PROTOCOL eTMS-PTSD-001

Electroencephalogram (EEG) personalized Transcranial Magnetic Stimulation (eTMS)

for Post-Traumatic Stress Disorder

(eTMS for PTSD)

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Wave Neuroscience, Inc., Newport Beach, California
United States

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STUDY SYNOPSIS

Study Objective	Evaluate the safety and efficacy of electroencephalogram (EEG) personalized transcranial magnetic stimulation (eTMS) for the treatment of Post-Traumatic Stress Disorder (PTSD).
Study Design	• Stage 1: Open-label Safety Pilot Study • Stage 2: Randomized, double-blind, sham-controlled trial of eTMS, with open label period following sham control.
Study Population	• Veterans and First Responders with PTSD • male or female • 22 – 65 years of age • any racial/ethnic background • who meet the eligibility criteria
Research Group	**Principal Investigator:** Bill Phillips, PhD Head of Research Wave Neuroscience, Inc. 1601 Dove St., #205 Newport Beach, CA 92660 714-883-7890 bill@waveneuro.com **Study Chair:** Adele M.K. Gilpin, PhD, JD Visiting Faculty Department of Neurobiology and Behavior 1400 Biological Sciences III University of California Irvine Irvine, CA 92697 410-961-7582 adele.gilpin@gmail.com ; agilpin@uci.edu

	Data Center: Maven LLC 904 East Broad Street Columbus, Ohio 43205 ***Point of contact*** Abram Cookson abram.cookson@argonaut.team **Clinical site#1:** Wright State University Center of Neuroimaging and Neuro-Evaluation of Cognitive Technologies 3640 Colonel Glenn Hwy. Dayton, OH 45435 ***Site Principal Investigator:*** Matthew Sherwood, PhD, MBA Director, Research Associate Professor 937-524-3924 Matt.sherwood@wright.edu **Additional Clinical sites:** Up to 3 additional Clinical Sites may be added in Stage 2 to increase enrollment and geographic diversity. **Supportive Treatment Center** JLC Services 2877 Valley Rd. Cuyahoga Falls, OH 44223 ***Point of Contact***: Joseph Charles 330-687-0742 jcharles@jlcservicesinc.com **FDA IDE Sponsor:** Wave Neuroscience, Inc. 1601 Dove Street, Suite 299 Newport Beach, CA 92660 ***President:*** Erik Won, DO ewon@waveneuro.com *This study was commissioned by the State of Ohio (2021 RFP Number SRC0000002472, Index Number DMH009) to address the ongoing crisis among Veteran population in the areas of mental health and substance use. The goal for this work is to develop therapies that work for the complex Veteran patient for whom there are currently no good therapeutic options.

Eligibility Criteria	***Inclusion Criteria*** Participants must meet all inclusion criteria to qualify for enrollment in the study: 1. Willing and able to consent to participate in the study via signed Informed Consent 2. Age 22 – 65 years 3. Provisional diagnosis of PTSD according to Veterans Administration PCL-5 rubric fulfillment AND cutpoint score of 31 or above 4. Positive identification as either a Veteran, or First Responder (e.g., emergency medical service provider, firefighter, or any other emergency response personnel) ***Exclusion Criteria*** Participants will be excluded from study participation if one or more of the following exclusion criteria apply: 1. Uncontrolled medical, psychological or neurological conditions including, but not limited to: a. Uncontrolled psychosis or mania b. Uncontrolled seizure disorder or EEG abnormalities that indicate risk of seizure, i.e., epileptiform discharges during the EEG recording c. Uncontrolled cardiac, pulmonary, or endocrine disorder (e.g., diabetes) d. Acute pain or illness e. Active, untreated addiction to prescription drugs, alcohol or illicit substances* (not including THC/CBD, which is available in many states under medical prescription or for recreational use) f. Clinically significant medical condition or abnormality that in the Investigator's judgment might pose a potential safety risk to the subject or limit the interpretation of the trial results 2. Pregnant, or female unwilling to use effective birth control during the course of the trial (unless cleared for participation by an obstetrician/gynecologist) 3. Presence of aneurysm clips or coils, cochlear or ocular implant, cortical epidural stimulator, deep brain stimulator, pacemaker or defibrillator, retained intracranial metal foreign body (bullets, shrapnel – excluding titanium and oral implants), steel stents or shunts, active vagal nerve stimulator, ventriculoperitoneal (VP) shunt 4. Past exposure to metal fragments, permanent piercings, and/or other possible metal sources in the head and neck 5. Unwilling or unable to adhere to the study treatment, data collection schedule, or study procedures, or any condition, that in

