Pilot Accelerated Theta Burst in Treatment-Resistant Bipolar Depression

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1. PURPOSE OF THE STUDY

a. Brief Summary

Intermittent theta-burst stimulation (iTBS) is a patterned form of repetitive transcranial magnetic stimulation (rTMS), an effective, neuromodulatory treatment for refractory major depressive disorder (MDD). Accelerated rTMS paradigms have become of increasing clinical interest to address the potential limiting factors of dose response variability and the burden in weeks of treatment at great financial expense. Even with reduced treatment time in iTBS compared with standard rTMS (10 mins vs the traditional 40 minutes, respectively), there remains a barrier in requiring weeks or months of daily treatment sessions for desired response. Our recent pilot data (IRB33797) assessing the safety, tolerability, and efficacy of an accelerated iTBS protocol has shown a 90% antidepressant response in individuals with treatment resistant MDD, over the course of only 5 days. (Cole et al. American Journal of Psychiatry, 2020).

This study intends to utilize our novel accelerated iTBS (aiTBS) treatment approach, titled Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for symptoms of bipolar treatment resistant depression (TRD), while assessing changes in neuroimaging biomarkers.

b. Objectives

1. To determine if bilateral, accelerated intermittent theta-burst stimulation (aiTBS) can provide a rapid reduction in depressive symptoms among a group of individuals with bipolar depression, that is equivalent to the efficacy of the traditional repetitive transcranial magnetic stimulation (rTMS) paradigm for unipolar depression.

2. To determine if responders to this protocol will have a similar change in functional connectivity between the left DLPFC and subgenual anterior cingulate cortex (sgACC) after treatment.

3. To determine whether similar covariates may operate as potential predictors of antidepressant treatment response and durability (time to relapse) in bipolar depression.

c. Rationale for Research in Humans

All transcranial magnetic stimulation treatment studies must be conducted in humans.

2. STUDY PROCEDURES

a. Procedures

We will recruit a total of 30 outpatient participants for an open label pilot study (aged 18-80 years old) using intermittent theta burst stimulation (iTBS) over the left dorsolateral prefrontal cortex (LDLPFC) and right dorsolateral prefrontal cortex (RDLPFC) (up to five days, up to 10x/day) with the MagPro rTMS System. Participants will be required to meet diagnostic criteria for Bipolar I or Bipolar II (without psychosis or rapid cycling), in a current depressive episode. History related to participant's mood cycle will be obtained to ensure treatment is delivered during a depressive cycle which will be expected to span beyond the length of the 5-day treatment period based on the participant's most recent depressive episode duration. Psychiatric history will be obtained through each participant's psychiatric provider records to confirm diagnosis and bipolar symptom cycle history, which will be reviewed and confirmed during screening.

Participants will be excluded if they have been hospitalized within the last 6 months due to suicidality, depression severity or hypomania.

Participants will be required to have stabilized on medications (including at least one of the following as a mood stabilizer Lithium with a level of at least 0.6, Depakote with a level of at least 50, or a therapeutic dose of carbamazepine, oxcarbamazepine, or an antipsychotic) without dose changes for at least 6 weeks prior to the active study time period.

They will be ruled out if they have had a manic episode in the past year or a hypomanic episode in the last 6 months.

Participants will be asked to stay on their psychotropic medications for stabilization throughout the screening, baseline, and active study time periods. Participants will be required to have an established psychiatric prescriber.

We will use an adapted baseline covariate of the Maudsley Staging Method for TRD bipolar depression.

