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Neuromodulation for Comorbid Hoarding Disorder and Depression

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.1, 8.2, 10.4	Consent procedures are now virtual- using UCSD Docusign	Consent procedures were changed to a virtual option to reduce assessment time and to ensure safety & understanding of MRI and TMS prior to booking appointments.
1.3, 5.1, 5.2, 6.1.1, 8.1	Update to data collection instruments- specifically the clinical interview for psychiatric comorbidities	The copyright for the MINI (previously approved instrument) is currently difficult to obtain due to legal issues with copyright holder.
3.0, 4.1	Increase total consent number	Three of the anticipated 12 individuals consented did not start rTMS. Funding/availability left for two additional individuals.

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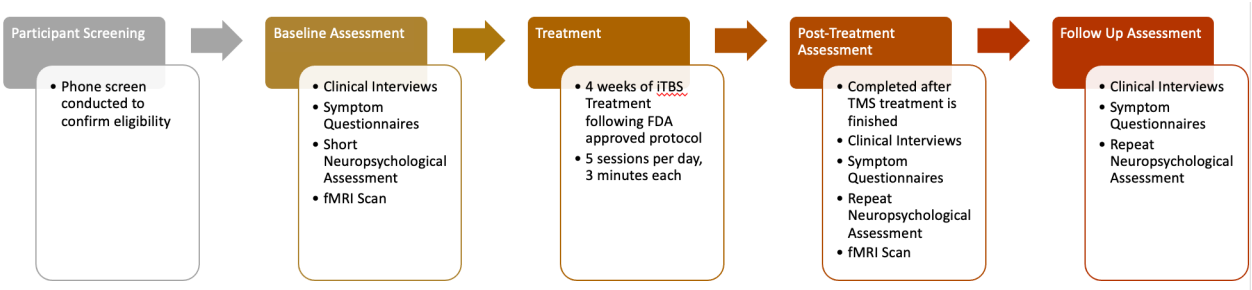
1 PROTOCOL SUMMARY

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1.1 SYNOPSIS

Title:	Neuromodulation for Comorbid Hoarding Disorder and Depression
Study Description:	The primary goal of this study is to evaluate whether intermittent theta burst stimulation (iTBS) is effective for treating depression in people who have depression and chronic hoarding disorder (HD). We will also evaluate whether this treatment can improve HD symptoms, cognitive performance, and brain region connectivity. We will investigate how the treatment works for depression, as well as other factors that can enhance or hinder treatment, such as pre- treatment level of depression, cognitive performance, or brain region connectivity.
Objectives:	*Primary Objective:* Investigate the feasibility and acceptability of repetitive transcranial magnetic stimulation (rTMS) treatment for major depressive disorder (MDD) in individuals with comorbid hoarding disorder (HD) and MDD for 4 weeks, with assessments at baseline, 4 weeks (post-treatment), and 8 weeks (follow-up). Our main outcome will be assessed through session attendance. *Secondary Objectives:* Explore the efficacy of rTMS treatment as well as the effects of rTMS on resting state functional connectivity in HD+MDD patients. Our secondary outcome will be assessed through symptom changes (both depression and hoarding), changes in neuropsychological performance, and resting state functional connectivity.
Endpoints:	*Primary Endpoint:* At end of treatment protocol (4 weeks from start of treatment) *Secondary Endpoints:* 4 weeks after the treatment protocol is completed
Study Population:	Adults who meet clinical criteria for both Major Depressive Disorder and Hoarding Disorder
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled following telephone screening. Participants are identified through an interest list of individuals who requested contact for research on hoarding disorder. All assessment and treatment procedures will be completed at appropriate UCSD facilities (e.g. UCSD Center for Functional MRI in La Jolla and TMS centers at in Rancho Bernardo, La Jolla, or Hillcrest).
Description of Study Intervention:	Participants will undergo 4-weeks of TMS treatment using FDA approved protocols for treatment of depression.
Study Duration:	1 year
Participant Duration:	Approximately 8 weeks, with a baseline assessment, 4 weeks of treatment and a follow up assessment 4 weeks after TMS treatment completion.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Admin Time (min)	Baseline (Wk 0)	Post-Tx (Wk 4)	Follow-Up (Wk 8)
Baseline Characterization Measures				
Enrollment Interview & Medical History	15	x		
Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND)	30	x		
Structured Interview For Hoarding Disorder	15	x		
Functional Magnetic Resonance Imaging (fMRI)	60	x	x	
Neuropsychological Tests				
Wide Range Achievement Test-4 Reading (estimated I.Q.)	5	x		
D-KEFS Trail Making Test (executive functioning)	6	x	x	x
D-KEFS Color Word Interference Test (processing speed, inhibition)	10	x	x	x
WMS-IV Digit Span (attention, working memory)	8	x	x	x
WAIS-IV Processing Speed (Coding, Symbol Search)	5	x	x	x
Hopkins Verbal Learning Test – Revised (learning, memory)	20	x	x	x
Neurobehavioral Measures				
Patient Health Questionnaire-9 (PHQ-9)	2	Weekly throughout study		
Hamilton Rating Scale for Depression (HAM-D)	20	x	x	x
Hoarding Rating Scale-Self Report (HRS-SR)	2	Weekly throughout Study		
Saving Inventory Revised (SIR)	15	x	x	x

2 INTRODUCTION

2.1 STUDY RATIONALE

We propose to conduct the first clinical trial of rTMS in comorbid HD+MDD. Determining the feasibility, acceptability, and efficacy of rTMS for HD+MDD could support implementing a new potential treatment approach for a common neuropsychiatric condition. Our central hypotheses are that rTMS will be feasible, acceptable, and will improve depression symptoms in HD+MDD, as well as possibly yield salutary effects on HD symptoms, and improvements in resting state functional connectivity.

