PROTOCOL TITLE:

Accelerated Image-Guided Robotically Delivered Transcranial Magnetic Stimulation for Combat PTSD

PRINCIPAL INVESTIGATOR:

Felipe S. Salinas, Ph.D.
Research Imaging Institute
210-567-8214
salinasf@uthscsa.edu

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Revision #	Version Date	Summary of Changes	Consent Change?
2	05/22/2025	1. TMS treatment parameters were clarified 2. patient payment section was updated to indicate . 3. COI section was updated per IRB direction.	yes

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for UT Health San Antonio and will adhere to the study requirements as presented, including all statements regarding confidentially. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Investigator: Felipe S. Salinas

Institution: University of Texas Health Science Center at San Antonio



02/18/2025

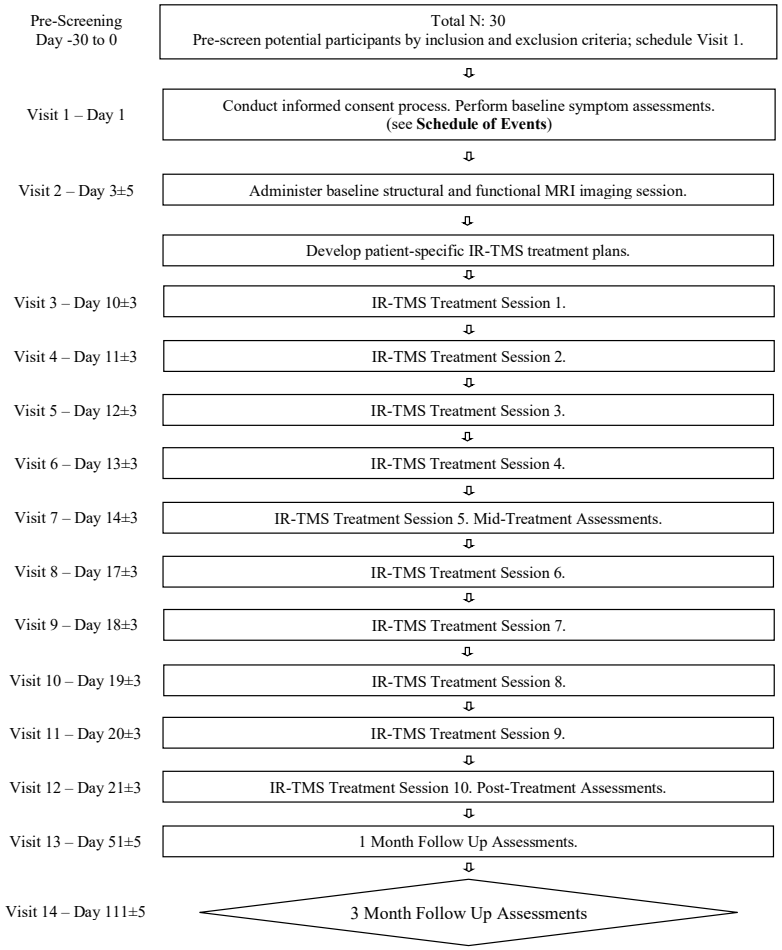
Investigator Signature Date

1. STUDY SYNOPSIS

Protocol Information	Description
Study Title	Accelerated Image-Guided Robotically Delivered Transcranial Magnetic Stimulation for Combat PTSD
Study Design	We propose an open-label, 2-week trial of Image-Guided Robotically Delivered Transcranial Magnetic Stimulation (IR-TMS) targeting the right, anterior dorsolateral prefrontal cortex (R-antDLPFC) in 30 Post Traumatic Stress Disorder (PTSD) participants. We will recruit Active-Duty Service Members and Veterans with combat PTSD, as determined by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Participants will be encouraged to complete as many IR-TMS sessions throughout a 2-3 week time period, with a maximum of 4 sessions per day. Treatments will be neuro-navigated and adapted for an accelerated TMS treatment schedule. Post-Treatment and durability of this treatment effect will be examined throughout the 1-month and 3-month FU assessments. Findings from this open-label trial of IR-TMS for PTSD will serve as preliminary data for a larger randomized clinical trial to further identify the stand-alone effects of IR-TMS versus a sham condition.
Objectives/Specific Aims	Primary Objective: Test for IR-TMS induced improvements in symptom scores of PTSD participants. We hypothesize that IR-TMS will significantly reduce PTSD symptom scores and that IR-TMS will significantly reduce depressive symptoms in all PTSD participants with co-morbid major depressive disorder (MDD). Secondary Objective: Functional connectivity (FC) will be modulated by IR-TMS throughout the targeted brain network. We hypothesize that the amount of FC modulation will correlate with the IR-TMS dose and that participants receiving more IR-TMS pulses will demonstrate faster and longer lasting network consolidation than those receiving fewer IR-TMS pulses.
Endpoints	Primary Endpoint: Post-Treatment Secondary Endpoints: 1-month and 3-month follow-up (FU) visits, as time allows
Research Intervention(s)/ Investigational Agent(s)	PTSD participants will undergo up to 40 accelerated IR-TMS treatments and longitudinal magnetic resonance imaging (MRI) scanning to determine treatment effects and durability. Active-duty and veteran military PTSD participants will be recruited from local VA and military treatment facility clinics. Each participant's R-antDLPFC target site will be determined by personalized functional connectivity (FC) maps.

	Participants will receive up to 4 IR-TMS treatments per day for up to 10 days in an open-label clinical trial.
IND/IDE #	# N/A ☒
Setting	The study will take place at two sites within UTHSA: Recruitment and consent may be performed (in-person or by teleconference) either at Dr. Moring's offices within UTHSA or at the Research Imaging Institute (RII). Imaging and IR-TMS treatments will be performed (in-person) at RII.
Study Population	Individuals will be Active-Duty Service Members and Veterans (male or female) with combat PTSD between the ages of 18-70 years. Subjects will be recruited through local military bases (e.g., Fort Sam Houston), and South Texas VA. Inclusion criteria: 1) meet diagnostic criteria for PTSD on the CAPS-5, 2) able to attend all clinic appointments; and 3) fluent in English. Exclusion criteria: 1) a documented diagnostic history of bipolar disorder, unmanaged or untreated schizophrenia or schizoaffective disorder or a psychiatric hospitalization in the last 12 months; 2) significant cognitive impairment determined by inability to comprehend screening assessment; 3) psychiatric problems and/or high suicide risk warranting immediate intervention, as assessed with the PHQ-9 (Item #9); 4) currently meeting a psychiatric diagnosis of alcohol and/or substance abuse that would prevent the participant from engaging in therapy; 5) any history or signs of serious medical or neurological illness including seizure disorders; 6) history of traumatic brain injury (TBI) with loss of consciousness for 20 minutes or more; 7) females will be excluded if they are pregnant; 8) any history or signs of metal objects deemed unsafe for MRI or that may adversely affect image quality of the brain region (e.g. surgical clips, cardiac pacemakers, metal implants, etc.) in the body at the time of screening.
Sample Size	30
Participant Duration:	3.5-5 months
Study Duration	16 months

1.1. SCHEMA



1.2. SCHEDULE OF EVENTS (SOE)

Procedures	Pre-screening (Pre-	Visit 1 - Day 1	Visit 2 - Day 3±5	Visit 3 - Day 10±3	Visit 4 - Day 11±3	Visit 5 - Day 12±3	Visit 6 - Day 13±3	Visit 7 - Day 14±3	Visit 8 - Day 17±3	Visit 9 - Day 18±3	Visit 10 - Day 19±3	Visit 11 - Day 20±3	Visit 12 - Day 21±3	Visit 13 - Day 51±5	Visit 14 - Day 111±5	Unscheduled Visit
Screening/Review Eligibility	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Informed Consent	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical history	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Height & Weight	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metal Screening	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Outcome Measures	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CAPS-5	-	R	-	-	-	-	-	-	-	-	-	-	-	R	R	-
PCL-5 (monthly)	-	R	-	-	-	-	-	-	-	-	-	-	-	R	R	-
PCL-5 (weekly)	-	-	-	-	-	-	-	R	-	-	-	-	R	-	-	-
PHQ-9	-	R	-	-	-	-	-	R	-	-	-	-	R	R	R	-
LEC-5	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
AUDIT	-	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GAD-7	-	R	-	-	-	-	-	-	-	-	-	-	R	R	R	-
MRI	-	-	R	-	-	-	-	R	-	-	-	-	R	R	R	-
TMS Motor Threshold Assessment	-	-	R	-	-	-	-	-	-	-	-	-	R	-	-	-
IR-TMS Treatment (up to 40 treatment sessions)	-	-	-	R	R	R	R	R	R	R	R	R	R	-	-	-
Concomitant Medications/Treatment Monitoring	-	R	-	R	R	R	R	R	R	R	R	R	R	R	R	R
Adverse Events Monitoring	-	-	R	R	R	R	R	R	R	R	R	R	R	R	R	R

2. INTRODUCTION

2.1 STUDY RATIONALE

PTSD is characterized as a psychological reaction to a Criterion A trauma, which is exposure to actual or threatened death, serious injury, or sexual violence (APA, 2013). Military members and veterans are at significantly higher risk for developing PTSD. Over 90% of service members and

veterans who deployed in service of Operation Iraqi Freedom/Operation Enduring Freedom have been exposed to at least one type of traumatic event during their deployments. Prevalence rates of PTSD range from 14% to 32% among military members and veterans (Gaylord et al., 2008), making PTSD the fourth most service-connected disability (VBA, 2022). A staggering $42.7 billion in total excess costs was spent for veterans with PTSD, in 2018 alone (Davis et al., 2022), driven by healthcare costs and disability. Indirect costs of PTSD include depression (Elhai et al., 2011), anxiety (Knowles et al., 2019), substance use (Jeffirs et al., 2019), medical problems (Kang et al., 2003), and impairment of daily functioning (Moye et al., 2021). Fortunately, evidence-based psychotherapies for PTSD, such as CPT (Resick et al., 2017) and PE (Foa et al., 2007) are effective within active-duty and veteran populations (Foa et al., 2018; Peterson et al., 2022; Peterson et al., 2023; Resick et al., 2017; Resick et al., 2021). However, these trauma-focused therapies are typically delivered once per week throughout 12-15 weeks and are very difficult for participants to engage with and are fraught with drop-out rates as high as 78% (Goetter et al., 2015) and only 56% of PTSD participants within community-based facilities receive an adequate dose of psychotherapy (Wang et al., 2005).