The study will have 4 time-periods:

- screening time period
- baseline time period
- active study time period

- follow-up time period

We will utilize a modified study design version of Williams (2018) and Cole et al (2020)

Reference: Cole EJ, Stimpson KH, Bentzley BS, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment Resistant Depression. Am J Psychiatry. 2020;177(8):716-726. doi:10.1176/appi.ajp.2019.19070720

Study Visit Schedule

Pre-screening	Screening Visit 1 Remote	Baseline visit2	Day1-5 Visit 3-7	Immediate Post) (Tuesday-Wednesday) Visit 8	Self-reports (Post 2,3week)	Post 4 week Visit 10 Remote visit (optional) Self-report(requirement)
Consent						
Initial screen consent	Screening consent	Study consent form Capacity consent				
Clinician Administered Assessments / Scales						
Demographic	Stanford demo					
Demographic II	inclusion/exclusion					
Dx - Psychiatrist - Tx Hx	MRI safety TASS (TMS safety) BSL-23(borderline)	MT	aTBS checklist			
Med & Psych Hx	Med Med & Psych	Self-report Mx review	Concomitant Mx review			

	Hx ATHF-current ATHF-lifetime	Concomitant Mx review				
Depression Sx - IDS-SR	Mausley+Thase Rush		randomization			
Mania Sx - Past - Current - Med	SCID-including BPD module MINI					
Psychotic Sx - Lifetime		UTox UPreg	UTox	UTox		
		COVID-19 screening	COVID-19 screening	COVID-19 screening		
Self-questionnaire						
	MADRS-S GAD-7	MADRS-S PHQ-8 GAD-7 BSS	MADRS-S-24h PHQ-8 BSS	PHQ-8 MADRS-S GAD-7 BSS	PHQ-8 (2,3w)	PHQ-8 MADRS-S GAD-7
Clinician rating						
Scanning safety	MADRS-C	MADRS-C HAMD-17	HAMD-6 YMRS	YMRS MADRS-C		MADRS-C HAMD-17

	YMRS	YMRS		HAMD-17		YMRS
Mx - MS - SSRI - SNRI - TCA - MAOi - APx - AED - Thyroid - BB - Amphetamine - MPH - Nonstimulant - Antianxiety - Insomnia - other	CSSRS MSSI	MSSI		MSSI		MSSI
		CGI-S		CGI-S CGI-I		CGI-S CGI-I
OTHER Self reports						
	Holmes & Rahe Stress					
	PSQI					
	SHAPS	SHAPS		SHAPS		SHAPS
		CTQ				

		Self-criticism scale					
Other measure							
		Resting EEG		Resting EEG			
			Adverse events				
			HRV				
		Resting state fMRI connectivity		Resting state fMRI connectivity			
		T1 anatomical		T1 anatomical			
		DWI		DWI			

b. Procedure Risks

These methods are the least risky because the intervals of stimulation have been shown to be appropriate for theta burst stimulation in the motor system with no adverse outcomes. The addition of R-DLPFC iTBS should provide an additional safety measure for the risk of hypomanic/manic conversion, although this risk is low. Additionally, all speech samples used for analyses will be based on randomly segmented splices of audiotapes; further, the 5-minute speech sample requires participants to answer a set of standardized questions without any reference to personal information.

c. Use of Deception in the Study

No deception will be used.

d. Use of Audio and Video Recordings

Video and Audio Recordings:

We will be video and audio recording study participants during the clinical assessments conducted with them while enrolled in the study. The video and audio recordings will be recorded using Zoom video from an encrypted Stanford owned laptop. The recordings will be available for training purposes for study personnel only or as otherwise consented to on the consent form. We will not use or distribute the recordings to outside personnel or scientific meetings etc. unless directly indicated by the participant on the consent form.

e. Alternative Procedures or Courses of Treatment

Participants with insurance could alternatively receive traditional rTMS, although not all insurance companies consider bipolar TRD to be covered under the FDA approved guidelines.

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

The participants will have the option of pursuing treatment as usual after the study (medications, therapy, traditional rTMS).

g. Study Endpoint(s)