2.2 BACKGROUND

Hoarding Disorder is one of the most common neuropsychiatric disorders in older adults, with devastating functional consequences. Retrospective studies indicate that HD symptom onset typically begins in adolescence, with symptom severity increasing with age [1-5] resulting in a 6% prevalence rate in individuals over age 55 [1, 6-8]. HD causes significant morbidity and mortality through risks for falls, fires, health code violations, as well as family discord and dysfunction [2, 3, 9-11]. Medical and psychiatric comorbidities are also common in HD, with 50-60% of individuals meeting criteria for major depressive disorder (MDD) [12-14]. There is an overlap in associated features of MDD and HD, including amotivation, decision making problems, lack of self- or home-care, and resulting clutter [7, 12, 15, 16]. Depression symptoms have been linked to increased HD symptom severity [17]. The gold standard treatment for HD is cognitive therapy, with an average symptom improvement of 12-38% [18-20]. HD treatment does not work for all patients, however, and evidence indicates that MDD limits response to HD treatments [9, 21, 22]. Additionally, HD treatment alone is not sufficient to improve MDD [18, 19].

There is a small but growing body of neurobiological research on HD. The current proposed neurobiological model of HD suggests an abnormal pattern of both hyper- and hypo-activation within specific brain networks [23]. During neutral tasks or at rest, key frontal brain regions are less active in HD patients than in healthy comparison participants [24-26]. However, during tasks that require objects to be discarded, HD patients show increased activation in key frontal regions [27, 28] including the anterior insula, orbital frontal cortex, anterior cingulate cortex, and the dorsolateral prefrontal cortex (dlPFC). Neural connection patterns (resting state functional connectivity) show similarities between patients with HD, MDD, and comorbid HD+MDD [27]. Despite the high frequency of comorbidity between HD and MDD, as well as overlapping areas of dysfunction in frontal brain regions, to date there has been no focus on targeted treatments for comorbid HD and MDD.

Repetitive transcranial magnetic stimulation (rTMS) is an effective, FDA-approved treatment for MDD. rTMS is a noninvasive procedure in which an electromagnetic coil is placed against the scalp and electromagnetic pulses are delivered to stimulate a specific brain area. rTMS for MDD involves stimulating the left dlPFC. Meta-analytic findings indicate robust anti-depressant effects of rTMS [29] in addition to effects on resting state functional connectivity [30]. However, there have been no trials of rTMS for individuals with HD+MDD to treat depression.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Participant Interviews, Neurobehavioral Assessments, Neurocognitive Assessments: Foreseeable risks or discomforts associated with the participant interviews, neurobehavioral assessment, or neurocognitive assessments are minimal. Participants may become bored, fatigued, or frustrated while completing assessments. Participants may also feel uncomfortable, embarrassed, anxious, etc., when answering personal questions about their mental health. Participants may take a break at any time or discontinue

participation if they feel uncomfortable. If this occurs, they may complete the assessment at another time or discontinue participation, without penalty. Assessments must be completed within one week and weekly assessments of symptoms during treatment must be completed within one day.

MRI Assessments: MRI does not involve radiation and has been approved by the FDA for routine clinical use. There are three main potential risks to take into account.

POTENTIAL PRESENCE OF METAL OBJECTS. A safety risk is posed by the attraction of magnetic metal objects by the high strength magnetic fields. The presence of a metal foreign object implanted is determined by interviewing each potential participant and completing a detailed screening questionnaire. Participants and staff are instructed to remove all metal objects, including clothing with metal clasps, before entering the magnet room. The magnetic properties of unknown material are tested outside the magnet room with a strong permanent magnet. Participants and staff are also instructed to enter the magnet room slowly and pause at the entrance to determine if any items on their person may be pulling toward the magnet.

POTENTIAL DISCOMFORT DUE TO CONFINEMENT. The second concern is the discomfort some participants encounter by the confinement within the donut-shaped MRI system. Some participants may feel uncomfortable or confined once positioned within the MRI system. This potential reaction is reduced by discussing the procedure prior to entry into the magnet room, by providing the subject with a mirror through which they can look out into the room, and by communicating with the subject over the intercom. During set-up and anatomical imaging, participants can choose to listen to music or the radio over their headphones. Nevertheless, if participants continue to feel uncomfortable, the imaging procedure is terminated, and the subject is removed from the magnet and excused from participation.

POTENTIAL RISK OF HEARING LOSS. The third concern is the loud noise made by the MRI scanner. These risks occur for all clinical MRI exams and are not increased by the proposed research. Participants are required to wear earplugs during scanning to reduce noise levels below FDA limits.