2.2. Background

The VA/DoD Clinical Practice Guidelines for PTSD expressed a great deal of interest for the utilization of TMS for PTSD, however, only a handful clinical trials have examined TMS benefits for PTSD. A recently completed clinical trial—performed by our team—combined TMS with an inpatient program for combat-related PTSD (IRB # HSC20160191H; inactivated on 4/20/21). Here, participants received compressed prolonged exposure (PE) therapy combined with daily, day-long augmentations throughout a 3-week, intensive inpatient program (IIP-PE). Concurrently, participants either received TMS that was optimized with structural and functional imaging and delivered with IR-TMS, 7 days per week, with a maximum of 20 sessions or they received sham TMS sessions for the same number of consecutive days. Stimulation for those in the Active IR-TMS condition was delivered with a figure-8 coil at an intensity of 80-95 V/m, at 20 Hz for 3,000 pulses/session for 20 sessions, and targeted the right, anterior DLPFC. We found significantly greater improvements in PTSD symptom remediation among veterans who received a combination of IIP-PE with IR-TMS (Active IR-TMS+IIP, N=55), versus those who received the same psychotherapy combined with a sham TMS condition (Sham IR-TMS+IIP, N=58; Figure 1). Interestingly, the largest difference between the Active IR-TMS+IIP and Sham IR-TMS+IIP groups (Hedges $g = 0.57$, $p = 0.009$) occurred 1 month after treatment ended. This finding was surprising and forced us to alter our proposed trial's functional MRI (fMRI) acquisitions to include scans for each time point to accurately track when PCL-5 scores and FC changes are most likely to occur.

In this randomized clinical trial, we targeted regions with strong DLPFC to sub-genual cingulate (SGC) cortex FC, but did not select the regions with the strongest FC anti-correlations (as is done in MDD). Instead, we focused on the largest absolute FC responses between these regions. The sign of the FC had no influence on therapeutic outcomes. Therefore, it is most likely that TMS disrupts maladaptive, symptom associated, re-entrant neural firing patterns, allowing the re-establishment of physiological rhythms, consistent with the network theory of mental disorders (Borsboom, 2017; Isvoranu et al., 2021). Therefore, more TMS pulses should result in more

disruption of these maladaptive firing patterns. For this reason, we propose to deliver 72,000 (rather than the 60,000 in our previous trial) in this trial. We will test this hypothesis by tracking PTSD (and co-morbid MDD) symptom scores and correlate symptom score changes with longitudinal neuroimaging (e.g. fMRIs) acquired throughout the study.

2.3. Risk/Benefit Assessment

2.3.1. Known Potential Risks

- Risks and Side Effects related to TMS applied to the Brain
- Physical injury by the robotic device.
- Claustrophobia in the MRI.
- Injury during the MRI from foreign bodies interacting with the magnetic field.
- Emotional distress during assessments.
- Breach of confidentiality.

2.3.2. Known Potential Benefits

- The potential benefit to participants is the potential for PTSD symptom relief.

2.3.3. Assessment of Potential Risks and Benefits

- Risks and Side Effects related to TMS applied to the Brain. The Magventure TMS system used in this study has been FDA-cleared for the treatment of MDD in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode (510(k) #K150641). TMS has been FDA-approved for the treatment of depression since 2008 (510(k) #K083538). In our previous randomized clinical trial of TMS in PTSD (IRB # HSC20160191H; inactivated on 4/20/21), we applied IR-TMS to in-patient PTSD patients as an adjunct to treatment as usual PTSD therapy. TMS was delivered to Active (N=60) and Sham (N=59) cohorts. In this trial, there were no serious adverse advents. Non-serious adverse events related to TMS were as follows: headache (active: 26.67%; sham: 32.2%), muscle twitching (active: 8.33%; sham: 1.69%), facial discomfort (active: 10%; sham: 0%), blurred vision (active: 1.67%; sham: 0%), dizziness (active: 1.67%; sham: 10.17%).
- Physical injury by the robotic device. Robotic devices must be used with caution in the presence of persons. The robotic device used here (Universal Robotics® UR5) poses no significant risk. The UR5 moves slowly, so that it can easily be stopped prior to any collision. Loss of electrical power renders the UR5 robot immobile in its current position, (i.e., it does not return to a "parking" position or make any sudden motions). The UR5 robot requires a hand-held switch and a recessed button press to actuate, being used only under direct supervision. Collectively, these features make the UR5 robot safe for use by and with humans. Axilum Robotics have received FDA-clearance for use of a computer controlled electromechanical arm (the UR5 collaborative robot) indicated for spatial positioning and orientation of the treatment coil of a TMS coil (510(k) #K182768). Our system, developed by Cerebral Magnetics, uses the same UR5 collaborative robot and

TMS coil as the Axilum neuronavigation system. Our previous randomized clinical trial of TMS in PTSD used the same software proposed in this study (with a different robot) and had no serious or non-serious adverse events related to the robot or TMS coil placement. The use of a UR5 collaborative robot in this proposal improves upon the high level of safety in our previous IRB-approved IR-TMS treatment trial (IRB # HSC20160191H).

- Claustrophobia in the MRI. Clear instructions and representations of what to expect while in the scanner will be given to each subject by trained MRI personnel prior to entering the scanner. If subjects feel confident that they can proceed with the scan, they will be positioned in the scanner and given a pressure sensitive bulb which may be used to indicate to the MRI technician that they would like to be removed from the scanner. Between the different scans performed in each MRI session, study personnel and/or the MRI technician will use the intercom system to communicate how much longer each subject will be in the scanner and determine if they are able to continue the scan. If subjects are still not able to complete their MRI scan, they will be removed from the scanner and withdrawn from the study. In our previous randomized clinical trial of TMS in PTSD, non-serious adverse events related to claustrophobia in the MRI occurred 1.67% of the time in the active group and 1.69% of the time in the sham group.
- Injury during the MRI from foreign bodies interacting with the magnetic field. MRI can have risk for persons with foreign bodies implanted in their body. Cardiac pacemakers and cochlear implants may cease to function and can be permanently damaged by the MRI. Surgical clips on aneurysms and intestines may be moved by the magnetic field. Ferrous metal filings in the eye (e.g., in machinists) can be moved by the magnetic field. Foreign body risk is minimized by including only volunteers with no known foreign bodies and no exposure to circumstances, which might predispose to foreign bodies (e.g., metal machine workers). Before receiving an MRI, participants will be asked about any metal objects that may be in their body. Our previous randomized clinical trial of TMS in PTSD had no serious or non-serious adverse events related to the foreign bodies in the MRI.
- Emotional distress during assessments. All clinical staff associated with assessment have experience in psychiatric evaluation and will implement protocol procedures in a sensitive and supportive manner. Interviews will be stopped if subjects become distressed or object to answering questions. Measures implemented to minimize risks are: 1) Before participating, subjects undergo careful psychiatric and medical evaluation. 2) Experienced study clinicians will be available at all times during the sessions to provide medical and psychiatric monitoring for subjects experiencing any difficulties during treatment. 3) All subjects will be seen repeatedly for ongoing assessment of behavioral symptoms. 4) If a subject's clinical condition significantly worsens, he or she will be withdrawn from the research protocol. In our previous randomized clinical trial of TMS in PTSD, non-serious adverse events related to increases in anxiety occurred 3.33% of the time in the active group and 3.39% of the time in the sham group.
- Breach of confidentiality. Study participants will be treated in individual offices located at the RII's TMS lab. Data will be stored using an assigned participant code number so that data records and specimens can be viewed by password-authenticated, authorized investigators and personnel. Digital audio recordings of assessments will be labeled with

the participant's study ID number and saved on a secure password protected server. Those recordings to be reviewed for fidelity to ensure that the assessment is being delivered in accordance with standardized procedures. There is no option for the reviewers to download or otherwise save the recordings to their computers. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Only authorized study staff, and members of the research team will have access to either the raw data or electronic study data. Our previous randomized clinical trial of TMS in PTSD had no serious or non-serious adverse events related to breach of confidentiality.

Research procedures *example:* • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Risks** List the reasonably expected risks under the following categories as appropriate:
Risks and Side Effects related to TMS applied to the Brain	Serious and likely; ○ none Serious and less likely; ○ In 100 people, approximately 5-10 may have dizziness or sleepiness. Serious and rare; ○ In 100 people, approximately 1-2 may have seizures. Not serious and likely; ○ In 100 people, approximately 20-30 may have mild headache, scalp and/or facial pain/discomfort, scalp and/or facial muscle twitching, and/or neck pain. Not serious and less likely ○ none

Risks and Side Effects related to the Robot placement of the IR-TMS	Serious and likely; ○ none Serious and less likely; ○ none Serious and rare; ○ In 100 people, approximately 0-1 may have physical injury from the robotic device. Not serious and likely; ○ none Not serious and less likely ○ none
Risks and Side Effects related to the MRI	Serious and likely; ○ none Serious and less likely; ○ none Serious and rare; ○ In 100 people, approximately 1-2 may have foreign bodies which may interact with the magnetic field of the MRI. Not serious and likely; ○ none Not serious and less likely ○ In 100 people, approximately 1 may have claustrophobia (fear of tight spaces). During the MRI scan, participants will be asked to remain perfectly still.

Risks related to the Assessments	Serious and likely; o none Serious and less likely; o none Serious and rare; o In 100 people, approximately less than 5 may experience a breach of confidentiality. Not serious and likely; o none Not serious and less likely o In 100 people, approximately 5-20 may have emotional distress when discussing their symptoms.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine if accelerated IR-TMS significantly reduces PTSD symptom scores, as determined by scores on the CAPS-5 and PCL-5.	Baseline, Post-Treatment, 1-Month FU, 3-Month FU	Significant symptom relief from baseline levels should be present at the End of Treatment and FU Timepoints.
Secondary		
Determine if participants receiving a higher number of IR-TMS pulses demonstrate more durable PTSD symptom score reductions throughout the FU periods compared to those with fewer IR-TMS pulses.	Baseline, Post-Treatment, 1-Month FU, 3-Month FU	The durability of symptom relief (from End of Treatment) should be maintained through the Last FU Assessment Visit.
Tertiary/Exploratory		
Determine if functional connectivity in the targeted brain networks is modulated by IR-TMS and if so, does the amount of modulation correlate with dose.	Baseline, Post-Treatment, 1-Month FU, 3-Month FU	The durability of functional connectivity changes in the targeted brain network should correlate with the number of sessions delivered and would be an important indicator for treatment duration and FU intervention timelines.