	the judgment of the Investigator might prevent the participant from completing the study 6. Inability to calculate the EEG intrinsic alpha frequency at Baseline 7. Current participation in any interventional research protocol 8. History of any type of ECT or rTMS 9. History of intracranial lesion or increased intracranial pressure 10. History of ischemic or hemorrhagic stroke 11. History of other neurologic conditions with associated cerebral damage 12. Family history of epilepsy or seizure in a first degree relative 13. An elevated risk of suicide or violence to others 14. A personal history of epilepsy or seizure 15. Clinically significant medical illness, psychopathology, or other condition, that in the judgment of the Investigator might pose a potential safety risk to the participant or limit the interpretation of study results
Study Equipment	• Zeto EEG • MagVita TMS Therapy System components (MagPro family stimulator and coils) • Coil: Cool-B65 Butterfly coil
Study Treatment Regimen: Stage 1	• Active eTMS: Personalized treatment stimulus rate between 8 and 13 Hz, determined by the participant's EEG intrinsic alpha frequency • Coil location: Fz (midline frontal/prefrontal cortex) • Coil: Cool-B65 Butterfly coil • Treatment stimulus intensity 50% of motor threshold • Dose is 1 study treatment: 5 seconds of repetitive stimulation, with an intertrain interval of 20 seconds, for 15 minutes • Doses per treatment day = 2 • Minimum rest time from the end of the first dose to the start of the second dose = 30 minutes • Duration: 10 treatment days over a maximum of 21 days beginning on day (Safety Day) SD+1
Study Treatment Regimen: Stage 2 Randomized	• **All participants** o Treatment stimulus intensity 50% of motor threshold o Dose is 1 study treatment: 5 seconds of repetitive stimulation, with an intertrain interval of 20 seconds, for 15 minutes o Doses per treatment day = 2 o Minimum rest time from the end of the first dose to the start of the second dose = 30 minutes o Coil location: Fz (midline frontal/prefrontal cortex)

	○ Coil: Two Cool-B65 Butterfly coils (one connected to the rTMS and one disconnected) ○ Duration: 10 treatment days over a maximum of 21 days beginning on (Randomized Day) RD +1 ○ A temporary barrier is positioned between the participant and the MagVita, preventing the participant from seeing the MagVita • **Active-assigned group** ○ Personalized treatment stimulus rate between 8 and 13 Hz, determined by the participant's EEG intrinsic alpha frequency • **Sham-assigned group** ○ An unconnected coil will be positioned at Fz, with the cable routed through the barrier, so that it appears to be connected. ○ The Connected coil will be kept on the MagVita behind the barrier. In this way, the participant hears the ticking sound of the rTMS emanating from behind the barrier, but no magnetic field is generated by the disconnected coil, so the sham-assigned participant receives no treatment
Study Treatment Regimen: Stage 2 Open Label	• Active eTMS: Personalized treatment stimulus rate between 8 and 13 Hz, determined by the participant's EEG intrinsic alpha frequency • Coil location: Fz (midline frontal/prefrontal cortex) • Coil: Cool-B65 Butterfly coil • Treatment stimulus intensity 50% of motor threshold • Dose is 1 study treatment: 5 seconds of repetitive stimulation, with an intertrain interval of 20 seconds, for 15 minutes • Doses per treatment day = 2 • Minimum rest time from the end of the first dose to the start of the second dose = 30 minutes • Duration: 10 treatment days over a maximum of 21 days beginning on day (Open Label Day) OD +1 • OD+1 to occur within 2 months of completion of F1 data collection
Schedule of Visits	Participants evaluated for eligibility via Screening phone call visit (SC). Following SC, a Baseline Visit (BL) will be conducted to gather assessments. All participants will be encouraged to utilize no-cost access to background supportive treatment (BST) made available through the Supportive Treatment Center. ***Stage 1: Safety Pilot Study:*** • Screening Visit (SC): SDay-28 to SDay-2 • Baseline Visit (BL): SDay-28 to SDay -1