Intervention: There are no known long-term health risks from the use of iTBS, which is a form of repetitive transcranial magnetic stimulation (rTMS), when operated within consensus safety guidelines. In 2008, the Food and Drug Administration (FDA) approved the use of high frequency rTMS in the treatment of depression and there have now been hundreds of research studies conducted with rTMS. rTMS produces no structural brain changes in humans, and reviews of systematic research and clinical practice of rTMS in thousands of healthy subjects and patients show that adverse events are very rare. We will follow all safety guidelines and have incorporated them into our screening and session procedures. Additionally, we will monitor for potential risks.

POTENTIAL RISK OF SEIZURE. rTMS stimulates the neurons at a level below what would be expected to cause a seizure. However, a number of seizures have happened with rTMS. The risk of seizure is related to the intensity, duration, frequency, and rest interval of stimulation. According to a recent report, the risk of rTMS-induced seizures under ordinary use with the figure-of-eight coil is estimated to be 1 in 30,000 treatments (0.003%). Parameters of stimulation used in the proposed study fall within

published safety guidelines. To our knowledge, stimulation with the parameters and settings we propose to use has never been reported to cause seizures. Before applying rTMS, we will carefully titrate each person's stimulation intensity to their resting motor threshold, defined as the lowest possible stimulation intensity to reliably induce a motor evoked potential. rTMS will not be applied above 120% of resting motor threshold, which is within the defined safety guidelines. However, if a seizure occurs, all study staff are trained to respond to seizure and emergency facilities are available.

POTENTIAL RISK OF HEADACHE. The most commonly reported side effect of rTMS is headache. This headache is typically of a muscle-tension type. When it occurs, it usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over-the-counter analgesics. We will ask the subject to report if they start to feel a headache and stimulation will be stopped right away.

POTENTIAL RISK OF HEARING LOSS. The discharge of the TMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to TMS have shown temporary hearing loss lasting at least 5 minutes though always less than 4 hours. Foam earplugs can protect against these changes and will be worn by the participants and the researchers present during iTBS sessions.

As with any study, a risk of breach of confidentiality exists. Multiple steps will be taken to ensure data security. As with all research studies, unknown risks are also possible and should one arise, procedures described in the protocol will be enacted as appropriate to the risk.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may or may not personally benefit from the intervention provided. Some participants in the iTBS intervention may find benefit, as it is FDA-approved for treatment of depression. As a society, this study may provide new information on how to treat a comorbid condition that currently has never been examined for efficacy or feasibility.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Abnormal findings: If abnormal findings are observed on any assessment, these will be confirmed by a clinician (e.g., incidental findings on MRI will be referred to the CFMRI radiologist); participants will be offered referral to the appropriate clinic or department.

Discomfort: If a participant experiences any discomfort during any study procedures, the participant or technician may stop participation at any time.

Adverse events: If new conditions emerge or existing conditions worsen, licensed providers on the study team will evaluate the participant to make recommendations for treatment and withdraw the participant if it is believed to be in the participant's best interest. For participants who endorse active suicidal or homicidal ideation with plan and/or intent, an attempt to complete a safety plan will be conducted. Standard clinical practice will be utilized. If necessary, the participant will be transferred to the emergency room. Any care provided for injuries related to study procedures will be provided free of charge by UCSD Health.

Study Monitoring: As this study is no greater than minimal risk and does not include the use of pharmaceuticals, independent clinical monitoring will not be necessary. However, regular monitoring will be performed by the study PI and co-investigators. Study investigators will meet within 24 hours to discuss any reported serious adverse events and unexpected problems. Adverse events such as headache will be reviewed at weekly study meetings.

Special Precautions: Safety questionnaires to determine that iTBS and MRI can be done safely will be administered early in the study screening process and repeated prior to iTBS and MRI procedures to ensure that iTBS and MRI will be safe to conduct (e.g., participant not pregnant and using reliable birth control if applicable; no non-removable metal in head or within 12" of the TMS coil). These forms are the MRI Safety Screening form, use routinely at UCSD's Center for Functional MRI and the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) which is routinely used in UCSD TMS Clinics.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Investigate the feasibility and acceptability of repetitive transcranial magnetic stimulation (rTMS) treatment for major depressive disorder (MDD) in individuals with comorbid hoarding disorder (HD) and MDD for 4 weeks, with assessments at baseline, 4 weeks (post-treatment), and 8 weeks (follow-up).	*14 participants with HD+MDD will enroll in the trial and will complete rTMS treatment at the same rate as is typical for MDD patients. Outcomes will be number of sessions attended as well as if assessments were completed, and if so, fully completed.*	*This is an open-label feasibility trial for a new population, those with comorbid MDD+HD.*
Secondary		
Explore the efficacy of rTMS for HD+MDD patients.	*Participants will MDD symptoms at 4 and 8 weeks post-treatment. Secondary outcomes will include any improvements in HD symptoms and neuropsychological performance. This will be monitored through changes scores of symptom levels at each week of treatment and across assessment timepoints.*	*As this is a feasibility study, there is not enough power to look at group level change, merely individual.*
Tertiary/Exploratory		
Explore the effects of rTMS on resting state functional connectivity in HD+MDD patients.	*Resting state functional connectivity markers will improve at 4 weeks.*	*Resting state markers have been used for changes in brain function with people with MDD following TMS treatment.*

4 STUDY DESIGN

4.1 OVERALL DESIGN

We propose to conduct the first clinical trial of rTMS in comorbid HD+MDD. Determining the feasibility, acceptability, and efficacy of rTMS for HD+MDD could support implementing a new potential treatment approach for a common neuropsychiatric condition. Our central hypotheses are that rTMS will be feasible, acceptable, and will improve depression symptoms in HD+MDD, as well as yielding salutary effects on HD symptoms and improvements in resting state functional connectivity. This will be an open label trial given the feasibility goals and will use approved FDA protocols for depression.