4. STUDY DESIGN

We propose to test 30 participants who meet criteria for PTSD as determined by the CAPS-5 and the outlined study inclusion criteria. We anticipate consenting and screening approximately 40 male and female participants, to meet the target enrollment goals and account for participant dropouts. For per-participant timelines, see the SoE table above.

The proposed study will take place at two sites within UTHSA: rea and consent will be performed by authorized members of Dr. Salinas' and/or Dr. Moring's team; the imaging and IR-TMS treatments will be performed at the RII by authorized members of Dr. Salinas' team. Self-report assessments may be completed at either site. The proposed open-label treatment trial will follow a

within-subjects, repeated measures, single-arm design to demonstrate the efficacy of IR-TMS as a standalone treatment for PTSD.

4.1. Scientific Rationale for Study Design

In the proposed open-label trial, an accelerated IR-TMS treatment format will be followed using the treatment parameters described in our previous randomized clinical trial (IRB # HSC20160191H). Stimulation will be delivered to the R-antDLPFC at a depth corrected intensity (e.g. 80-95 V/m), using a TMS stimulation protocol which delivers 1,800 pulses/session. Sessions will be compressed and delivered up to 4 times per day, over the course of 2-3 weeks. If the hypotheses are supported, findings from this open-label trial of IR-TMS for PTSD will serve as preliminary data for a larger randomized clinical trial to further identify the stand-alone effects of IR-TMS versus a sham condition.

In the proposed open-label treatment trial, we will follow a within-subjects, repeated measures, single-arm design to demonstrate the efficacy of IR-TMS as a standalone treatment for PTSD. Longitudinal assessments (self-reports and MRIs) will give us all the information we need to assess the efficacy of the proposed IR-TMS treatment approach and its durability. A within-subject, repeated measures design may also inform on the need and/or timing of maintenance IR-TMS interventions for sustained symptom relief.

4.2. Justification for Intervention

TMS applies a strong (~2 Tesla), rapidly changing electro-magnetic field at the scalp to induce electrical current flow in underlying brain tissues and has well-established applications in basic neuroscience and psychiatric therapies and can alter cerebral neurophysiology in a long-term manner. TMS is a neuromodulation therapy approved by the U.S. Food and Drug Administration (FDA) as a stand-alone treatment for MDD (O'Reardon et al., 2007) and obsessive-compulsive disorder (Carmi et al., 2019), but not yet for PTSD. Although TMS is FDA-approved for several indications, TMS devices and procedures in clinical use are far from optimal. Psychiatric TMS treatments are most commonly performed using a hand-held TMS coil to locate M1hand cortex, followed by a scalp-surface measurement (5-6 cm anterior) to identify the treatment target site: the DLPFC. Coil orientation is established using the nose as the aiming point in a manner crudely optimized for M1hand (by orienting the E-field quasi-normal to the central sulcus; Brasil-Neto et al., 1992; Mills et al., 1992) rather than optimized for DLPFC gyral anatomy. Moreover, in participants with larger head sizes, the "5 cm rule" would target more posterior portions of the DLPFC (or even premotor cortices), whereas participants with smaller heads may be effectively targeting the anterior DLPFC (Herwig et al., 2001; Fitzgerald et al., 2009; Fox et al., 2012). With this in mind, ongoing work in MDD has demonstrated that TMS efficacy is maximized by: 1) targeting brain networks known to be altered in the condition being treated; 2) treatment personalization through image guidance; 3) repeatable TMS coil delivery systems (neuronavigation); and 4) "accelerated" treatment, with multiple TMS treatment sessions per day (Fitzgerald, 2020; 2021). We hope to utilize these advancements (based on MDD studies) to demonstrate their efficacy standalone treatment for PTSD.

A participant is considered to have evaluable data if he or she has completed the baseline assessments, up to 10 treatment sessions and Mid-Treatment assessments.

A participant is considered to have completed treatment if he or she has completed the baseline assessments, up to 40 treatment interventions, Mid-Treatment and Post-Treatment assessments.

4.3. End-Of-Study Definition

A participant is considered to have completed the study if he or she has completed the baseline assessments, up to 40 treatment interventions, Mid-Treatment and Post-Treatment assessments, and the 1-month and 3-month FU assessments. If time does not allow for follow-up assessments, follow-up assessments will not be completed and participants will be informed.

The end of the study is defined as completion of the 3-month FU assessment shown in the SoE.

5. STUDY SETTING

The proposed study will take place at two sites within UTHSA: Dr. Moring's offices within UTHSA or at the RII. Recruitment and consent may be performed by either Dr. Moring or Dr. Salinas' research team. The CAPS-5 assessments will be performed by Dr. Moring either in his office or at the RII. The MRI and IR-TMS visits will all take place at the RII. Self-report assessments may be completed at either study site. The proposed open-label treatment trial will follow a within-subjects, repeated measures, single-arm design to demonstrate the efficacy of IR-TMS as a standalone treatment for PTSD.

6. STUDY POPULATION

Thirty PTSD participants between the ages of 18 and 70 will be studied. Participants Subjects will be recruited through local military bases (e.g., Fort Sam Houston), and the South Texas Veterans Administration (VA) clinics. Investigators (Fox and Moring) have an established history of successful collaboration with local military and veteran facilities. Interested candidates will be directed to contact the research team either by telephone or e-mail. Self-identified candidates (i.e., those calling the research team) are pre-screened by telephone for eligibility using a screening questionnaire emphasizing exclusion criterion, including: age < 18 or > 70 years; a documented diagnostic history of bipolar disorder, unmanaged or untreated schizophrenia or schizoaffective disorder or a psychiatric hospitalization in the last 12 months; diagnosed medical, neurological or psychiatric conditions; prescription medications other than for allergies; implanted medical devices; metallic foreign bodies; pregnancy. If a prospective participant passes the telephone pre-screening, he/she is provided with a consent form to review by e-mail and scheduled for the study. At the RII, the prospective participant is further screened by an MRI safety questionnaire. For study candidates judged ineligible, no records of the screening questionnaire are retained. For study candidates passing the screening, informed consent is obtained in the usual manner. A trained member of the research team will carry out this consenting procedure, which will be witnessed by a 3rd party who is not a member of the research team. A copy of the signed consent form will be given to the subject for their records.

Inclusion of Women and Minorities

Both males and females will be recruited in equal numbers. Participants will be recruited according to the racial demographics of the San Antonio community. The total number of participants involved in the study will be 30. Of those, we estimate that approximately 52% will be women. The estimated racial/ethnic breakdown of the study may approximately be that 6.8% may be Black or African American, 1.6% may be Asian, and 0.8% may be Native Hawaiian-Pacific Islander. Approximately 58.7% of the participants may be Hispanic. While this provides only an estimated breakdown of the study population, efforts will be made to ensure equitable recruitment of individuals that meet the Eligibility requirements below.

6.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. between the ages of 18 and 70 years
2. meet diagnostic criteria for PTSD on the CAPS-5
3. able to attend all clinic appointments
4. fluent in English

6.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. a documented diagnostic history of bipolar disorder, unmanaged or untreated schizophrenia or schizoaffective disorder or a psychiatric hospitalization in the last 12 months
2. significant cognitive impairment determined by inability to comprehend screening assessment
3. psychiatric problems and/or high suicide risk warranting immediate intervention, as assessed with the PHQ-9 (Item #9)
4. currently meeting a psychiatric diagnosis of alcohol and/or substance abuse that would prevent the participant from engaging in therapy
5. any history or signs of serious medical or neurological illness including seizure disorders
6. history of traumatic brain injury (TBI) with loss of consciousness for 20 minutes or more
7. females will be excluded if they are pregnant
8. any history or signs of metal objects deemed unsafe for MRI or that may adversely affect image quality of the brain region (e.g. surgical clips, cardiac pacemakers, metal implants, etc.) in the body at the time of screening.

6.3. Inclusion of Vulnerable Participants N/A ☒

6.4. Inclusion of Pregnant Women, fetuses or neonates N/A ☒

6.5. Lifestyle Considerations N/A ☒

6.6. Screen Failures

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful treatment of a previous affective disorder, and the lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as for the initial screening.

6.7. Strategies for Recruitment and Retention

Subjects will be recruited through local military bases (e.g., Fort Sam Houston, Lackland, Camp Bullis, etc.), and the South Texas VA. The Investigators have an established history of successful collaboration with local military and veteran facilities. Additionally, our team will also promote the study using other advertising methods (e.g. study flyers). Upon referral/inquiry, each participant will be given an information sheet describing the study and screened to determine inclusion/exclusion criteria. If they meet all study criteria and they are interested in participating, each participant will be shown a video describing the treatment trial and each of the tools/treatments used throughout the study (i.e. MRI and IR-TMS).

The screening procedure described above will be performed under an IRB approved Health Insurance Portability and Accountability Act (HIPAA) Waiver of Authorization, Waiver of Informed Consent, and Waiver of Documentation of Informed Consent. Study personnel will conduct a brief prescreening intake interview where the basic study inclusion and exclusion criteria will be reviewed to help the individual determine if he or she meets the study criteria or has obvious exclusions from the study protocol. This information will be maintained as a secure file with the following information: name, phone number, name of study, referral date, referral source, potential eligibility status, reason if not eligible, and verbal permission to contact the caller in the future for other studies. Subjects who agree to study participation will sign a consent document before any further screening takes place. Any individually identifiable information and PHI collected on individuals who do not consent to participation will not become part of the research data. If subjects agree to participate in the research, the identifiable data collected will become part of the subjects' research records and will be stored according to the research confidentiality plan. Since the study requires multiple visits, our team will schedule and coordinate all research visits for the study. Participants will be sent visit reminders (via phone call, text message, or email) and will regularly be asked for confirmation that they will attend each visit. Participants will be compensated (see below) for each completed study visit. These payments are meant to compensate participants for their time and may also improve participant retention throughout the trial.