	• Begin Active eTMS on SDay +1
	• Finish Active eTMS between SDay +10 and SDay +21
	• BST from SDay +1 through SDay +21
	• F1 data collection visit after the last eTMS treatment - between SDay +10 and SDay +21
	Stage 2: Randomized Controlled Trial
	• All participants
	  o Screening Visit (SC): RDay-28 to RDay-2
	  o Baseline Visit (BL): RDay-28 to RDay -1
	  o Randomization: RDay +1 prior to first study treatment
	  o Begin Assigned study treatment (Active or Sham) on RDay+1
	  o Finish Assigned study treatment (Active or Sham) between RDay+10 and RDay+21
	  o BST from RDay +1 through RDay+70
	  o F1 data collection visit after last randomized, blinded treatment - between RDay +10 and RDay +21
	  o F2 data collection target day = RDay +71
	  o F3 data collection target day = RDay +180
	• Sham eTMS-assigned Group:
	  o Begin Open Label Active eTMS within 60 days of completing F1 on ODay +1
	  o Finish Open Label Active eTMS between ODay +10 and ODay +21

Outcomes	***Stage 1*** ***Primary Outcome*** Safety - Adverse Events – Incidence, severity, relatedness, type, subsequent treatment/intervention required, and resolution status ***Stage 2*** ***Primary Outcome*** <u>PTSD</u> – Symptom reduction in PTSD symptoms as calculated by arithmetic reduction in PCL-5 between BL and F1. ***Safety Outcome*** <u>Adverse Events</u> – Incidence, severity, relatedness, type, subsequent treatment/intervention required, and resolution status
Data collection	• DSM-5 PTSD Checklist (PCL-5) • Veterans RAND 36-Item Health Survey (VR-36) • TMS Screening Form (TMSs) • Mini Mental Status Exam (MMSE) • Columbia Suicide Severity Rating Scale (CSSRS) • Ohio State University Traumatic Brain Injury Identification Method (OSU-TBI-ID)

	• Drug History Questionnaire (DHQ) • Life Events Checklist for DSM-5 (LEC-5) • Clinical Global Impression (CGI) • Braincheck Neuropsychological Battery (Braincheck) • Somatic Symptom, Anxiety, Depression Screen (PHQ-SADS) • Alcohol Use Disorders ID Test (AUDIT) • Morphine Equivalent Dose (MED) • Opiate Craving Scale (OCS) • Drug Abuse Screening Test (DAST-10) • Pittsburgh Sleep Quality Index (PSQI) • Side Effects Questionnaire (SEQ) • EEG/ECG • Brief Pain Inventory (BPI) • Blinding Assessment • Body Temperature • Blood Pressure • Concomitant physical and neuromodulation treatments • Concomitant medications • Concomitant drug use • Concomitant alcohol use • Adverse Events • Demographics/Military/First Responder • Medical/Psychiatric History • Pregnancy
Randomization (Stage 2)	• 2 treatment groups: o Active eTMS Group o Sham eTMS Group • 1:1 allocation ratio • Random permuted blocks: 2,4,6 • Stratification variables: o Clinic
Sample Size Justification	***Stage 1*** • Total recruitment goal: o 30 o 26 completers • Sample size selected to allow detection of safety concerns in the broad PTSD population to be recruited for Stage 2 • A maximum of 400 individuals will be screened in order to achieve the recruitment goal ***Stage 2*** • Total recruitment goal: o 120 o 108 completers (90%) • Assignment ratio =1:1 for Active eTMS vs. Sham eTMS

	• Primary outcome time point = F1
	• Planned estimated effect size +0.8 $SD_{difference}$, for a difference in Active eTMS versus Sham eTMS group mean pre-post PCL-5 scores = 15, with pooled $SD_{difference}$ = 18.68
	• Type 1 error = 0.05 (2-sided)
	• Statistical power = 98.5 %
	• Method of calculation – Sample size and power for given detectable difference between two mean difference scores using Student's t-test according to method of Dupont & Plummer
	• Design variable is change in PCL-5 between BL and F1.
	  o Mean in a first responder population = 38.73 (SD = 18.68) (Morrison, Su, Keck, & Beidel, 2021)
	  o Clinically important difference (MCID) = 10 - 20