Aim 1. Investigate the feasibility and acceptability of rTMS treatment for MDD in individuals with comorbid HD+MDD for 4 weeks, with assessments at baseline, 4 weeks (post-treatment), and 8 weeks (follow-up).
Hypothesis 1: 14 participants with HD+MDD will enroll in the trial and will complete rTMS treatment at the same rate as is typical for MDD patients.

Aim 2. Explore the efficacy of rTMS for HD+MDD patients.
Hypothesis 2: Participants will report improved MDD symptoms at 4 and 8 weeks post-treatment. Secondary outcomes will include any potential improvements in HD symptoms and neuropsychological performance.

Aim 3. Explore the effects of rTMS on resting state functional connectivity in HD+MDD patients.
Hypothesis 3: Resting state functional connectivity markers will improve at 4 weeks.

General Study Procedures. Participants will be screened for inclusion and exclusion criteria using short MDD and HD screening forms as well as both the standard UCSD MRI safety screening form and the Transcranial Magnetic Stimulation Adult Safety Screen. Once eligibility is confirmed, consent forms will be reviewed. Following written informed consent, participants will complete baseline assessments, including clinical interviews, self-report measures, a short neuropsychological assessment, and an fMRI scan. Neuropsychological assessments will be conducted to assess for any changes in cognitive status pre-to-post treatment and during follow-up. The assessment will both target key areas of functioning known to be affected by depression, as well as general global functioning. Treatment will be scheduled for 4 consecutive weeks, with rTMS sessions occurring for 3 minutes each weekday (20 sessions total). Self-reported MDD and HD symptoms will be collected weekly, and measures of current depression symptomatology (including suicidality) and hoarding severity will also be obtained at baseline, post treatment and follow up. The neuropsychological assessment will be repeated at 4 and 8 weeks. The fMRI scan will be repeated at 4 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As this is an FDA approved protocol known to reduce depression symptoms, this is not a trial for depression effectiveness. This is a feasibility trial for individuals with depression who have co-occurring hoarding disorder. This is an open label pilot to determine feasibility and acceptability in this population.

The FDA does not limit iTBS to individuals with depression and no other comorbidities. Thus, iTBS can be provided to individuals with depression and other comorbid disorders.

4.3 JUSTIFICATION FOR DOSE

Dose is at the FDA approved level which is not restricted or changed based on the presence of other psychiatric comorbidities.

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

UCSD and the VA San Diego Healthcare System are the only two sites in the country with ongoing HD treatment research programs, both directed by close collaborator Dr. Catherine Ayers. Currently, Dr. Ayers' interest list includes over 450 individuals who screened positive for HD and agreed to be contacted for research studies. Due to the over 50% comorbidity rate for HD+MDD, we anticipate at least half of the people on the interest list will meet the inclusion criteria for the proposed project.

Pre-consent telephone screening will be based upon the screening tool (i.e., inclusion/exclusion criteria). Current MDD and HD diagnoses and other inclusion/exclusion criteria will be confirmed. If the individual does not meet criteria or declines to participate, screening materials will be destroyed.

Individuals who remain interested and eligible will then be scheduled and consented prior to participation. Consent will be completed via secure video platform (Zoom or Teams) and signed via UCSD Docusign electronic forms, followed by official screening for TMS and MRI safety. Upon completion of consent and passing of the official screening, the participant will be scheduled for their first study visit. Participants who are determined not to meet inclusion/exclusion criteria will be withdrawn from the study.

Inclusion Criteria

1) *Signed and dated informed consent form*
2) Stated willingness to comply with all study procedures and availability for the duration of the study
3) *Male, female, or non-gender conforming individuals (i.e. those who do not identify as male or female)*
4) *All racial and ethnic groups*
5) *Ages 18 to 70*
6) *Meets criteria for current Major Depressive Episode within the context of Major Depressive Disorder, per HAM-D and DIAMOND.*
7) *Meets criteria for current Hoarding Disorder, per SIHD*
8) *Score of 18 or higher on the HAMD-17, indicating moderate to severe depressive symptoms*

9) *Stable on psychiatric medications for 6 weeks, with no changes to psychiatric medications expected during the study period*
10) *No contraindications to TMS (passes the TMS Adult Safety Screening questionnaire)*
11) *No contraindications to MRI (passes MRI safety screening questionnaire)*
12) *Able to commit to the treatment schedule*
13) *Able to complete assessment procedures in English*
14) *Intact decision-making capacity and ability to provide voluntary informed consent*