6.7.1. Costs

Participants will not incur or be responsible for any research study costs, including the costs of assessments, MRI scans, IR-TMS treatment planning, or IR-TMS treatment visits. Participants will be responsible for securing transportation to and from each research visit, but other than the cost of transportation (gas, rideshare, etc.) and their time, participants will not be charged for any study procedures.

6.7.2. Compensation

Participants will be compensated $50 for each completed RII visit. These visits include: baseline, 10 IR-TMS treatment visits, mid-treatment MRI, post-treatment MRI, the 1 month follow up, and the 3 month follow up visit. Compensation ($50) will be based on the number of completed research visits (i.e. 15 total research visits equals $750 compensation). Participants will be provided with a check upon completion of their study visits. If a participant withdraws from the study, they will be compensated for each completed study visit. These payments are meant to compensate participants for their time and may also improve participant retention throughout the trial.

7. STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

7.1. Study Interventions(s) or Experimental Manipulations(s) Administration

7.1.1. Study Intervention or Experimental Manipulation Description

In this non-randomized, open-label trial, all 30 PTSD participants will receive the same IR-TMS treatment, targeting the R-antDLPFC. The primary outcome of treatment efficacy will be measured using the PCL-5 at baseline and Post-Treatment assessments. The secondary outcomes of treatment efficacy will be measured using the CAPS-5 and PHQ-9 at baseline and Post-Treatment assessments. The impact of treatment adherence (i.e. number of IR-TMS treatment pulses delivered) on the durability of symptom relief (as measured by the PCL-5, CAPS-5, and PHQ-9) will also be assessed at the 1 month and 3 month FU timepoints. We will also determine if functional connectivity in the targeted brain networks is modulated by IR-TMS and if so, does the amount of modulation correlate with dose within the Baseline, Mid-Treatment, Post-Treatment, 1-Month FU, 3-Month FU visits. The durability of functional connectivity changes in the targeted brain network should correlate with the number of sessions delivered and would be an important indicator for treatment duration and FU intervention timelines.

7.1.2. Administration

A trained RII team member will deliver IR-TMS at the participant's TMS treatment target using an accelerated TMS treatment protocol (e.g. 45 trains of 20 Hz TMS pulses; train duration = 2 seconds; inter-train interval = 11 seconds). This accelerated IR-TMS protocol consists of 1,800 IR-TMS pulses per session, delivered at intensity ranges which are designed to deliver depth-

corrected E-fields of 80-95 volts/meter. These intensity ranges will be determined when the participant's treatment plan is developed, and will be given to the treatment technicians with the IR-TMS treatment plan. Once a patient's IR-TMS treatment plan has been created, it will be transferred to the RII's IR-TMS systems and will not be modified. The same IR-TMS treatment plan will be used for each treatment session.

Participants will receive up to 4 treatment sessions per weekday, for up to 40 sessions. In each treatment session, a total of 1,800 pulses will be administered within the 10 minute IR-TMS session. After each session, participants will be given the opportunity to take a break (e.g. rest, go to the bathroom, stretch, etc.) for a 5 to 20 minute period. Once ready, the next IR-TMS treatment session will begin, for up to 4 treatment sessions per day. The IR-TMS protocol will administer a total of up to 72,000 pulses over the 10-weekday period. If study participants decide, at any time, that they cannot tolerate the IR-TMS treatments, they will be withdrawn from the study (see Discontinuation and Withdrawal of Participants Section below) and will be assisted in finding appropriate after-study care.

7.2. Fidelity

Our team has refined TMS delivery by developing an IR-TMS system to guide each TMS stimulation. IR-TMS gives Interventionists the ability to accurately position the TMS coil at each participant's target site in a repeatable manner. IR-TMS treatment technicians will verify that each IR-TMS treatment is delivered in the same manner for each session by recording the physical location of the TMS coil before and after each IR-TMS treatment session. These coordinate locations will be saved in the participant's treatment log file each session.

7.2.1. Interventionist Training and Tracking

The RII's IR-TMS technicians will undergo intensive (> 3 day), training on IR-TMS delivery by Dr. Salinas and/or Dr. Fox. This training consists of 1) reading and familiarizing themselves with the IR-TMS manual, 2) viewing a recorded step-by-step demonstration video of how to operate the IR-TMS system, and 3) an in-person (or videoconference) assessment of the trainee's proficiency in independently operating the IR-TMS system. The RII's IR-TMS technicians must demonstrate proficiency using the robotic arm, digitizer, and IR-TMS software before being certified to perform IR-TMS treatments. All RII IR-TMS technicians involved (in this study) must be certified to independently operate the IR-TMS system prior to scheduling their first participant's treatment session. Their proficiency in operating the IR-TMS system will be reviewed and documented quarterly. If their proficiency drops, they will be required to undergo retraining on the proper use of the IR-TMS system.

The robotic IR-TMS system implements a high-resolution digitizer to 1) calibrate the robotic arm's location in the digitizer's space, 2) reference the participant's head to that digitizer space, and 3) check the final treatment (i.e. coil) location after the robot has moved the coil to the prescribed treatment site. This level of treatment tracking far exceeds any other TMS treatment system currently in use. If the IR-TMS system reports inaccurate robot arm registrations (e.g. > 1 mm), the IR-TMS technician will restart the calibration procedure and re-register the robot to the digitizer's space. If the IR-TMS system reports inaccurate head registrations (e.g. > 2 mm), the

IR-TMS technician will re-register the participant's head to the digitizer's space. The accuracy of each treatment session will be logged (by the IR-TMS technician) in the participant's treatment file after each IR-TMS treatment session.

7.3. Measures to Minimize Bias: Randomization and Blinding N/A ☒

7.4. Study Intervention/Experimental Manipulation Adherence

Participant's will have to come to the RII for baseline, 10 IR-TMS treatment days, 1 month FU, and 3 month FU visits. Attendance for each visit will be documented in their participant and treatment log files. A participant will be considered lost to FU if he or she fails to return for 3 scheduled visits (IR-TMS or assessments) and is unable to be contacted by the study site staff.

7.5. Concomitant Therapy

For this protocol, participants may use non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications. Medication usage will be assessed at each study visit and documented in the relevant Case Report Form (CRF).

7.5.1. Rescue Therapy N/A ☒

8. DISCONTINUATION AND PARTICIPANT WITHDRAWAL

8.1. Discontinuation of Study Intervention/Experimental Manipulation

Participants are free to discontinue IR-TMS at any time upon request. If a participant chooses to discontinue IR-TMS treatments, the data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.
- If the participant is due to complete assessments within 5 days of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation. Thereafter, the participant will be withdrawn from the study.

8.2. 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 a participant from the study for the following reasons:

- Significant study intervention non-compliance
- Lost-to-follow up; unable to contact participant (see **Lost to Follow-Up**)

- Clinical deterioration during the IR-TMS treatment period; a 25% increase in the PCL-5 at any time during the treatment phase of the trial is an objective criteria for clinical deterioration
- Any event or medical condition or situation occurs such that continued collection of FU study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Screen Failure
- Participant has completed the study FU period.

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Participants who sign the informed consent form and complete some (or all) of the baseline assessments but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and complete all of the baseline assessments and receive the full course of the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced. Participants who sign the informed consent form, and complete all of the baseline assessments and receive an incomplete course of the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

8.3. Lost to Follow-up

A participant will be considered lost to FU if he or she fails to return for 3 scheduled visits (IR-TMS or assessments) 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 one weekday of the original appointment 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 FU, 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 medical record or 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 FU.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. SCREENING PROCEDURES

9.1.1. Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in person or telephone communications with prospective participants.

Participants will be recruited on a referral basis through local military bases and South Texas VA by Dr. Moring and Dr. Salinas. Upon referral, prospective participants will be screened (over the phone) for inclusion/exclusion criteria, sent (via email) information about the treatment trial (Form D-IS) and shown a video describing the treatment trial and each of the tools/treatments used throughout the study (i.e. MRI and IR-TMS).

Female participants cannot take part in this study if they are pregnant since the safety of IR-TMS has not been studied in pregnant participants. During the pre-screening process, we will ask if a female participant is pregnant (or may be pregnant). If they answer "yes," they will not be enrolled in the study. Only females who are sure that they are not pregnant will proceed to the consent phase of the study.

Under an IRB approved HIPAA Waiver of Authorization, Waiver of Informed Consent, and Waiver of Documentation of Informed Consent, study personnel will conduct a brief pre-screening intake interview where the basic study inclusion and exclusion criteria will be reviewed to help the individual determine if he or she meets the study criteria or has obvious exclusions from the study protocol. This information will be maintained as a secure file with the following information: name, phone number, name of study, referral date, referral source, potential eligibility status, reason if not eligible, and verbal permission to contact the caller in the future for other studies. Subjects who agree to study participation will sign an informed consent document before any further screening takes place. Any individually identifiable information and PHI collected on individuals who do not consent to participation will not become part of the research data. If subjects agree to participate in the research, the identifiable data collected will become part of the subjects' research records and will be stored according to the research confidentiality plan.

An authorized and trained member of the research team will engage the potential participant in an interactive explanation of the study guided by the ICD. After the participant has read the ICD, he or she will be given the opportunity to consider participation and discuss the research with family and friends. Once the potential participant has reached a decision, the advising staff member will review the purpose of study, duration of study, study procedures, the experimental components of the study, the potential risks and discomforts, the potential benefits, any alternatives to participation, protection of participant's confidentiality, and the contact information for both the researchers and the regulatory bodies overseeing the conduct of the study with the participant to ensure the participant has an understanding of the study. If the individual is agreeable to participation, the advising staff member will then have the individual sign the consent form in the presence of a witness. A copy of the signed ICD will be given to the participant for their reference. Over the conduct of the study, the Research Team will be available to answer any questions about the research. Following consent, the participant meets regularly with the research staff. Ongoing discussions occur to ensure the participant's questions and concerns are addressed during the

conduct of the study. Potential participants will have the study explained to them in a safe and private location before any assessments are conducted.

9.1.2. Screening activities performed after a consent has been signed

The following activities will be performed only after the participant has provided signed consent for this study. Assessments performed at outside facilities or on another protocol within the time frames below may also be used to determine eligibility once a participant has signed the consent.

Study Phase I: Baseline Assessment.

Following consent, a research team member will discuss the study with the participant again to fully explain the study procedures being conducted. At the baseline assessment, all female participant's will be asked if they still have a menstrual cycle. If they affirm that they do, we will ask them to take a urine human chorionic gonadotropin pregnancy test to confirm that the participant is not pregnant at the time of enrollment.