Statistical Methods (Stage 1)	• Adverse events characterized by:
	  o Frequency
	  o Relatedness
	  o Severity
	  o Type
	• DSMB to review and make recommendations regarding:
	  o Whether to proceed to Stage 2
	  o Protocol changes for Stage 2
	• A supplementary IDE to FDA for approval to proceed to Stage 2

Statistical Methods (Stage 2)	• Intention to Treat (ITT) population to analyze the primary outcome, with secondary analyses using Per Protocol (PP) population • Primary outcome tested by linear regression of change score between Baseline (BL) and end of treatment (F1) at 5% Type 1 error rate • Multiple linear regression imputation of missing data assuming missing at random (MAR), and best-case/worst-case sensitivity analyses • Poolability of data from all sites tested • Exploratory outcomes tested, as appropriate, according to level of data (e.g., categorical, ratio), number of time points at which measured, and fulfillment of statistical assumptions • DSMB monitors emerging safety, efficacy, recruitment and performance data • DSMB to recommend continuation/termination • One interim analysis of efficacy data after approximately 50% completers o Haybittle-Peto alpha-spending and stopping rule

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LIST OF ABBREVIATIONS

A/D conversion	analog to digital conversion
AE	Adverse Event
AUDIT	Alcohol Use Disorders Identification Test
Biometrics-guided	EEG-guided
BI	Blinding Index
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CDRH	U.S. FDA Center for Devices and Radiological Health
CES	Cranial Electrotherapy Stimulation
CFR	Code of Federal Regulations
CIDI	World Health Organization Composite International Diagnostic Interview
CNS	Central Nervous System
CONSORT	CONsolidated Standards of Reporting Trials
Course of trial	Period of time between beginning of SC Visit until end of F2 Visit for participants opting out of the open-label extension, or until end of F3 data collection for participants opting in to the open-label extension
COVID-19	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CP	Conditional power
CPG	Clinical practice guideline
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
C-SSRS FU	Columbia-Suicide Severity Rating Scale Follow-up
DAR	Data at Rest
dB	decibel
DC	Data Center
DLPFC	Dorsolateral left prefrontal cortex
DMZ	Demilitarized Zone: A small computer between a trusted internal network and an untrusted external network
DoDI	Department of Defense Instruction
DQQ	Data Quality Query
DSM-III	Diagnostic and Statistical Manual of Mental Disorders Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
dTMS	deep Transcranial Magnetic Stimulation
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
EEG	Electroencephalogram
EMDR	Eye-movement desensitization and reprocessing
ESS	Epworth Sleepiness Scale
eTNS	External Trigeminal Nerve Stimulation
F1	Follow-up Visit 1 (end of blinded study visit
F2	Follow-up Visit 2 (end of open-label treatment extension visit)
F3	Follow-up Visit 3 (end of long-term follow-up data collection)
FDA	United States Food and Drug Administration
FFT	Fast Fourier Transform

Fz	Frontal Midline (as per the 10/20 system)
GABA	gamma-amino-butyric acid
GCP	Good clinical practice
HAMD	Hamilton-Montgomery Depression Rating Scale
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
HZ	Hertz
Hz	Hertz
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IAF	Intrinsic alpha frequency derived from EEG
ICD	International Classification of Diseases
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions For Use
IOM	Institute of Medicine
IRB	Institutional Review Board
iTBS	intermittent Theta burst stimulation
ITP	Intelligent Temperature Prediction
ITT	Intent to Treat analysis population
LASSO	least absolute shrinkage and selection operator
LEC-5	Life Events Checklist for DSM-5
LPFC	left prefrontal cortex
MAOI	monoamine oxidase inhibitor
MAR	missing at random
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Affairs
MeRT^{SM}	Biometrics-guided Magnetic EEG Resonance Therapy
MHI	Minor head injury
MINI	Mini-International Neuropsychiatric Interview (Screen and Standard)
MoP	Manual of Procedures
MM	Medical Monitor
MRI	Magnetic resonance imaging
MT	Motor Threshold
mTBI	Mild traumatic brain injury
NDRI	Norepinephrine-dopamine reuptake inhibitor
OCD	Obsessive-Compulsive Disorder
OSHA	Occupational Safety and Health Administration
OSU-TBI-ID	Ohio State University TBI Identification Questionnaire
PCL-5	PTSD Checklist – 5 (DSM V compatible revision)
PHI	Protected Health Information
PHQ-9	Personal Health Questionnaire Depression Scale (9 item)
PI	Principal Investigator
PII	Personally Identifiable Information
PP	Per Protocol analysis population