5.2 EXCLUSION CRITERIA

Exclusion Criteria

1) History of other neurological condition including but not limited to: conditions associated with increased intracranial pressure; space occupying brain lesions; cerebral aneurysm; stroke; transient ischemic attack within past two years; Parkinson's disease; Huntington's disease; dementia; multiple sclerosis; history of brain surgery; epilepsy; seizure except those therapeutically induced by electroconvulsive therapy (ECT) or a febrile seizure of infancy
2) Implanted medical devices that are not explicitly recognized as MRI safe, including cardiac pacemaker, medication pump, aneurysm clip, shunt, stimulator, cochlear implant, electrodes, or any other metal object within or near the head (excluding the mouth) that cannot be safely removed
3) Active manic or psychotic illness per DIAMOND
4) Current substance use disorder per DIAMOND
5) Current active suicidal or spontaneously disclosed homicidal ideation. Active suicidal ideation for this study is defined as a score of 3 or greater on the HAMD-17 and/or 3 or more on the PHQ-9.
6) Pregnant or intending to become pregnant within the study period; breastfeeding
7) Other sensory conditions or illnesses precluding participation in assessments or treatment
8) Current dose of lorazepam 2 mg or greater daily (or benzodiazepine equivalent) or any anticonvulsant due to the potential to limit iTBS efficacy
9) Taking medication that lowers seizure threshold
10) Previous failed treatment with rTMS, iTBS, or ECT

5.3 LIFESTYLE CONSIDERATIONS

not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because they do not meet full clinical criteria for MDD or HD via clinical interviews will not be rescreened, they will be withdrawn from consideration and referred to alternative treatment options (i.e. talk therapy, medication) with area providers. They will be encouraged to reach out to their primary care provider for specific and appropriate recommendations for their individual circumstances.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

General Study Procedures. Participants will be screened for inclusion and exclusion criteria using short MDD and HD screening forms as well as both the standard UCSD MRI safety screening form and the Transcranial Magnetic Stimulation Adult Safety Screen. Once eligibility is confirmed, consent forms will be reviewed. Following written informed consent, participants will complete baseline assessments, including clinical interviews, self-report measures, a short neuropsychological assessment, and an fMRI scan. Neuropsychological assessments will be conducted to assess for any changes in cognitive status pre-to-post treatment and during follow-up. The assessment will both target key areas of functioning known to be affected by depression, as well as general global functioning. Treatment will be scheduled for 4 consecutive weeks, with rTMS sessions occurring for 3 minutes each weekday (20 sessions total). Self-reported MDD and HD symptoms will be collected weekly, and measures of current depression symptomatology (including suicidality) and hoarding severity will also be obtained at baseline, post treatment and follow up. The neuropsychological assessment will be repeated at 4 and 8 weeks. The fMRI scan will be repeated at 4 weeks. Participants will be compensated for their time spent in assessments ($70 per assessment X 3 in-person assessments = $210; $50 per fMRI session X 2 sessions = $100; $310 maximum total compensation).

Mental and Cognitive Assessment. The baseline assessment will consist of a clinical interview, self-report measures, and a brief neuropsychiatric assessment. Clinical interviews and self-report measures will consist of demographic information collection, followed by Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND) to determine their current psychiatric status. Diagnoses of MDD and HD diagnoses will be confirmed through gold-standard measures of the Hamilton Depression Rating Scale (HAM-D) and the Structured Interview for Hoarding Disorder (SIHD). In addition, the Saving Inventory-Revised (SI-R) and the Hoarding Rating Scale-Self Report (HRS-SR) will be administered to assess symptom severity. The Patient Health Questionnaire-9 (PHQ-9) will be given to rate current symptoms as well as to monitor for changes in suicidality. Neuropsychological assessment will collect measures of attention, working memory, processing speed and decision making, lasting approximately one hour. Neuropsychological tests were selected to include broad sampling of cognitive domains relevant to MDD and HD. Tests will include the Wide Range Achievement Test-4 (WRAT-4) to estimate intellectual abilities; D-KEFS Trail-Making Test (TMT) to measure visual, psychomotor, and executive processes; D-KEFS Color-Word Interference to measure inhibition and switching; WAIS-IV Digit Span as a measure of verbal working memory; WAIS-IV Processing Speed Index (Coding and Symbol Search) as a measure of visual scanning and information processing speed. Primary metrics for each

measure will be converted to standard scores using published normative data. These same measures excluding the DIAMOND and SIHD will be given at post-treatment, as well as weeks 4 and 8 post-treatment. The self-report PHQ-9 and HRS-SR will be given weekly throughout treatment.

Functional MRI Procedures, MRI data will be collected the UCSD Center for Functional MRI (CFMRI) using a 3-T Siemens Prisma with a 32-channel phased-array head coil. High-resolution T1-weighted MRI scans will be acquired with isotropic voxel resolution of 1 mm^3 along with 8 minutes of standard resting-state echo-planar imaging (TR = 3,000 ms, TE = 30ms, FA=85, 3 mm^3 voxels). Subjects will be instructed to remain still, stay awake, and to keep their eyes open. MRI data will be inspected for head motion and data quality, and physiological noise will be accounted for in our models by using FMRIB's Software Library (FSL) PNM toolbox. Multiple regression analyses will use the FSL FEAT toolbox (FMRI Expert Analysis Tool). Subsequent seeded connectivity analyses will follow procedures described below that are based on established techniques reported in the literature for identifying connectivity between left DLPFC and the sgACC.

Subject-level, seed-to-voxel analyses will first be performed on the resting-state data by calculating whole-brain statistical maps, consisting of bivariate Pearson's correlations between residual blood oxygen level–dependent time courses extracted from a seed region in the sgACC and all other brain voxels. Subject-level seed maps will be converted to Fisher-transformed Z scores to conform to the assumptions of generalized linear models. Seed-based functional connectivity will then be performed using the MarsBaR Toolbox to create seeds by drawing spheres around reported coordinates in Montreal Neurological Institute (MNI) space for the sgACC (left: MNI –4 26 –8, right: MNI 5 26 –8) and left DLPFC (MNI –44 40 29).