The study will be terminated if either:
a) 6 participants reach hypomania as defined by a score of greater than 10 on the YMRS scale or
b) if 2 participants meet DSM-5 clinical criteria for mania without resolution after switching to full right sided DLPFC treatment within 24 hrs.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Bipolar disorder (BD) is an episodic illness comprised by periods of disabling depressive, elevated and/or mixed mood states, affecting approximately 4.8% of adults each year (Merikangas, et al., 2011; Miller, Dell'Osso, & Ketter, 2014). Individuals with BD are more impacted by symptoms of depression than mania or mixed symptoms; however, antidepressant medications remain controversial due to the potential concern of manic or hypomanic conversion (Judd et al., 2003; Thase, 2005; Tondo, Isacsson, & Baldessarini, 2003). Compared to the general population, individuals with BD are at greater risk to attempt (1:3) and complete (1:20 to 1:40) suicide, with a greater risk among those experiencing longer periods of depression than manic states (Baldesarini et al., 2006; Leverich et al., 2006). Not only are first line treatments limited in BD, but treatment resistance can be up to two times higher when compared to unipolar depression (Li et al, 2012; Tondo et al., 2014). Despite some advances in recent decades with the use of pharmacologic and psychotherapeutic interventions for bipolar disorder symptoms, few treatment modalities allow for both phases of symptom clusters (depressive and mania/hypomania) to be treated (Geddes & Miklowitz, 2013).

Repetitive transcranial magnetic stimulation (rTMS) is a safe, neuromodulator clinical tool utilized in the treatment of depression, which when applied to the left dorsolateral prefrontal

cortex (LDLPFC) has shown to be safe and effective in treating individuals with both unipolar and bipolar depression (Rachid, Moeglin & Sentissi, 2017; Rostami, et al., 2017; Tavares et al., 2017). Additional studies have shown that high frequency rTMS over the RDLPFC is effective in treating symptoms of bipolar mania (Grisaru, Chudakov, Yaroslavsky and Belmaker, 1998; Praharaj, Ram and Arora, 2009; Saba et al., 2004). Intermittent theta burst stimulation (iTBS) is a form of patterned rTMS, recently deemed "non-inferior" to standard rTMS in the treatment of unipolar major depressive disorder (MDD) (Blumberger et al., 2018; Chung, Hoy, & Fitzgerald, 2015). With a significant benefit in reduced treatment time in iTBS (10 minutes daily) compared with the standard rTMS treatment time (40 minutes daily) for 4-6 weeks, time constraints, transportation, and the financial resources to attend daily sessions over weeks of time remain cumbersome limitations (Bakker et al., 2015). Accelerated rTMS has recently been explored to determine the safety, tolerability, and efficacy in delivering multiple sessions over fewer days, to achieve a similar outcome compared with a standard series of rTMS (Sonmez et al., 2018). Reducing treatment time is important not only to reduce the individual time and resource strain, but also to address accelerating antidepressant response in more severely depressed individuals, at greater risk for suicide. Despite advancements in the clinical use of rTMS for depression, individual variation, and extensive burden of resources over time require further development. As individuals with bipolar disorder tend to have more treatment resistance with more time in depression and at greater risk for suicide, the development of symptom cluster targeting, non-invasive treatment options are of great importance.

Our recent pilot study utilized prior evidence to further enhance the propensity of antidepressant response to iTBS by modifying parameters in pulse spacing, dosage and treatment target location (Cazzoli et al., 2012; Fox et al., 2012; Gamboa, Antal, Moliadze, & Paulus, 2010; Noh, Fuggetta, Manganotti, & Fiaschi, 2012; Nyffeler, Cazzoli, Hess, & Muri, 2009). Applied in a small pilot sample of individuals with unipolar (n=20) and bipolar (n=5) TRD, the use of an accelerated iTBS paradigm yielded approximately 90% response and remission rates in depressive symptoms, in both unipolar and bipolar TRD patients (Cole et al., Manuscript in preparation). Of the 5 bipolar TRD patients, all met depression remission criteria within 5 days of treatment, with no hypomania/mania conversion observed during treatment or at follow-up. This study aims to further explore the use of an adapted accelerated iTBS protocol for bipolar TRD.

