in MDD patients with TRD.

The analysis for Aim 2 will be the same as that described for Aim 1, except that the rTMS group will be used in place of the aripiprazole group.

Power Calculation for Primary Outcome Measure Analyses of Aims 1 and 2: The proposed analysis will involve a modified intent-to-treat (MITT) approach (all randomized patients with at least one post-baseline measurement will be included in the effectiveness analysis), and a mixed-effects model with repeated measures (MMRM) approach for missing data. Since two different augmentation arms will be compared with switching, alpha will be set at 0.05/2=0.025. Beta will be set at 0.8, as is standard in antidepressant clinical trials. For effect size estimation, there is only a single randomized study in the literature comparing switching versus combination of the antidepressant fluoxetine with an older antidepressant occasionally used in Europe and not FDA-approved (Mianserin; Ferreri et al., 2001) yielding a Traditional Cohen's effect size of d=0.56 (this analysis, conducted in 2001, used a last-observation-carried forward (LOCF) approach). Since it is questionable whether such an effect size could be replicated, selecting a small-to-medium effect size would ensure that, were there any clinically significant finding, our study would have sufficient power to detect it. Setting the effect size higher would carry a risk of allocating funds to an underpowered study, while setting the effect size lower carries the risk of allocating excessive funds to detect a clinically insignificant treatment effect. Under the MMRM approach, assuming a small-to-medium effect size of f=0.12 (based on Cohen's f for analysis of variance where f=0.10 is a small effect (Cohen, 1988)), and a total of seven remote assessment observations (baseline, and visits 1-7), each treatment arm will require N=170, for a total sample size of 510 patients. Minimal important difference is set at f=0.12 for all other outcome measures as well including the patient-centered outcome measure. Hence, the study will be adequately powered to detect a statistically significant difference for all outcome measures, including the patient-centered one. Although efforts will be made to keep patients in the study, attrition is inevitable. Patients who drop-out without providing any post-baseline data will not be included in the primary analysis which will decrease the power of the study. Patients who provide some post-baseline data but do not complete the study will be included in the MMRM analysis, but the power of the study will still be diminished because these patients do not contribute as much data as completers (Leon et al., 2006). Of the three agents, tested, the atypical antipsychotic agent aripiprazole is viewed as the one associated with a relatively greater burden of adverse events, with a discontinuation due to intolerance in registrational studies of, approximately, 14%- Nelson et al, 2009). To be more conservative, we assume a higher rate for our trial of 20%. Therefore, the sample size will be increased by 20% to 639 with the goal of obtaining 510 completers. This approach will ensure that adequate power is available even after accounting for attrition.

Secondary Aim 1: To compare the impact of aripiprazole and venlafaxine XR/duloxetine treatment arms on quality of life in MDD patients with TRD.

This will be analyzed as per the study primary aim 1, substituting the Q-LES-Q scale for the MADRS.

Secondary Aim 2: To compare the impact of rTMS and venlafaxine XR/duloxetine treatment arms on quality of life in MDD patients with TRD.

This will be analyzed as per the study primary aim 2, substituting the Q-LES-Q scale for the MADRS.

Tertiary Aim 1: To compare the impact of aripiprazole and venlafaxine XR/duloxetine treatment arms on cognition in MDD patients with TRD.

This will be analyzed as per the study primary aim 1, substituting the CPFQ scale for the MADRS.

Tertiary Aim 2: To compare the impact of rTMS and venlafaxine XR/duloxetine treatment arms on cognition in MDD patients with TRD.

This will be analyzed as per the study primary aim 2, substituting the CPFQ scale for the MADRS.

Additional analyses: These will be fully developed prior to the final locking of the study dataset.

N. PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP as described in ICH guideline E6 and to hospital Institutional Review Boards.

_____

Clinical Site

_____ _____

Principal Investigator Signature Date

_____

Principal Investigator

Printed Name

APPENDIX 1

CONCOMITANT MEDICATIONS

Medications Allowed (Y) and Not Allowed (N) as Concomitant Medications

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Analgesics (Opioids, Tryptans, and Tramadol)	Y	Y	Medically appropriate episodic use of narcotic analgesics is allowed for acute medical indications but is limited to no more than 3 days for each episode. Chronic use is allowed as long as dose has been stable for at least 4 weeks prior. **Tramadol is not allowed.**
Analgesics (Non-prescription)	Y	Y	NSAIDS and Tylenol are allowed
Anesthetics, general	Y	N	**Ketamine and Nitrous Oxide are not allowed.**
Anesthetics, local	Y	N	—
Anorexics	N	N	—
Antacids	Y	Y	—
Antiacne	Y	Y	**Topical agents only, including topical antibiotics. Isotretinoin (Accutane) is not allowed.**
Antianginal agents	N	N	—
Antiarrhythmics	N	Y	**Amiodarone and class 1A antiarrhythmics are excluded**
Antiasthma agents	Y	Y	—
Antibiotics	Y	Y	Chronic use of topical antibiotics for acne is allowed, with the exception of the **MAOIs linezolid (Zyvox) and isoniazid, which are not allowed. Erythromycin, clarithromycin, rifampin are excluded**.
Anticoagulants	N	N	**Warfarin (Coumadin) is not allowed.** Antiplatelet agents are allowed (see "Antiplatelets").