TMS Treatment Procedures. The UCSD rTMS treatment clinics provide key benefits to this novel study. There are multiple locations available, enhancing accessibility for patients. UCSD is a leader in using intermittent theta-burst stimulation (iTBS), a more rapid rTMS technique that is less burdensome and therefore better suited for future implementation. iTBS is equivalent to standard rTMS in terms of depression outcomes and requires significantly less time (3-min sessions for iTBS compared to 37-min sessions for rTMS).

iTBS Procedures. iTBS will be delivered to individualized targets within the left dorsolateral prefrontal cortex (DLPFC) that are determined through electric-field modeling of seeded fMRI connectivity to the subgenual nucleus of the accumbens (sgACC) according to the procedures described below.

Prior to the commencement of iTBS treatment, single pulse TMS will be used to measure the resting motor threshold (RMT) for the abductor pollicis brevis in the right hand of all participants using standard published methods [108]. Electric-field (E-field) modeling, however, will be used to determine the treatment intensity with the RMT value assessed only for comparison and as a means to report the stimulation intensity in standard form.

iTBS will be delivered as 3-pulse 50-Hz bursts, applied at 5 Hz (i.e., 50 Hz burst of 3 pulses delivered every 200 ms) with a 2-second train of TBS repeated every 10 seconds (i.e., 2 seconds of TBS followed by an 8 second rest). The total number of pulses is 600. iTBS will be administered with a commercially available TMS device that delivers both active and sham stimulation (MagVenture MagPro R30 using a standard figure-of-8 coil, the MagVenture Cool-B65 A/P).

There is considerable variability in the literature in regard to the optimal stimulation intensity to be provided during TBS experiments. TBS was originally developed using subthreshold stimulation intensities, with all of the original publications establishing the technique providing stimulation at

intensity significantly below RMT. However, the THREE-D study, which established non-inferiority of left DLPFC iTBS in the treatment of depression, provided stimulation at 120% of the RMT (33) and as such this approach has been adopted where iTBS is used in clinical practice, including at all current trial sites. Therefore, we will use E-field modeling to provide stimulation intensity that, on average, matches 120% RMT.

6.1.2 DOSING AND ADMINISTRATION

Not Applicable

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not Applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not Applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not Applicable

6.2.4 PREPARATION

Not Applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not Applicable

6.4 STUDY INTERVENTION COMPLIANCE

Intervention compliance will be assessed by number of sessions attended. Should the participant wish to stop treatment this will be considered the last session attended. They will still be asked to complete post-treatment and follow up assessments at the standard timelines or withdrawn from the study if that is their preference.

6.5 CONCOMITANT THERAPY

Not Applicable

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from rTMS treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

Should individuals halt or be halted from the rTMS procedures, we will encourage them to complete any subsequent post-treatment and follow-up assessments on the timeline as planned.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

Pregnancy
Significant study intervention non-compliance
If any clinical adverse event (AE), such as a medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
Participant unable to receive rTMS for 4 days in sequence.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Research participants who sign the informed consent form but do not receive the study intervention may be replaced. Research participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled rTMS visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit within 48 hours and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Participants will be pre-screened via the submitted phone screen, as well as the TMS Adult Safety Survey (TASS), the UCSD MRI Safety Survey, the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND), and an enrollment interview. The enrollment interview will obtain information regarding contact information, demographics, educational history, and medical history including psychiatric treatment history. This information will be used for the purpose of confirming study eligibility and other inclusion/exclusion criteria as well as for secondary data analyses. The DIAMOND will be used to confirm current psychiatric status. Diagnoses of Major Depressive Disorder and HD diagnoses will be confirmed through gold-standard measures of the Hamilton Depression Scale (Ham-D) and the Structured Interview for Hoarding Disorder (SIHD. In addition, the Saving Inventory-Revised (SI-R) and the Hoarding Rating Scale-Self Report (HRS-SR) will be administered to assess symptom severity. The Patient Health Questionnaire-9 (PHQ-9) will be given to rate current symptoms as well as to monitor for changes in suicidality. Neuropsychological assessment will collect measures of attention, working memory, processing speed and decision making, lasting approximately one hour. These same measures excluding the DIAMOND and SIHD will be given at post-treatment, as well as week 8 post-treatment. The self-report PHQ-9 and HRS-SR will be given weekly throughout treatment.

8.2 SAFETY AND OTHER ASSESSMENTS

Brief screenings along with the descriptions of fMRI protocols and rTMS protocols will be conducted as part of the participant screening process. Full safety screenings will be conducted immediately following consent procedures including the TMS Adult Safety Survey (TASS), the UCSD MRI Safety Survey. Baselien assessment including MRI will be scheduled post-consent and with confirmed safety screening. Active suicidality will also be screened for, as we are seeking individuals with major depressive disorder. Should the participant be deemed ineligible for fMRI or rTMS protocols, they will be withdrawn from the study and encouraged to seek alternative therapies. Should the participant indicate active suicidality, emergency services will be called, and the participant will be withdrawn from the study. Should the participant indicate passive suicidality, then a safety plan will be completed with a licensed clinical study staff member (e.g. Dr. Twamley). Weekly monitoring of depression symptoms is planned throughout treatment and this will include any individuals who endorse passive suicidality and any changes will be closely monitored.