PPCS	Persistent Post Concussive Symptoms
PPE	Personal protective equipment
PSQI	Pittsburgh Sleep Quality Index
PTSD	PostTraumatic Stress Disorder
q-EEG	Quantitative Electroencephalogram
RCT	Randomized controlled trial
rTMS	repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Screening Visit
SD	Standard Deviation
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOP	Standard operating procedure
Sponsor	FDA IDE Sponsor - Wave Neuroscience, Inc.
SSRI	Selective serotonin reuptake inhibitor
TBI	Traumatic brain injury
tACS	transcranial Alternating Current Stimulation
tDCS	transcranial Direct Current Stimulation
TE	Traumatic Experience
tES	transcranial Electric Stimulation
tMS	transcranial Magnetic Stimulation
TNS	Trigeminal Nerve Stimulation
tRNS	transcranial Random Noise Stimulation
UADE	Unanticipated Adverse Device Event
UP	Serious Unanticipated Problems
VR-36	Veterans RAND 36-Item Health Survey
WAVE	Wave Neuroscience, Inc. (FDA IDE Sponsor)
WHO	World Health Organization

INTRODUCTION AND RATIONALE

Post-Traumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that occurs in response to certain traumatic experiences (TE). The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines a TE for purposes of PTSD as exposure to - actual or threatened - death, serious injury or sexual violence. The exposure may be direct, or may be indirect (witnessing the event, learning of the event occurring to a loved one, or repetitive confrontation with aversive details of such an event – usually in the course of professional duties). PTSD is characterized by responding to the TE by persistently re-experiencing it, avoiding thoughts or reminders of it, having new negative thoughts or feelings, becoming more aroused and reactive, and experiencing distress or functional impairment (e.g., socially or professionally). To meet diagnostic criterion, the symptoms may not be due to medication, substance abuse, or other illness. The DSM-5 recognizes two specifications for this disorder, a delayed onset subgroup, where full diagnostic criteria are not met until 6 or more months after the TE, and a subgroup that experiences high levels of dissociation, either through depersonalization ("not happening to me") or derealization ("things are not real"). (American Psychiatric Association, 2013). Evidence for the existence of this highly symptomatic dissociative subgroup was buttressed by Wolf et. al. using latent class analysis, appearing to be highly specific to TEs involving sexual assault both in children and adults. (Wolf, et al., 2012)

PTSD was first recognized in the DSM-III in 1980, largely in response to political pressure on the mental health field to recognize the psychological effects of war observed in Vietnam and concentration camp survivors. Recognition paved the way for treatment of victims of TEs (Galatzer-Levy & Bryant, 2013) (Helzer, Robins, & McEvoy, 1987) rather than court-martialing them or ignoring their conditions. (Gersons & Carlier, 1992) The characterization of this disorder, both for diagnostic, treatment, and research purposes, has evolved significantly since it was first recognized as a separate phenomenon. This evolution culminated, in 2013, in significant changes between the DSM-IV and the DSM-5, which elevated by 8-fold the number of heterogeneous symptom combinations meeting diagnostic criterion. (Galatzer-Levy & Bryant, 2013) The changes are energetically criticized by some and defended by others. Hoge et al. level the criticism that the new definition disrupted the long chain of links, established through epidemiological, neurobiological, and treatment studies, that provided the foundation of current practice for patients with PTSD. (Hoge, et al., 2016) Galatzer-Levy and Bryant describe the DSM-5 classification of PTSD as nondescript and highly heterogeneous, while also opining that the DSM was never intended for research use, and that its usefulness for such purpose has only deteriorated with each DSM revision. (Galatzer-Levy & Bryant, 2013) On the other hand, Miller et al. report explorations of the DSM-5 schema support the DSM-5 symptom clusters. (Miller, et al., 2012) Additionally, Reiger et. al, report that DSM-5 PTSD has one of the highest test-retest reliabilities of any diagnosis (kappa=0.69, 95% CI [0.59-0.78]); for example, in the same cohort Alcohol Use Disorder, Major Depressive Disorder, Mild Traumatic Brain Injury, and Borderline Personality Disorder had test-retest kappa statistics of 0.40, 0.25, 0.36, and 0.34 respectively. (Reiger, et al., 2013)