The participant will be asked to complete the following assessments:

1. *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)* is a structured diagnostic interview and gold standard for assessing PTSD. It has excellent psychometric properties and diagnostic efficiency (Weathers et al., 2018). The scale also assesses social and occupational functioning, dissociation, and the validity of symptom reports. The CAPS was revised to accommodate the changes made in DSM-5, to reduce administration time, and to facilitate learning administration and scoring procedures. The CAPS for DSM-5 (CAPS-5; Weathers et al., 2013a) now uses only a single 5-point ordinal rating scale to measure symptom severity. Symptom severity ratings combine information about symptom frequency and intensity obtained by the interviewer. CAPS-5 scores range from 0 to 80 with higher scores indicating greater PTSD symptom severity. At the same time, the CAPS-5 was revised with an eye toward maintaining backward compatibility with the DSM-IV version of the instrument. Because the measure is new, psychometrics and diagnostic cutoffs are still being evaluated. The CAPS-5 will be administered by Dr. Moring, a certified CAPS-5 evaluator, at the baseline, 1 month FU, and 3-month FU visits. This assessment may be administered over the phone or in-person.
2. *PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013b)* is similar in form to the PTSD Checklist (PCL) based on the DSM-IV. The PCL has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity. The PCL-5 is a 20-item self-report measure, selected for its dimensional sensitivity, with higher scores reflecting greater PTSD severity. Scoring is based on how much the participant has been bothered by the symptoms in the past month on a scale from "0 = not at all" to "4 = extremely." There are two versions (weekly or monthly) of the PCL-5. The only difference between the versions exists in the Instructions, which states: "Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past week." The monthly version refers to the problem bothering you over the past

month. Due to our SOE, we will use each version of the PCL-5 at specific acquisition visits. The self-report PCL-5 (monthly) will be administered by an authorized and trained member of the research team at baseline, 1 month FU, and 3-month FU visits. The self-report PCL-5 (weekly) will be administered at Mid-Treatment and Post-Treatment visits. This assessment may be administered over the phone or in-person.

3. *Participant Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001).* The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the DSM diagnostic criteria for MDD. Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The PHQ-9 has high internal consistency (e.g., alpha ranging from .83 to .92), and correlates strongly with other measures of depression (Kroenke et al., 2001). The PHQ-9 may be administered by an authorized and trained member of the research team at baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3-month FU visits. This assessment may be administered over the phone or in-person.
4. *Life Events Checklist for DSM-5 (LEC-5).* The LEC-5 (Weathers et al., 2013c) includes the same list of 16 different potentially traumatic life events from the original LEC that are commonly associated with PTSD symptoms and designed to facilitate PTSD diagnosis. There is also a blank for specifying an additional stressful event not encompassed in the 16 events. For each potentially traumatic life event, respondents rate their experience of that event on a 6-point nominal scale (1 = happened to me, 2 = witnessed it, 3 = learned about it, 4 = part of my job, 5 = not sure, and 6 = doesn't apply). The primary addition to the LEC-5 is a category involving occupational exposure ("for example, paramedic, police, military, or other first responder"). There has not been a publication on the psychometric properties of the LEC-5, but the measure is nearly identical to the original LEC. In a group of 108 undergraduate psychology students the LEC demonstrated good convergence with the Traumatic Life Events Questionnaire (average kappa = 0.55) and correlated with the Posttraumatic Stress Disorder Checklist – Civilian version (reliability coefficients 0.34 to 0.48). The LEC demonstrated good test-retest reliability over 7 days. In 131 combat veterans the LEC was related in the predicted directions with other measures of psychopathology known to be associated with potentially traumatic life events as assessed by the Posttraumatic Stress Disorder Checklist – Military version, Clinician-Administered PTSD Scale, and the Mississippi Scale for Combat-Related PTSD. The LECL-5 will be administered by Dr. Moring at baseline. This assessment may be administered over the phone or in-person.
5. *Alcohol Use Disorders Identification Test (AUDIT) self-report version* (WHO et al., 2001). The AUDIT will be used to identify people with hazardous or harmful patterns of alcohol consumption and to index the severity of these problems. It will be administered as a self-report form. The AUDIT is a 10-item screening measure, developed by the World Health Organization (WHO), with three subscales (alcohol consumption, drinking behavior, and alcohol-related problems) that are scored on a 4-point scale for a highest possible total score of 40. The AUDIT has good internal consistency as well as sensitivity and specificity. The AUDIT's time-frame is the last 12 months. Therefore, for trials without long-term FU, the AUDIT will be administered only at baseline. For studies with long-term FU (e.g., up to 12 months after the end of treatment), the AUDIT will be administered at both baseline and final FU. The AUDIT will be administered by Dr. Moring at baseline. This assessment may be administered over the phone or in-person.
6. *Generalized Anxiety Disorder Screener (GAD-7; Spitzer et al., 2006).* The GAD-7 will be used to assess generalized anxiety symptomology. This is a 7-item measure that asks participants to rate the frequency with which they have been bothered by anxiety symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant anxiety symptoms (0-4), mild anxiety symptoms (5-9), moderate anxiety symptoms (10-14), and severe anxiety symptoms (>15). Respondents also indicate the degree to which their anxious symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The GAD-7 has been shown to have high internal consistency (e.g., $\alpha = .89$) and has been shown to reliably discriminate between anxious and non-anxious diagnostic groups. The GAD-7 will be administered by Dr. Moring at baseline. This assessment may be administered over the phone or in-person.

Study Phase I: Baseline MRI.

Once the participant has completed the consent process and psychological assessments required to determine inclusion/exclusion criteria, eligible participants will be scheduled for an imaging session at the RII at UTHSA. When the participant arrives, the participant will undergo an anatomical and fMRI session. Earplugs will be provided at every MRI session. MRIs use strong magnets and radio waves to non-invasively acquire images of organs and tissues. Unlike X-rays, MRIs do not expose subjects to radiation, therefore it is considered safe to obtain many MRIs in a single scanning session or over multiple days; the initial MRI scan visit may take up to 2 hours. In the event that the participant cannot tolerate the MRI procedure, they will be withdrawn from the study. Participants will be imaged at the RII using a research-dedicated 3T Siemens Prisma MRI scanner (Siemens, Erlangen, Germany) with a 64-channel phased array coil. Structural imaging will be obtained only once, at baseline. Structural images will be used for IR-TMS treatment planning (described below) and for spatial normalization to a standard anatomical template. FMRI and diffusion tensor imaging (DTI) will be obtained five times (i.e. baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3 month FU) and used to detect symptom-specific network abnormalities and treatment-induced plasticity. We will also perform motor threshold assessments for each participant at the baseline and Post-Treatment visits (immediately after each MRI). The Post-Treatment motor threshold assessment are important to the future establishment of safety guidelines for accelerated IR-TMS treatment of PTSD.

Structural MRI.

T1 and T2-weighted structural MRIs will be used for IR-TMS treatment plan computation (described below) and for spatial normalization of functional images. Total structural MRI scan time is approximately 15 minutes. To ensure accurate IR-TMS treatment planning, we will also acquire DTI. The total DTI sequence acquisition time will be 10-12 min.

Task fMRI for motor threshold assessment.

Task fMRIs will also be used to identify each subject's primary motor cortex for motor threshold assessment. Task fMRI will be acquired in a block design paradigm utilizing gradient echo planar images with the following parameters: TR = 2.5 s, TE = 30 ms, a flip angle of 90º, and slice thickness = 4.0 mm. Thirty-six continuous slices will be acquired, with an in-plane spatial resolution of 1.7 x 1.7 mm^2, or a similar fMRI acquisition protocol. During the task fMRI scan, participants will perform abduction and adduction of the right index finger (in a block design); this has been shown to maximally activate the first dorsal interosseous muscle area of the hand's motor cortex. The task and rest periods are 30 seconds long and are interleaved during the 5-6 minutes of data acquisition. During the rest period, the participants will be instructed to remain motionless, to keep their eyes open, and to perform no behavioral task.

Intrinsic Connectivity by rs-fMRI for computing treatment plans.

Intrinsic connectivity networks will be measured using rs-fMRI. Rs-fMRI is the most robust and widely used pulse sequence for intrinsic connectivity modeling. Rs-fMRI images will be used for computing treatment plans and for testing for intrinsic connectivity changes by symptom score at various time points. This sequence requires 10-15 minutes. Rs-fMRI will be used to map per-subject the voxel-wise intrinsic connectivity of the R-antDLPFC with the SGC cortex; this will guide IR-TMS aiming parameters.

Baseline Motor Threshold Assessment.

After the baseline MRI session, each participant will undergo a brief motor threshold assessment by single pulse TMS to their primary motor cortex hand region which elicits a contraction of the targeted hand muscle. The motor threshold assessment begins by locating the hand region and applying single pulses of TMS—with at least 5 seconds between successive pulses—at increasing levels of TMS intensity. We continue to ramp up the TMS intensity with each TMS pulse until we observe a contraction of the targeted hand muscle in 5 out of 10 pulses at a given TMS intensity. This TMS intensity will then be recorded as that participant's resting motor threshold. Using the participant's rs-fMRI functional map of the primary motor cortex, we can calculate their coil-to-cortex depth and use this information to determine the correct IR-TMS treatment intensity for the R-antDLPFC and also determine the correct train duration needed to safely deliver TMS in each participant using published safety guidelines on appropriate train durations at specific TMS frequencies and intensities.

Study Phase II: Treatment Phase.

IR-TMS Treatment Planning.

All TMS treatments will be planned for IR-TMS delivery by Dr. Salinas. The acquired MRI images will be used to compute a participant-specific treatment plan, which will be stored and used during their respective IR-TMS sessions at the RII. Image guidance will be based on treatment plans developed from the participant's high-resolution structural MRI and rs-fMRI scans. From the T1-weighted MRI (described above), two surface models are computed: a model of the scalp surface, for use in registration of the participant to the treatment plan; and, a model of the cortical surface including cortical surface normals. The scalp surface model is based on the air-scalp interface, which is readily obtained by simple thresholding. The cortical surface model is based on pre-classification of brain tissue into gray, white and CSF surfaces, using fMRIPrep's pre-processing pipeline.