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Anticholinergics	Y	Y	**Except for scopolamine.**
Anticonvulsants	N	Y	Anticonvulsants are allowed, as long as the dose has been stable for at least 4 weeks prior.
Antidepressants	N	Y	**Stable (for at least 4 weeks prior to screening), ongoing antidepressant therapy is required during the course of the study. For patients randomized to ariprazole or rTMS, no dose changes are allowed during the study. For patients randomized to switch to venlafaxine**/duloxetine**, antidepressant(s) (including doses of trazodone greater than 200mg daily) must be discontinued on the day of the randomization visit. Monoamine oxidase inhibitors (which may have unknown drug-drug interactions) are excluded.**
Antidiarrheal preparations	Y	N	Only loperamide HCl (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed.
Antifungals, systemic	N	Y	—
Antifungals, topical	Y	Y	**Ketoconazole and itraconzole are excluded**
Antihistamines	Y	Y	
Antihypertensives	Y	Y	However, **diltiazem and verapamil are excluded**
Anti-impotence medications	Y	Y	—
Anti-inflammatory drugs	Y	Y	**Indomethacin (Indocin) and systemic corticosteroids are not allowed**. NSAIDs are permitted.
Antifungal	Y	Y	**ketoconazole is excluded**

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Antinauseants/Antiemetics	Y	N	Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), cola syrup are allowed. 5-HT_3 receptor antagonists (e.g., ondansetron) are allowed if stable for at least 4 weeks prior. **Scopolamine is not allowed.**
Antineoplastics/ Immunosuppressant agents	N	Y	**Interferons, methotrexate, and other immunomodulating agents are not allowed.** Call MGH CTNI for approval for certain cases in cancer remission maintaining therapy.
Antiobesity/Appetite suppressants	N	N	**OTC Alli (Xenical), sibutramine (Meridia), and phentermine (Adipex-P and others) are not allowed.**
Antiplatelet agents	N	Y	Aspirin (maximum 325 mg/day) and clopidogrel (Plavix) are allowed.
Antipsoriatic treatments	Y	Y	Only topical agents are allowed. **Acitretin (Soriatane) is not allowed.**
Antipsychotics	N	N	
Antismoking medications	N	Y	**Varenicline (Chantix) is not allowed.**
Antiviral agents	Y	Y	**Interferons are not allowed.**
Anxiolytics	N	Y	Dose must be stable for at least four weeks prior.
Barbiturates	N	N	**Barbiturates are not allowed.**
Benign prostatic hyperplasia treatments	Y	Y	
Buspirone	N	Y	Stable in dosing at least four weeks prior is allowed.
Cough/cold preparations	Y	N	**Use of cough and cold preparations containing phenylephrine, pseudoephedrine or dextromethorphan for more than 3 days is not allowed.**

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Diuretics	Y	Y	
Dopaminergic Agents	N	Y	Must be stable in dose for at least four weeks prior.
Gastrointestinal: H_2-blockers/ proton pump inhibitors/ pro-kinetic agents	Y	Y	**Cimetidine (Tagamet) is not allowed. Metoclopramide is not allowed.**
Hormonal (non-contraceptive) therapies	N	Y	See below.
Hormones: reproductive	N	Y	Systemic hormonal contraceptives (oral contraceptives of estrogen and progestin combinations, depot injections such as Depo-Provera, the contraceptive implant Implanon, or transdermally delivered contraceptives such as Ortho Evra) are allowed
Hormones: thyroid	N	Y	Thyroid hormone replacement is allowed (dosage of thyroid medication should be stable for 4 weeks prior).
Hypoglycemic agents	Y	Y	Oral hypoglycemic agents are allowed. Insulin is allowed
Hypolipidemics: fibrates	N	Y	Gemfibrozil and fenofibrate are allowed
Hypolipidemics: niacin	N	Y	
Hypolipidemics: statins	N	Y	Lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, and rosuvastatin are allowed
Laxatives	Y	Y	Only fiber-based products and docusate sodium (Colace) are allowed
Lithium	N	Y	Stable in dosing at least four weeks prior to randomization is allowed.
Muscle relaxants	N	N	—
NMDA receptor antagonist (except ketamine)	N	Y	Must be stable in dose for at least four weeks prior.
Opioid antagonists (e.g., naltrexone, naloxone, nalmefene)	N	Y	Must be stable in dose for at least four weeks prior.

Drug Name or Class	Episodic Use (PRN)	Chronic Use	Restrictions/Comments
Sedatives/hypnotics	N	Y	Must be stable in dose for at least four weeks prior. Up to 200mg of trazodone may be used for sleep. In such cases, he dose of nighttime trazodone should remain constant throughout the study and need not be tapered and discontinued if subject is randomized to switch to venlafaxine.
Steroids/systemic	Y	N	Systemic steroid treatment will be allowed only for medical emergencies, such as severe allergic reactions
Steroids/topical and inhalant	Y	Y	—
Steroids/intra-articular	Y	NA	—
Stimulants	N	Y	Must be stable in dose for at least four weeks prior.
Vaccines	Y	NA	—

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