If new conditions emerge or existing conditions worsen, licensed providers on the study team will evaluate the participant to make recommendations for treatment and withdraw the participant if it is believed to be in the participant's best interest. Standard clinical practice will be utilized. If necessary, the participant will be transferred to the emergency room. Any care provided for injuries related to study procedures will be provided free of charge by UCSD Health.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

As previously detailed, should adverse events occur (headache, changes in reported suicidality, etc), the clinical team will be notified. As this study is no greater than minimal risk and does not include the use of pharmaceuticals, independent clinical monitoring will not be necessary. However, regular monitoring will be performed by the study PI and co-investigators on a weekly basis in study meetings or with an emergency meeting should a SAE arise.

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All procedures will be followed per IRB regulations for report AE as with SAE detailed below.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

If any serious adverse events or unanticipated problems occur, they will be notified and re-consented.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-

approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If any serious adverse events or unanticipated problems occur, participants will be notified and re-consented.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is primarily focused on feasibility and acceptability of study procedures, as indicated by participant attendance. There is no formal Statistical Analysis Plan.

No inferential statistics will be computed. Effect sizes will be calculated for the primary and secondary outcomes listed below.

Primary Efficacy Endpoint(s):

Changes in depression symptom measures.

Secondary Efficacy Endpoint(s):

Changes in hoarding symptom measures, neuropsychological functioning, and changes in resting state fMRI regions of interest.

9.2 SAMPLE SIZE DETERMINATION

This is not an adequately-powered trial, but rather a pilot trial designed to demonstrate feasibility and acceptability of trial procedures, along with initial effect size estimates of efficacy.

9.3 POPULATIONS FOR ANALYSES

All individuals who complete consent and any subsequent study components will be counted together as measures of feasibility and acceptability. All individuals who complete at least one week (5 sessions) of treatment and complete symptom surveys for that week will be included in efficacy considerations.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Adherence to treatment throughout the 4 week protocol will be assessed.

Markers of clinically meaningful change in symptoms will be calculated for all key measures to identify effects of treatment. This includes symptom score totals, neuropsychological test change scores, and resting state left DLPFC-sgACC functional connectivity change scores. Effect sizes will be reported using Cohen's *d* (small = 0.2; medium = 0.5; large = 0.8) or standardized regression coefficients (β) (small = 0.14; medium = 0.39; large = 0.59).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Effect sizes, as above.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Effect sizes, as above.

9.4.4 SAFETY ANALYSES

Safety will be evaluated by tracking and examining AEs, SAEs, and UPs.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

As this is an open-label pilot study, participant characteristics (descriptive) will be computed.

9.4.6 PLANNED INTERIM ANALYSES

As this is an open-label pilot study, no interim analyses are planned.

9.4.7 SUB-GROUP ANALYSES

As this is an open-label pilot study, no sub-group analyses are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

As this is an open-label pilot study, data will be listed for each individual by data point.

9.4.9 EXPLORATORY ANALYSES

As this is an open-label pilot study, there are no additional exploratory analyses beyond stated aims.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

Determination of unexpected, significant, or unacceptable risk to participants

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, and Institutional policies.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Not Applicable

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator
Elizabeth Twamley, PhD, *Professor of Psychiatry*
UC San Diego
9500 Gilman Drive (MC 9116A), *La Jolla, CA. 92093*
858-642-3848
etwamley@health.ucsd.edu

10.1.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI and co-Investigator Cory Weissman, MD, who oversees all clinical TMS services in the Department of Psychiatry. As this study is using an FDA-approved, non-invasive treatment, on label, there is no DSMB.

10.1.6 CLINICAL MONITORING

Not Applicable

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report

form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2 ADDITIONAL CONSIDERATIONS

Not Applicable

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
4	6/6/23	Added e-consent to allow for full safety screenings prior to scheduling baseline MRI	Added e-consent to allow for full safety screenings prior to scheduling baseline MRI to ensure participant is safely eligible to participate.