4. DEVICES USED IN THE STUDY

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

Investigational Device 1	
Name:	MagPro X100
Description:	Transcranial Magnetic Stimulation Device with theta burst stimulation
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The 'traditional 10Hz TMS' is on label and the theta burst stimulation is off label. It is the same device for both. The Magventure is about to be approved by the FDA for depression in 2 weeks. When that happens, the 'traditional 10Hz' stimulation will be on label with an approved device. The theta burst stimulation is minimal risk because the risk of seizure is very low (only reported once in literature) and there is no other risk other than minimal scalp irritation. We will be using an approved device 'off label' stimulation parameters which has a lower risk profile than the on label approved parameters.
Investigational Device 2	
Name:	**Lucus Center MRI (GE)**

Description:	It is a non-invasive imaging scanner. Some of the radio frequency imaging coils, imaging software and devices being used in the scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There are currently no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. There is a small risk of heating from the cables associated with these devices. However, they do not pose a serious risk to the health, safety, or welfare of a subject.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	We will be using the exact same MRI device at the Lucas Center as we have been using at the CNI. The CNI is closing for 3 months for renovations, and to keep the study moving forward, we will use the same device at the Lucas Center.
Investigational Device 3	
Name:	3T UHP
Description:	It is a non-invasive imaging scanner. Some of the radio frequency imaging coils, imaging software and devices being used in the scan are not approved by the FDA but are similar to counterparts that have been approved by the FDA. There are currently no known harmful side-effects associated with temporary exposure to the strong magnetic field used by MRI scanners. There is a small risk of heating from the cables associated with these devices. However, they do not pose a serious risk to the health, safety, or welfare of a subject.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The 3T Ultra-High Performance (UHP) MRI scanner from GE is an upgrade to the 3T MR750 which was a commercial FDA-approved system. The UHP system utilizes many components from GE's 3T Signa Premier, including gradient drivers, power supply, transmit and receive system electronics, but uses a higher performance gradient coil. The 3T UHP system is not FDA approved, and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-2-33 (ed 3.1) -- meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. In addition, the MR research being conducted requires highly specialized software that does not exist in the clinical MR market, so it is designed and implemented by researchers at the CNI. Any such software will be considered investigational, will function as a non-significant risk device, and is subject to the 21 CFR 812 investigational device (IDE) regulations as well as 21 CFR 50 and 56. The investigational image acquisition software will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation (dB/dt), and acoustic noise.

5. PARTICIPANT POPULATION

a. Planned Enrollment

b. We will recruit a total of 30 outpatient participants for an open-label pilot study (aged 18-80 yo) using bilateral intermittent theta burst stimulation (iTBS) over the left dorsolateral prefrontal cortex (LDLPFC) and right dorsolateral prefrontal cortex (RDLPFC) (five days, 10x/day) with the MagPro rTMS System**.**

c. Age, Gender, and Ethnic Background

We will recruit 30 participants ages 18-80, all gender and ethnic backgrounds.

d. Vulnerable Populations

The patient population will not include children or pregnant women as these individuals will not be candidates for psychiatric interventions. The sample will include economically/educationally disadvantaged as long as they have a fixed phone number by which to be contacted. Employees and students will be included as long as they are not lab members (due to HIPAA).

e. Rationale for Exclusion of Certain Populations

Women and minorities are included. Children are not included because they are typically excluded from psychiatric interventions e.g., aTBS and children will not be clinical staff numbers.

f. Stanford Populations

N/A

g. Healthy Volunteers

N/A

h. Recruitment Details

Patients will be recruited through the outpatient clinic in the psychiatry department, through a database of potential research subjects that have consented to contact for future research through the depression research clinic and through physician referral. Patients will either directly contact the research team for study participation, or they will give consent to the referring physician and the physician will communicate directly with the study team.

We have a bipolar pre-screening REDCAP database which we will use to screen eligibility.

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

For participants who participate in studies IRB 33797 and IRB 37224, data will be shared with studies IRB 33797 and IRB 37224.