Up to two R-antDLPFC target sites may be created for each participant's treatment plan. The R-antDLPFC treatment target sites will be based on connectivity strength with SGC using region-seeded rs-fMRI. Coil orientation will be corrected for the underlying gyral anatomy at each site, using a T1-MRI derived cortical surface model to align the E-field according to the cortical column cosine (C3) model. Stimulation intensity will be corrected for the distance of the stimulation site from the scalp/coil surfaces. Each of the three prospective sites will be ranked (primary or secondary) by their C3-based E-field strengths and these rankings will be relayed to the IR-TMS technician by their numerical order in the IR-TMS treatment plan. Intensity ranges will be individually adjusted for each participant and their ranked treatment sites—to deliver depth-corrected E-fields between 80 volts/meter and 95 volts/meter. This TMS intensity information will also be relayed to the IR-TMS technician in the participant's treatment plan.

IR-TMS Treatment Sessions.

IR-TMS treatment visits will take place at the RII starting as soon as possible after the treatment plan is completed, expected to be 1-5 working days following baseline scanning. For each subject, the coil pose will be pre-computed from pre-processed structural and fMRI scans and stored as an individualized treatment plan. Each subject's treatment plan will be registered to his/her head by creating a scalp model with a high-resolution digitizer, an integrated component of the IR-TMS system. In each arm, the TMS coil will be positioned and held by the robot (under the treatment technician's supervision). IR-TMS treatment will use a liquid cooled figure-8 MagPro coil (MagVenture, Denmark).

IR-TMS Treatment Protocol.

A trained RII team member will deliver IR-TMS at the participant's "primary" TMS treatment target using an accelerated TMS treatment protocol which falls within the previously published safety guidelines for TMS treatments. This accelerated IR-TMS protocol consists of 1,800 IR-TMS pulses per session. Intensity ranges (designed to deliver depth-corrected E-fields of 80-95 volts/meter) will be determined when the participant's treatment plan is developed, and these intensity ranges will be given to the treatment technicians with the IR-TMS treatment plan. The

participant's resting motor threshold will be used to determine the participant's lowest possible stimulation intensity (e.g. 80% of the resting motor threshold). On the first day of IR-TMS treatment, the participants will be given brief trains of TMS pulses beginning at the lowest intensity level (e.g. 80% of resting motor threshold) at their "primary" target site. The intensity will be adjusted upward (in 5 volt/meter increments up to 95 V/m) until a participant-determined comfort level is found. Once established, that final intensity will be used throughout the remaining treatment phase for that participant. If the participant decides that they cannot tolerate the lowest prescribed IR-TMS intensity (e.g. 80% of the resting motor threshold) at their "primary" target site, the above procedure will be repeated at the "secondary" site. If none of the treatment sites at any of the prescribed intensities are tolerable, the participant will be withdrawn from the study (see Discontinuation and Withdrawal of Participants Section below).

IR-TMS treatment guidelines recommend that the train duration of TMS pulse protocols remain within the limits of published safety guidelines (reached by a consensus of TMS practitioners). For example, most TMS protocols deliver pulses at an intensity equivalent to 80-110% of the participant's resting motor threshold. If our 80-95 V/m dosages are higher than these general limits, then we must adjust our TMS timing parameters (e.g. train duration) so that we may still safely deliver the correct number of pulses (i.e. 1,800) within the limits of these safety recommendations. We may also adjust the inter-train interval to ensure that we deliver all our treatment pulses within the allocated treatment session (e.g. 10 minutes). For example, if a participant needs a TMS intensity equivalent to 130% of their resting motor threshold, we will deliver 90 cycles of TMS pulses (e.g. train duration = 1 seconds; inter-train interval = 5.5 seconds; 20 pulses per train), which would still require about 10 minutes of treatment time to deliver the desired number of TMS pulses in each session (i.e. 1,800 pulses). The primary IR-TMS treatment parameters number of pulses per session (i.e. 1,800), and maximum number of sessions (i.e. 40) will remain the same across participants. We may only adjust the participant's intensity, the protocol's stimulation frequency, train duration, and inter-train intervals so that they fall within the safety limits of repetitive TMS treatments. Any alterations to the participant's treatment protocol will be noted in their treatment log.

Participants will receive up to 4 treatment sessions per weekday, for up to 40 sessions. In each treatment session, a total of 1,800 pulses will be administered within the 10 minute IR-TMS session. After each session, participants will be given the opportunity to take a break (e.g. rest, go to the bathroom, stretch, etc.) for a 5-20 minute period. Once ready, the next IR-TMS treatment session will begin; for up to 4 treatment sessions per day. Including the time needed for set up, the total time required for each treatment visit should be less than two hours per day.

After completion of the fifth IR-TMS treatment visit (i.e. 20 sessions), and before the next IR-TMS treatment visit, the participant will complete the Mid-Treatment assessment. Participants will undergo a second MRI and also be asked to complete the PCL-5 (weekly) and PHQ-9 self-reports at this visit. This Mid-Treatment assessment scanning visit should take approximately 45 mins.

The IR-TMS protocol will administer a total of up to 72,000 pulses over the 10-weekday period. If study participants decide, at any time, that they cannot tolerate the IR-TMS treatments, they will be withdrawn from the study (see Discontinuation and Withdrawal of Participants Section below) and will be assisted in finding appropriate after-study care.

Study Phase II: Post-Treatment Follow-Up

Post-Treatment Assessments.

Immediately following the last IR-TMS treatment at the end of the 2nd week, a third MRI scan and assessment battery will be conducted to assess potential treatment effects. The Post-Treatment assessment may occur any time after last treatment with up to a 3-day window for completion. In rare instances, if scheduling circumstances (such as weekends and institution holidays, MRI staff outages, participant scheduling issues) prevent the Post-Treatment assessment from occurring after all treatment sessions have been completed, the Post-Treatment assessment may be conducted before the final treatment session, and any remaining treatment sessions will occur after the Post-Treatment assessment. The actual time between the final IR-TMS session and Post-Treatment assessment will be documented in the participant study file and will be considered during data analysis. After the Post-Treatment MRI session, each participant will also undergo another brief motor threshold assessment to document any changes which may be used to inform future safety guidelines for accelerated IR-TMS treatment protocols. Participants will also be asked to complete the PCL-5 (weekly) and PHQ-9 self-reports at this visit. This Post-Treatment assessment should take approximately 60 mins.

Study Phase III: 1 Month/3 Month Follow-Up

The 1 month FU assessment will occur (at the RII) 30 days after the last IR-TMS treatment session—within a 5-day window. The 3 month FU assessment may occur 90 days after the last IR-TMS treatment session—also within a 5-day window. The actual time between the final IR-TMS session and each FU assessment will be documented in the participant study file and will be considered during data analysis. At each FU visit, participants will undergo MRI scanning as well as symptom assessments. After each MRI, Dr. Moring will perform the CAPS-5 interview; participants will also be asked to complete the PCL-5 (monthly) and PHQ-9 self-reports. Each FU visit should take approximately 90 mins. If time does not allow for follow-up assessments, follow-up assessments will not be completed and participants will be informed.

9.2. Study Evaluations & Procedures

Administration of questionnaires, interviews, or other instruments

Participants will complete the following assessments at baseline: CAPS-5, PCL-5, PHQ-9, LEC-5, AUDIT, and the GAD-7. These self-reports and interviews may take up to 3 hours to complete.

Participants will complete the following assessments at Mid-Treatment and Post-Treatment: PCL-5 and PHQ-9. These self-report assessments may take up to 15 minutes to complete.

Participants will complete the following assessments at 1 month FU and 3 month FU: CAPS-5, PCL-5, and PHQ-9. These self-reports and interviews may take up to 1 hour to complete.

Radiographic or other imaging assessments.

Participants will undergo anatomical and fMRI sessions throughout the study. Earplugs will be provided at every MRI session. MRIs use strong magnets and radio waves to non-invasively acquire images of organs and tissues. Unlike X-rays, MRIs do not expose subjects to radiation, therefore it is considered safe to obtain many MRIs in a single scanning session or over multiple days; the initial MRI scans may take up to 1 hour. In the event that the participant cannot tolerate the baseline MRI procedure, they will be withdrawn from the study. Participants will be imaged at the RII using a research-dedicated 3T Siemens Prisma MRI scanner (Siemens, Erlangen, Germany) with an 64-channel phased array coil. Structural imaging will be obtained only once, in the baseline MRI visit. Structural images will be used for IR-TMS treatment planning (described above) and for spatial normalization to a standard anatomical template. fMRI and DTI images will be obtained five times (baseline, Mid-Treatment, Post-Treatment, 1 month FU, 3 month FU) and used to detect symptom-specific network abnormalities and treatment-induced neuroplastic effects. MRI acquisition dates and scan comments will be recorded in each participant's treatment record.

9.2.1. Biospecimen Evaluations

We will not collect any biospecimen data in this study.

9.3. Safety Assessments N/A ☐

- **Special assays or procedures required**.
  - We will perform motor threshold assessments for each participant (at baseline and Post-Treatment visits, immediately after each MRI) to determine the correct intensity and train durations needed to safely deliver IR-TMS in each participant's IR-TMS Treatment Phase. Motor threshold assessments will be recorded in each participant's treatment record.
- **Assessment of adverse events.**
  - We will monitor adverse events (AEs) in each participant at each scheduled visit. If a participant wishes to report an adverse event between visits, we will document their AE in their participant log.

9.4. Adverse Events and Serious Adverse Events

9.4.1. Definition of Adverse Event

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

9.4.2. Definition of Serious Adverse Events (SAE)

An 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, or a

congenital anomaly/birth defect. 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.

9.4.3. Classification of an Adverse Event

9.4.3.1. Severity of Event

For AEs, 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.

9.4.3.2. Relationship to Study Intervention/Experimental Manipulation

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures)

and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.4.3.3. Expectedness

A clinician with appropriate expertise in IR-TMS will be responsible for determining whether an 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 procedures.

9.4.4. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or 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, not otherwise precluded per the protocol, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (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 will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric 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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Research Assistants and/or Sub-Investigators will record 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.