11 REFERENCES

1. Samuels, J.F., et al., *Prevalence and correlates of hoarding behavior in a community-based sample.* Behav Res Ther, 2008. **46**(7): p. 836-44.
2. Tolin, D.F., et al., *Family burden of compulsive hoarding: results of an internet survey.* Behav Res Ther, 2008. **46**(3): p. 334-44.
3. Tolin, D.F., et al., *The economic and social burden of compulsive hoarding.* Psychiatry Res, 2008. **160**(2): p. 200-11.
4. Tolin, D.F., et al., *Neural mechanisms of decision making in hoarding disorder.* Arch Gen Psychiatry, 2012. **69**(8): p. 832-41.
5. Wheaton, M., et al., *Characterizing the hoarding phenotype in individuals with OCD: associations with comorbidity, severity and gender.* J Anxiety Disord, 2008. **22**(2): p. 243-52.
6. Cath, D.C., et al., *Age-Specific Prevalence of Hoarding and Obsessive Compulsive Disorder: A Population-Based Study.* The American Journal of Geriatric Psychiatry, 2017. **25**(3): p. 245-255.
7. Ayers, C.R., et al., *Age at onset and clinical features of late life compulsive hoarding.* Int J Geriatr Psychiatry, 2010. **25**(2): p. 142-9.
8. Grisham, J.R., et al., *Age of onset of compulsive hoarding.* J Anxiety Disord, 2006. **20**(5): p. 675-86.
9. Ayers, C.R., et al., *Hoarding severity predicts functional disability in late-life hoarding disorder patients.* Int J Geriatr Psychiatry, 2014. **29**(7): p. 741-6.
10. Kim, H.J., G. Steketee, and R.O. Frost, *Hoarding by elderly people.* Health Soc Work, 2001. **26**(3): p. 176-84.
11. Harris, J., *Household hoarding and residentile fires.*, in *Int Congr Appl Psychol*. 2010: Melbourne, Australia.
12. Frost, R.O., G. Steketee, and D.F. Tolin, *Comorbidity in Hoarding Disorder.* Depression and anxiety, 2011. **28**(10): p. 876-884.
13. Vieira, L.S., et al., *Identifying psychiatric and neurological comorbidities associated with hoarding disorder through network analysis.* Journal of Psychiatric Research, 2022.
14. Archer, C.A., et al., *Relationship between symptom severity, psychiatric comorbidity, social/occupational impairment, and suicidality in hoarding disorder.* Journal of Obsessive-Compulsive and Related Disorders, 2019. **21**(April): p. 158-164.
15. Ayers, C.R., et al., *Behavioral and experiential avoidance in patients with hoarding disorder.* Journal of Behavior Therapy and Experimental Psychiatry, 2014. **45**(3): p. 408-414.
16. Novara, C., et al., *Hoarding Symptoms Are Not Exclusive to Hoarders.* Front Psychol, 2016. **7**: p. 1742.
17. Raines, A.M., et al., *Hoarding and depression: The mediating role of perceived burdensomeness.* J Psychiatr Res, 2016. **83**: p. 24-28.
18. Mathews, C.A., et al., *Randomised clinical trial of community-based peer-led and psychologist-led group treatment for hoarding disorder.* BJPsych Open, 2018. **4**(4): p. 285-293.
19. Ayers, C.R., et al., *Cognitive rehabilitation and exposure/sorting therapy (CREST) for hoarding disorder in older adults: A randomized clinical trial.* The Journal of clinical psychiatry, 2018. **79**(2): p. 3927.
20. Thompson, C., et al., *A systematic review and quality assessment of psychological, pharmacological, and family-based interventions for hoarding disorder.* Asian J Psychiatr, 2017. **27**: p. 53-66.
21. Mackin, R.S., et al., *Cognitive functioning in individuals with severe compulsive hoarding behaviors and late life depression.* Int J Geriatr Psychiatry, 2011. **26**(3): p. 314-21.

22. Tolin, D.F., et al., *Cognitive behavioral therapy for hoarding disorder: a meta-analysis.* Depress Anxiety, 2015. **32**(3): p. 158-66.
23. Tolin, D.F., *Toward a biopsychosocial model of hoarding disorder.* Journal of Obsessive-Compulsive and Related Disorders, 2023. **36**: p. 100775.
24. Hough, C.M., et al., *Comparison of brain activation patterns during executive function tasks in hoarding disorder and non-hoarding OCD.* Psychiatry Res, 2016. **255**: p. 50-9.
25. Mathews, C.A., et al., *Error-related brain activity dissociates hoarding disorder from obsessive-compulsive disorder.* Psychol Med, 2016. **46**(2): p. 367-79.
26. Stevens, M.C., et al., *Functional Neuroimaging Test of an Emerging Neurobiological Model of Hoarding Disorder.* Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2020. **5**(1): p. 68-75.
27. Levy, H.C., et al., *Distinct resting state functional connectivity abnormalities in hoarding disorder and major depressive disorder.* J Psychiatr Res, 2019. **113**: p. 108-116.
28. Levy, H.C., et al., *An Examination of the Association Between Subjective Distress and Functional Connectivity During Discarding Decisions in Hoarding Disorder.* Biol Psychiatry Cogn Neurosci Neuroimaging, 2021. **6**(10): p. 1013-1022.
29. Sehatzadeh, S., et al., *Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades.* Journal of Psychiatry and Neuroscience, 2019. **44**(3): p. 151-163.
30. Beynel, L., J.P. Powers, and L.G. Appelbaum, *Effects of repetitive transcranial magnetic stimulation on resting-state connectivity: A systematic review.* Neuroimage, 2020. **211**: p. 116596.
31. Blumberger, D.M., et al., *Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial.* The Lancet, 2018. **391**(10131): p. 1683-1692.
32. Voigt, J.D., A.F. Leuchter, and L.L. Carpenter, *Theta burst stimulation for the acute treatment of major depressive disorder: A systematic review and meta-analysis.* Translational psychiatry, 2021. **11**(1): p. 1-12.
33. Weissman, C.R., Blumberger, D.M., Brown, P.E., Isserles, M., Rajji, T.K., Downar, J., Mulsant, B.H., Fitzgerald, P.B., & Daskalakis, Z.J. (2018). Bilateral repetitive transcranial magnetic stimulation decreases suicidal ideation in depression. *Journal of Clinical Psychiatry, 79*, 17m11692.