Social media platforms such as Facebook will be used, as well as Craigslist. Flyers and brochures will be used to recruit as well.

i. Eligibility Criteria

i. Inclusion Criteria

1. Participants aged 18yo-80yo with a primary diagnosis of bipolar I or II disorder in a current major depressive episode or bipolar affective disorder II in a current major depressive episode.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about adverse events and other clinically important information.
3. Currently diagnosed with Bipolar Depression, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)
4. Meet the threshold on the total HAMD17 score of >/=20 at screening/baseline.
5. Not in a current state of mania (Young Mania Rating Scale) or psychosis (MINI)
6. In good general health, as ascertained by medical history.
7. Access to clinical rTMS after trial completion
8. Must have a stable psychiatrist during study enrollment, who confirms diagnosis of BPD I or II.
9. Must be on a mood stabilizer regimen for 6 weeks prior to study enrollment and agree to continue this regimen during study period
10. Meet the threshold on the MADRS, with a total score of >/=20 at screening/baseline.
11. History of ECT intolerance or exposure is permitted.
12. If traveling from out of town for the study, participants will need to have a companion with whom they're staying with while receiving open-label treatment.

ii. Exclusion Criteria

1. Any structural lesion e.g., structural neurological condition, more subcortical lesions than would be expected for age, stroke effecting stimulated area or connected areas or any other clinically significant abnormality that might affect safety, study participation, or confound interpretation of study results.
2. Metal implant in brain (e.g., deep brain stimulation), cardiac pacemaker, or cochlear implants
3. History of epilepsy/ seizures (including history of withdrawal/ provoked seizures)
4. Shrapnel or any ferromagnetic item in the head
5. Pregnancy
6. Autism Spectrum disorder
7. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation
8. Active substance abuse (<1 week) or intoxication verified by toxicology screen--of cocaine, amphetamines, benzodiazepines
9. Cognitive impairment (including dementia)
10. Current severe insomnia (must sleep a minimum of 5 hours the night before stimulation)
11. Current mania or psychosis
12. Showing symptoms of withdrawal from alcohol or benzodiazepines
13. IQ<70
14. Parkinsonism or other movement d/o determined by PI to interfere with treatment

15. Any other indication the PI feels would comprise data.
16. No access to clinical rTMS after discharge
17. Active suicidal ideation
18. A diagnosis of obsessive-compulsive disorder (OCD)
19. Any history of psycho surgery for depression
20. Any history of myocardial infarction, CABG, CHF, or other cardiac history
21. The presence or diagnosis of prominent anxiety disorder, personality disorder or dysthymia
22. History of intractable migraine
23. Mania in the past year, and/or hypomania in the past 6 months.

j. Screening Procedures

Participants will be seen in the bipolar research clinic for treatment consultation. At that time, standard of care treatments will be offered as well as this protocol. The bipolar research clinic screening database will be used to identify potential participants, as for all bipolar research clinic studies.

k. Participation in Multiple Protocols

We will not enroll participants that are involved in any other treatment trial. We will coordinate with any
ongoing biomarker studies to ensure that the treatment follows the biomarker study.

l. Payments to Participants

There will be payment given for the Probabilistic Reward Task. The Probabilistic Task is a neurocognitive assessment to test motivation in depressed patients. Each participant will be paid a total of $72 for participation in the Probabilistic Reward Task at each of the 3 defined time points above: Baseline visit, Immediate post-treatment follow-up and 1 month-visit (roughly ~$24/visit for a total of $72 across all 3 visits). Anhedonia, defined as the lack of reactivity to pleasurable stimuli, is a common symptom in depression. The goal of this task is to determine the degree of blunted reward-response in depressed participants.

m. Costs to Participants

No cost to the participant.

n. Planned Duration of the Study

The estimated duration for screening activities is one day.

The estimated duration for active participation is a maximum of 10 days. The active study period includes pre-measurements, 5 stimulation days, and immediate post and 1-month post-measurements). Following the 1-month follow-up, we will continue following patients biweekly for up to 6 months since their last aiTBS treatment. These follow-ups will be done via online self-reports until participants are no longer responders.

The estimated duration for analysis of participant data is 6 months.

6. RISKS

a. Potential Risks

i. Investigational devices

Potential risks for rTMS includes:

- Mania/hypomania
- Seizure

Currently, no known cases of either risk in iTBS according to a review in The Journal of Nervous and Mental Disease (Rachid 2017). According to a review published in the International Journal of neuropsychopharmacology, there have been 4 cases of treatment-emergent mania induced using rTMS (3 bipolar patients, 1 MDD patient) (Xia et al. 2008).

FDA approved rTMS has a 1:30,000 chance of seizure.