9.4.5. Adverse Event Reporting

UT HEALTH AE REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
AE	UTHSCSA IRB in a summary format as part of the continuing review application.	Annually
UPIRSO - life threatening	UTHSCSA IRB	within 48 hours of the Principal Investigator (PI) determining a UPIRSO exists (*VA is within 1 hour)
UPIRSO - non-life threatening	UTHSCSA HEALTH IRB	within 7 days of the PI determining a UPIRSO exists (*VA is within 5 days)

9.4.6. Serious Adverse Event Reporting

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the Sponsor, IRB and the FDA as required.

9.4.7. Events of Special Interest N/A ☐

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of events of special interest and shall report the results of such evaluation to the Sponsor, IRB and the FDA as required. Such events may include psychiatric hospitalization, and significant changes in behavior (e.g., interpersonal violence, substance abuse).

9.4.8. Reporting of Pregnancy N/A ☐

Female participants cannot take part in this study if they are pregnant since the safety of IR-TMS has not been studied in pregnant participants. During the pre-screening process, we will ask if a female participant is pregnant (or may be pregnant). If they answer "yes," they will not be enrolled in the study. Only females who are sure that they are not pregnant will proceed to the consent phase of the study. At the baseline assessment, all female participant's will be asked if they still have a menstrual cycle. If they affirm that they do, we will ask them to take a urine human chorionic gonadotropin pregnancy test to confirm that the participant is not pregnant at the time of enrollment. Participants who become pregnant after consent, but before the last IR-TMS treatment, will be withdrawn from the study. If a participant becomes pregnant after the last IR-TMS treatment but before the 3 month FU visit, they will be allowed to continue through the FU period. Reports of a pregnancy will be included in the participant's treatment record and reported to the study leadership and/or sponsor.

9.5. UNANTICIPATED PROBLEMS

9.5.1. Definition of Unanticipated Problems

Unanticipated problem involving risk to subjects or others (UPIRSO) includes any incident, experience or outcome that meets all 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; **and**
- Definitely 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 (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

9.5.2. Reporting Requirements

The investigator will report UPIRSOs to the IRB as per OIRB Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO)/ And Unanticipated Adverse Device Effects (UADE) Policy and Procedure.

10. STATISTICAL CONSIDERATIONS

Analyses will be intent to treat and include all participants who completed a baseline regardless of the extent of study participation. Prior to developing statistical models, variables will be examined with the use of frequency distributions, scatter plots, and histograms. Descriptive statistics will be employed to evaluate participant demographics, where means, variability (standard deviation; standard error), ranges, and estimates of skewness and kurtosis will be computed and used as guidelines in the application analyses. Analyses will be completed using R statistical software. As needed, we also have access to SAS 9.4, IBM-SPSS 28, Stata 14.2, and Mplus 8.4 software. FC

10.1. STATISTICAL HYPOTHESIS

- Primary Endpoint(s): The primary study objective is to determine the effect of IR-TMS therapy for PTSD in a non-randomized, open label clinical trial design. It is expected that IR-TMS will result in significant reductions in PTSD symptom scores as measured by the PCL-5 (primary outcome of interest) at end of the accelerated IR-TMS two-week treatment.

- Secondary Endpoint(s): Secondary outcome measures will be: PCL-5, CAPS-5 and PHQ-9 total scores. PCL-5 and PHQ-9 will be obtained at five time points: baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3 months FU. CAPS-5 will be obtained at three timepoints:

baseline, 1 month FU and 3 months FU. Treatment differences in symptom scores at each time point will be analyzed using a generalized linear mixed model (GLMM) with fixed effects of time. Advantages of likelihood-based regression models over conventional (Analysis of Variance (ANOVA) include the ability to use data from all participants even if they have only baseline data, relaxation of the assumption of equal variances before and after treatment, specification of data distributions other than normal such as Poisson or log-normal, and the ability to analyze longitudinal data in the presence of missing data given the assumption that data are missing at random. GLMMs are a powerful and flexible statistical extension of linear mixed models that can examine outcome variables from different distributions, such as normal (continuous) and binary outcomes. Statistical models will include all available data collection timepoints. Secondary objectives of interest will also include validation of brain FC as a quantitative biomarker for PTSD and recovery and safety (i.e., adverse events). To examine FC, we will employ unified Structural Equation Modeling (SEM) analyses. Unified SEM is a recommended approach for imaging analyses. It differs from traditional SEM by accounting for autocorrelations in imaging timeseries data. Specifically, each timeseries is represented by the timeseries and the lagged timeseries, where each timepoint is offset by one. In this way, each lagged variable models autoregressive covariation. To assess connectivity between brain regions of interest, all combinations of both the lagged and unlagged loadings are considered. Alpha will be set at p = .05 for analyses. Adverse events will be examined using standardized, validated adverse events monitoring procedures. Descriptive statistics will be employed to evaluate the frequency, severity, and relatedness of adverse events that occurred during treatment and at each FU assessment.

Missing Data and Attrition

Missing data and attrition are common challenges to clinical studies. They are particularly challenging with trauma related avoidance symptoms. To address attrition and missing data, participants will have frequent FUs to maintain contact with the study team. Participants choosing to discontinue treatment will be asked their reasons for dis-continuing treatment as soon as possible at the point of drop-out. All available assessments will be used in growth model estimations for each patient; missing data will not be imputed. Effect sizes will be computed with Hedges g. Reliable Change Indices will be used to evaluate the proportion of participants who demonstrated reliable change at Post-Treatment, 1 month FU, and 3 months FU.

10.2. SAMPLE SIZE DETERMINATION

Sample size was determined for 80% power with 1-tailed 5% level hypothesis test designed to detect PCL-5 total score changes between time points. Our previous RCT had a moderate Hedges g effect size of 0.57 (described in Significance). However, assuming a conservative effect size of 0.25, the sample size estimate for a repeated measures ANOVA is 21 participants. In addition to the treatment response aspects of this trial, the power analysis for FC changes was also assessed. In our previous RCT, we acquired fMRI scans at baseline and Post-Treatment, however, our largest treatment effects were observed at the 1 month FU time point (Figure 1). In that RCT, the DLPFC-to-SGC FC differences between the Active IR-TMS+IIP and Sham IR-TMS+IIP groups at Post-Treatment was Z = 2.19. With a sample size of 30 at five time points, the required effect size would be 0.20. Therefore, both aspects of our proposal are well powered.

10.3. POPULATIONS FOR ANALYSES

We will use a Modified Intention-to-Treat Analysis approach for our analyses. Participants who took at least one dose of study intervention and have some FU outcome data will be included in the analyses.

10.4. STATISTICAL ANALYSES

10.4.1. Analysis of the Primary Endpoints

The primary outcome measure will be the PCL-5 total score at end of the accelerated IRTMS two-week treatment. Secondary outcome measures will be: CAPS-5 and PHQ-9 total scores. PCL-5 and PHQ-9 will be obtained at five time points: baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3 months FU. CAPS-5 will be obtained at three timepoints: baseline, 1 month FU and 3 months FU. Treatment differences in symptom scores at each time point will be analyzed using linear growth models. For each outcome, a piecewise approach will be taken such that linear slope from baseline to Post-Treatment and from Post-Treatment to Last FU will be estimated separately. All available assessments will be used in growth model estimations for each participant; missing data will not be imputed. Effect sizes will be computed with Hedges g. Reliable Change Indices will be used to evaluate the proportion of participants who demonstrated reliable change at Post-Treatment, 1 month FU, and 3 months FU.

10.4.2. Analysis of the Secondary Endpoint(s)

We hypothesize that FC will be modulated by IR-TMS throughout each participant's targeted brain network and that the amount of FC modulation will correlate with the IR-TMS dose. We also hypothesize that participants receiving more IR-TMS pulses will demonstrate faster and longer lasting network consolidation than those receiving fewer IR-TMS pulses.

The primary outcome measure will be the PCL-5 total score at end of the accelerated IRTMS two-week treatment. Secondary outcome measures will be: CAPS-5 and PHQ-9 total scores. PCL-5 and PHQ-9 will be obtained at five time points: baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3 months FU. CAPS-5 will be obtained at three timepoints: baseline, 1 month FU and 3 months FU. Treatment differences in symptom scores at each time point will be analyzed using linear growth models. For each outcome, a piecewise approach will be taken such that linear slope from baseline to Post-Treatment and from Post-Treatment to Last FU will be estimated separately. All available assessments will be used in growth model estimations for each participant; missing data will not be imputed. Effect sizes will be computed with Hedges g. Reliable Change Indices will be used to evaluate the proportion of participants who demonstrated reliable change at Post-Treatment, 1 month FU, and 3 months FU.

Our secondary objective models IR-TMS' local and network-wide effects when targeting each participant's R-antDLPFC. Five timepoints acquired in 30 participants will be assessed: baseline, Mid-Treatment, Post-Treatment, 1 month FU, and 3 months FU. Two types of response-predictive models will be created for each time point: a seed-to-whole brain FC map and MACM node-and-edge models. The seed-to-whole brain FC maps will be determined using FSL's FEAT toolbox. A mixed-effects, repeated measures ANOVA will be used to capture both week-to-week FC changes and baseline comparisons across all timepoints. Covariates of no-interest (age, gender, etc.) will be regressed out for each analysis. Post-hoc tests will be used to determine if specific time points significantly differ from each other. The MACM node-edge models will be determined using the Activation Likelihood Estimation (ALE) map of PTSD described in the Significance. The time series for each of the significant ALE clusters will be

calculated and their cross-correlations will be estimated. R-to-Z transforms will be applied to the correlations will be combined to create the PTSD MACM. This MACM will be used to determine the nodes and edges for each participant at each time point. Edge quantification will be computed using unified SEM (AMOS, 7th edition). Nodes-and-edge models for each network will be compared using: the chi-square (χ_2) statistic, root-mean square error, and the Bayes information criterion. The number of TMS pulses delivered may also be included in each of these analyses to determine its effect on each model.

10.4.3. Safety Analyses

We will perform motor threshold assessments for each participant (at baseline and Post-Treatment visits, immediately after each MRI) to determine the correct intensity and train durations needed to safely deliver IR-TMS in each participant's IR-TMS Treatment Phase. Motor threshold assessments will be recorded in each participant's treatment record and any group-wise changes in motor threshold between these timepoints will be analyzed and reported.