The literature reports varying prevalence figures for a variety of reasons. First, the diagnostic criteria have been a moving target since the recognition of PTSD as a separate psychiatric

condition, including not just revisions of the Diagnostic Statistical Manual, but also changes to the alternative World Health Organization (WHO) classification scheme, the International Classification of Diseases (ICD). The ICD-10 (endorsed in 1990 by the 43rd World Health Assembly) and ICD-11 (released in 2018) have also represented revisions of diagnostic criteria. (Stein, et al., 2014) ICD revisions also include their companion research embodiments (ICD-R). In addition to the temporal challenges of case identification comparisons across the literature, resulting from revisions to classification schemes, there are multiple ways of either selecting or defining TE/symptom pairings used to make the diagnosis which lie outside of the simple pairing of a single qualifying event with a qualifying symptom menu. Methods include: (1) requiring symptom thresholds to be met in response to a single event, (2) requiring symptom thresholds to be met for one type of TE (e.g., sexual assault type, disaster type, combat, or warzone type, etc.), where one or more events in the same category, or type, could contribute to the symptoms (used by Kilpatrick et. al. as the "Same-Event" definition), and (3) requiring symptom thresholds to be met in response to a combination of more than one type of event (used by Kilpatrick et. al. as the "Composite-Event" definition). An additional challenge to synthesizing the literature is that where just one index TE or TE type is required for diagnosis, if an individual has experienced multiple qualifying TE/symptom pairings, a study may choose to focus only on one of these. This one TE/symptom pairing selected for study may, for example, be selected at random from all available pairings meeting diagnostic criterion or may be selected by the self-report of the participant as being the first or the worst. Finally, within each definition (Same-Event or Composite-Event), studies may report any of a number of PTSD time periods, e.g., Lifetime, Past 12 months, or Past 6 months. For example, Kilpatrick et. al. investigated all three of these time periods in a methodological study (Kilpatrick, et al., 2013).

The same concerns in literature synthesis are also issues in diagnostic eligibility criteria for interventional trials; where operationalization of the diagnosis requires selection from a menu that may be characterized as a multiplicative function of choices such as those exemplified above. Stein et. al. investigated the impact of using "narrow" versus "broad" approaches to qualifying PTSD diagnoses for study. (Stein, et al., 2014) The authors compared the overlap and exclusion of individuals meeting diagnostic criterion using the DSM-5, DSM-IV, ICD-11 and ICD-10 systems of classification in an international cohort of 29,936 respondents. The ICD-10 was judged to be the most inclusive and the DSM-IV the most exclusive. Only 1/3rd of all cases meeting criterion in one system also met criterion in the other 3 systems. Also, 1/3rd of cases met criterion in one system alone. The more striking result was that significantly elevated indicators of clinical significance were found even in cases meeting criterion for only one system. This caused the authors to recommend that cases be diagnosed as PTSD-positive if criterion is met for any one of these diagnostic systems.

There is disagreement as to the magnitude, and implications, of exclusion or inclusion of individuals in PTSD diagnosis depending on whether DSM-IV or DSM-5 criteria are used for assessment. Kilpatrick et al. indicated that national estimates of PTSD prevalence suggest that DSM-5 rates were about 1-2 % lower than DSM-IV for both lifetime and past-12-month diagnoses. (Kilpatrick, et al., 2013) Same-Event comparisons indicated that about 75% of persons who met DSM-IV criterion also met DSM-5 criterion and that 88% of persons who met DSM-5 criterion also met DSM-IV criterion. Differences were attributed to only a few reasons. When cases met criteria for DSM-IV but not DSM-5, this was attributed overwhelmingly to 2

factors: the DSM-5 exclusion of indirect exposure to non-violent deaths, and from failure to exhibit at least one active avoidance symptom. When cases met criteria for DSM-5 but not DSM-IV, this was attributed by the authors to either not meeting the DSM-IV avoidance/numbing criterion or not meeting the DSM-IV arousal criterion. The authors conclude that revision from DSM-IV to DSM-5 had minimal effect on PTSD prevalence among the US adult population in general.