Additionally, the following expected AEs were reported in association with TMS in a recent publication (Downar et al, 2018): Headache, nausea, dizziness, fatigue, insomnia, anxiety, or agitation, back or neck pain, vomiting, tinnitus, migraine aura, abnormal sensations, unrelated accidents, and unrelated medical problems such as cold and flu. Citation: Downar et al (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomized non-inferiority trial. The Lancet.

Potential risks for MRI include:

- Claustrophobia during MRI
- Localized twitching (not painful) sensation during MRI
- Tinnitus after MRI

The MR magnet will attract some metals and affect some electronic devices. Participants must notify the operator of any metal on their bodies (ex. surgical clips, devices, or tattoos) to see if they are MRI compatible.

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents, or chemicals

N/A

iv. Procedures

The risks of the rTMS procedure being performed are Mania/hypomania and Seizure.

The potential risks for MRI procedures are:

- Exposure to magnetic field of MRI which may possibly lead to a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful.
- Dizziness or nausea may occur if you move your head rapidly within the magnet.
- The scanner uses a very strong magnet that will attract some metals and affect some electronic devices. These devices include cardiac pacemakers, surgical clips and implants that are in or on your body.
- Some of the radio frequency imaging coils, the imaging software and other devices being used to perform scans are not approved by the FDA, thus are considered experimental in nature.
- Some of the images, words, and sounds presented while you are in the scanner will have an emotional content and so could be mildly upsetting to some individuals.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

Participants will have all measures exerted to reduce the chances of seizure and discomfort from stimulation

vii. Psychological well-being

Participants will be placed in a relaxing environment to promote psychological well-being.

viii. Economic well-being

Participant's economic well-being will be looked at for as the participant will be receiving an intervention that would normally cost $10,000 and not paid for by most insurers.

ix. Social well-being

We would anticipate that particularly the responders that perceived social wellbeing would improve. We do not anticipate that there would be any worsening

x. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

We will have a trained rTMS treater monitoring for changes in level of consciousness at all times. We will eliminate any offending agents that may increase risk of seizure.

Monitoring participants depressive symptoms will allow the identification of individuals at risk of suicide and therefore the risk of this occurring can be minimized. The patient's psychiatrist will be immediately notified if participants show signs of suicidal ideation, hypomania/mania (increase of 4 or more items by at least 1 point on the YMRS scale) or display depressive symptoms which are worse than baseline (by 5 points on the HAMD compared to the HAMD score the patient had before study enrollment. If any study personnel believe a participant is at risk, the PI Dr. Nolan Williams (psychiatrist) will be notified immediately and an emergency consultation between him and the participant will be had. If the PI considers it necessary, the patient will be referred for emergency psychiatric treatment.

If the participant displays an increased YMRS score (>/=2 points) on 2 questions, stimulation will be switched to all right sided treatment to prevent any possibility of further inducing hypomania or mania. If these symptoms persist or increase to any greater degree during that same treatment series, the patient will be treated with Ativan and their primary psychiatrist will be contacted by the PI. If any of the research team or clinical staff believe that the participant may be showing signs of hypomania/mania, the YMRS will be administered by trained personnel immediately, the researchers will not wait until the daily assessments are conducted.

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d. Study Conclusion

The experiment will terminate when the final participant has completed their treatment and all data has been analyzed.

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e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Adverse events, protocol deviations, aggregate data will all be frequently reviewed by the Study PI and Protocol Director (PD).

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

The Principal Investigator and Protocol Director

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

If there is evidence of significant risk to the participants such as multiple seizure events or worsening of
psychiatric state in more than 20% of the participants.

v. DSMB Reporting

N/A

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

f. Risks to Special Populations

N/A

7. BENEFITS

Participants have a good chance of improvement in their mood symptoms as versions of this new type of rTMS treatment have already demonstrated consistent efficacy. Our recent open label study included 5 patients with bipolar depression, all of whom remitted with this accelerated TMS protocol. As this population was not included in the seminal FDA trials, it could further benefit this population who have limited treatment opportunities for bipolar depression symptoms.

8. PRIVACY AND CONFIDENTIALITY

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