We will also monitor AEs in each participant at each scheduled visit. If a participant wishes to report an adverse event between visits, we will document their AE in their participant log. The number of occurrences of each AE (and its severity) will be recorded at each visit. The likelihood of each AEs relationship to the treatment will be assessed in our team's weekly meetings and will be discussed on a case-by-case basis. Summary statistics of the occurrence, severity, and duration of each AE will be analyzed at each timepoint to help inform future safety/treatment guidelines for IR-TMS.

10.4.4. Baseline Descriptive Statistics

Each participant's baseline characteristics will be assessed using descriptive statistics including the mean, median, and standard deviation values of their age, gender, and assessment scores measured using the PCL-5, CAPS-5, and PHQ-9.

10.4.5. Planned Interim Analyses

There are no planned interim analyses for this study.

10.4.6. Sub-Group Analyses

There are no planned sub-group analyses for this study.

11. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1. INFORMED CONSENT PROCESS

11.1.1. Waiver of Consent N/A ☐

Recruitment: This waiver is needed for identification of eligible subjects for recruitment into the study only. In order identify potentially eligible subjects for the research, potential particiapnts (referred by their providers or via flyers) will contact the study team, who will pre-screen the

participants to determine if they meet the study's basic eligibility criteria. If the participant passes pre-screening and is still interested in the study, we will provide (via email) a brief summary of the study (Form D-IS) and a video describing the treatment trial and each of the tools/treatments used throughout the study (i.e. MRI and IR-TMS). No additional research procedures or continued access to identifiable private information will occur until after subjects have given valid consent to participate in the research study.

The risk of this activity is minimal to the subjects, because the information collected will be limited only to information allowing researchers to determine eligibility for the study and contact information. Only the minimum information necessary to determine eligibility will be recorded.

Screening: The only study procedure that will take place under this waiver is screening questionnaires to check for eligibility. The screening procedure consist of answering a set of questionnaires.

Researchers have been granted access to the medical record data by the institution(s) and will protect the data they use and record for this activity according to institutional and HIPAA standards for protecting privacy and maintaining confidentiality. If the subjects identified decline participation in the research, the data collected (under this waived activity) will not become part of the research data. If subjects agree to participate in the research, the identifiable data collected will become part of the subjects' research records and will be stored according to the research confidentiality plan.

The researchers need to access the data from the medical records in order to identify eligible subjects to approach for this research. Without this waiver, the research would not be practicable as the eligible subjects would likely not be identified, contacted and recruited in time to complete the required sample.

11.1.2. Consent/Assent Procedures and Documentation **N/A ☒**

11.1.3. Consent for minors when they reach the age of majority **N/A ☒**

11.1.4. Consent of Subjects who are, or become, decisionally impaired. **N/A ☐**

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that participants enrolled in the protocol may permanently lose the capacity to consent for themselves during the study. In the event this occurs, the participants will be withdrawn from the study.

11.2. 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 PI will promptly inform study participants, the 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
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and, as applicable, the FDA, or other relevant regulatory or oversight bodies.

11.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. 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, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the RII. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by RII research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the RII.

11.3.1. Measures Taken to Ensure Confidentiality of Data Shared per the Data Sharing Policies N/A ☐

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

11.4. Future use of Stored Specimens and Data N/A ☐

Data collected for this study will be analyzed and stored at the RII. After the study is completed, the de-identified, archived data will be transmitted to and stored at the RII, for use by other researchers including those outside of the study. Permission to transmit data to the RII will be included in the informed consent.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. However, withdrawal of consent with regard to data may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the RII.

11.5. Safety Oversight

Safety oversight will be under the direction of a Medical Monitor with appropriate expertise in non-invasive brain stimulation and MRI. The Medical Monitor will be independent from the study conduct and free of conflict of interest. The Medical Monitor will meet at least semiannually to assess safety and efficacy data from the study. The Medical Monitor will review all safety-related data to track participants' health and monitor for any potential issues. If an AE occurs, the Medical Monitor will be notified by the study personnel. that will be written and reviewed prior to Each data element that the Medical Monitor needs to assess will be clearly defined. The Medical Monitor will provide its input to the PI and Co-PI of the study.

11.6. Clinical Monitoring N/A ☒

11.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent—Study staff will review both the documentation of the consenting process as well as each of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data—Data will be initially captured on source documents (see **Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity—Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Interventionist Training and Tracking**.

Protocol Deviations–The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

11.8. Data Handling and Record Keeping

11.8.1. Data Collection and Management Responsibilities

Data collection will be the responsibility of the clinical trial staff at the RII under the supervision of the PI. The investigator will be 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 consented/enrolled in the study. Data recorded in the electronic CRF derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Complion, a 21 CFR Part 11-compliant data capture system provided by the UTHSA. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Human Data Sharing, including Genomic Data Sharing, and Publication

11.8.2. Study Records Retention

Study documents should be retained per sponsor retention guidelines and/or institutional requirements listed in the UT Health SA Records Retention Schedule per HOP 7.10.1. No records will be destroyed without the written consent of the sponsor, if applicable.

11.9. PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the Institutional Review Board. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11.9.1.1. Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations (violation): Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the participant, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of participants or others, or the scientific integrity or validity of the study.

12. COLLABORATIVE AGREEMENTS N/A ☒

13. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the neuromodulation industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

Dr. Salinas and Dr. Fox have intellectual property and have disclosed financial interests in Cerebral Magnetics—the vendor for the IR-TMS technology used in this trial. The terms set forth by each investigator's Conflict of Interest management plan state the following and have been instituted in this study.

Dr. Salinas must:

a) disclose his financial association with Cerebral Magnetics in the human subjects informed consent documents and in any interactions with the FDA, as required.
b) recuse himself from verifying eligibility of human subjects in any research sponsored by or benefiting Cerebral Magnetics or involving the IR-TMS system.
c) recuse himself from delivering Treatment Plans at the RII using the IR-TMS system.
d) recuse himself from consenting any patient who participates in research sponsored by or benefiting Cerebral Magnetics or involving the IR-TMS system. All such patient informed consent must be performed by a non-conflicted investigator. UTHSCSA reserves the right to have a consent monitor present during the patient consent process in accordance with current IRB procedure.
e) implement robust controls to prevent the modification of Treatment Plans after they have been completed in CMCloud using C3Plan® and transmitted to the C3Nav® console.

f) ensure that image acquisition for all IR-TMS clinical-trial awards and proposals are managed through the RII's MRI Division, overseen by Dr. Geoffrey Clarke.
g) ensure an immutable audit trail that is secure and cannot be altered or manipulated is maintained for each Treatment Plan to include but not limited to unique patient identifiers, creator name, date-of-creation and treatment-planning session start and end dates.
h) recuse himself from verifying participant outcomes or treatment efficacy.
i) ensure that an Investigator, who has no relationship with or financial interest in Cerebral Magnetics or the IR-TMS system, verifies outcomes and documents each adverse event determination.
j) ensure that controls are in place that prohibit his access to interim data generated from human subject protocols involving the IR-TMS system.

Dr. Fox must:

a) disclose his financial association with Cerebral Magnetics in the human subjects informed consent documents and in any interactions with the FDA, as required.
b) not be involved in the consenting or verification of eligibility of human subjects.
c) not verify or document any adverse events.
d) not participate in data analysis in his role as RII Director. Any such analysis must be conducted during his personal time and after completion of the human subjects research. Data analysis must not affect the independent judgement and or reporting of events by the UTHSCSA Principal Investigator or study staff.
e) implement robust controls to prevent the modification of Treatment Plans after they have been completed in CMCloud using C3Plan® and transmitted to the C3Nav® console.
f) ensure that image acquisition for all IR-TMS clinical-trial awards and proposals are managed through the RII's MRI Division, overseen by Dr. Geoffrey Clarke.
g) ensure an immutable audit trail that is secure and cannot be altered or manipulated is maintained for each Treatment Plan to include but not limited to unique patient identifiers, creator name, date-of-creation and treatment-planning session start and end dates.
h) recuse himself from verifying participant outcomes or treatment efficacy.
i) ensure that an Investigator, who has no relationship with or financial interest in Cerebral Magnetics or the IR-TMS system, verifies outcomes and documents each adverse event determination.

14. ABBREVIATIONS

AE	Adverse Event
ALE	Activation Likelihood Estimation
ANOVA	Analysis of Variance
AUDIT	Alcohol Use Disorders Identification Test
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CFR	Code of Federal Regulations
C3	Cortical Column Cosine
CRF	Case Report Form
DTI	Diffusion Tensor Imaging
FC	Functional Connectivity
FU	Follow-Up
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GAD-7	Generalized Anxiety Disorder Screener
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
HIPAA	Health Insurance Portability and Accountability Act
IIP	Intensive Inpatient Program
IR-TMS	Image-Guided Robotically Delivered Transcranial Magnetic Stimulation
IRB	Institutional Review Board
LEC-5	Life Events Checklist for DSM-5
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
OIRB	Office of the Institutional Review Board
PCL-5	PTSD Checklist for DSM-5
PE	Prolonged Exposure
PHQ-9	Participant Health Questionnaire-9
PI	Principal Investigator
PTSD	Post Traumatic Stress Disorder
QC	Quality Control
R-antDLPFC	Right, anterior dorsolateral prefrontal cortex
RII	Research Imaging Institute
SAE	Serious Adverse Event
SEM	Structural Equation Modeling
SGC	Sub-Genual Cingulate
SOE	Schedule of Events
TBI	Traumatic Brain Injury
UADE	Unanticipated Adverse Device Effects
UPIRSO	Unanticipated Problem Involving Risk to Subjects or Others
US	United States
VA	Veterans Administration
WHO	World Health Organization

15. REFERENCES

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16. APPENDICES

Assessments and Questionnaires

A. CAPS-5 Interview
B. PCL-5 (monthly) Self-Assessment
C. PCL-5 (weekly) Self-Assessment
D. PHQ-9 Self-Assessment
E. LEC-5 Self-Assessment
F. AUDIT Interview
G. GAD-7 Self-Assessment

FDA Correspondence Regarding Our IR-TMS System

H. FDA Device Pre-Submission Materials
I. FDA Device Pre-Submission Meeting Minutes
J. FDA Device Pre-Submission Meeting Minutes Approval
K. FDA Decision on Using Our IR-TMS system in Healthy Control Subjects (UTHSA IRB #HSC 20170718HU)

Safety Certification for Our IR-TMS System

L. International Electrotechnical Commission 60601 Compliance Approval Letter

C3Nav® User Manual

M. C3Nav® User Manual