Lifetime prevalence of PTSD is estimated at 5 to 8% of men and 10 to 14% of women, making it one of the most common psychiatric disorders. (Breslau, et al., 1991) (Kessler, et al., 1995) (Yehuda, et al., 2002) (Kilpatrick, et al., 2013) Breslau et.al. estimate that it affects 15-24% of people exposed to a traumatic event. (Bresslau, et al., 2001a) Yehuda et. al. report that 55% of rape victims develop PTSD. (Yehuda, et al., 2002) In addition, large numbers of service members develop PTSD following combat exposure. In a survey of members of the National Guard following combat in Iraq, 23.4% developed PTSD with some functional impairment, and 8.9% developed PTSD with serious functional impairment. (Thomas, et. al., 2010)

To explore the epidemiology of traumatic events, Kilpatrick et. al. studied a sample of 2953 U.S. adults recruited online who then completed an assessment using the National Stressful Events Survey, a structured self-administered survey. Of these, 89.7% reported exposure to at least one DSM-5 criterion TE type; where the modal number of such TE types experienced was 3 (mean=3.3, SD-2.32), and at least 30% of the sample experienced 6. In addition to the majority of participants reporting multiple events, many were exposed to more than one type of TE. Percentages reported were: (1) disaster 50.5%, (2) accident/fire 48.3%, (3) exposure to hazardous chemicals 16.7%, (4) combat or warzone exposure 7.8%, (5) physical or sexual assault 53.1%, (6) witnessed physical/sexual assault 33.2%, (7) witnessed dead bodies/parts unexpectedly 22.6%, (8) threat of injury to family or close friend due to violence/accident/disaster 32,4%, (9) death of family/close friend due to violence/accident/disaster 51.8%, and (10) work exposure 11.5%. The prevalence of sexual assault as a separate category was 29.7% overall, where women reported 42.4% and men reported 15.8% exposure. (Kilpatrick, et al., 2013) Benjet et al. reported international results of the World Mental Health Survey Consortium in a 24-country cohort of 68,894 adults where 29 types of TE and their interrelationships were examined. (Benjet, et al., 2016) This study also supports the observation that exposure to TEs is nearly omnipresent, and the majority of TE experiencers are exposed to multiple TEs. The authors indicate that further research is required to illuminate the mechanisms accounting for associations of prior TEs with subsequent TEs.

Kilpatrick et al. express the view that a simple single-event criterion for PTSD diagnosis is not realistic. Multiple TE exposures is the norm, with the probability of PTSD increasing with increased exposures; cumulative effects and bi-directional associations between PTSD and TE exposure are important to explore – and will have implications for treatment and for identification of risk factors. (Kilpatrick, et al., 2013) The picture that emerges is that interpretation of the response to any specific event requires referral to prior events, and interpretation of ongoing response to prior events requires referral to subsequent events. In regard to multiplicity of exposures, the effect of age of exposure cannot be disregarded. Felitti et al. (Felitti, et al., 1998) examined childhood exposures and found that for persons reporting any single category of childhood exposure, there was a median 80% probability of exposure to an

additional category of event, with a median 54.5% probability of exposure to 2 or more additional categories of exposure. Long-term health consequences (including the 10 leading causes of death and specific health conditions) were dose-dependently associated with multiplicity of exposure categories. (Felitti, et al., 1998) Thus, one could speculate that the research participant pool of persons with childhood index TEs generally will have a more complex PTSD picture, be less healthy, and potentially more refractory to intervention.

PTSD has a high association with other psychiatric comorbidities. In a study of members of the National Guard deployed to Iraq, PTSD was associated with higher impairment in social adjustment and lower quality of life than all other diagnoses in the survey, including depression, other forms of anxiety and alcohol abuse. (Kehle, et al., 2011) Civilians with PTSD also have a high risk of developing comorbid psychiatric disorders, including a 5.7 times higher risk of having a major depressive episode than the general population, 15.5 times greater risk of developing mania, and a 6 to 15 times higher risk of a suicide attempt. (Davidson, et al., 1991) (Kessler, R.C, 2000) Interestingly, the elevated risk of developing secondary psychiatric diagnoses disappears with the remission of PTSD symptoms. (Kessler, R.C, 2000) In addition, in patients with PTSD and comorbid substance abuse, treatment of PTSD improves symptoms of substance abuse, but treatment directed toward substance abuse does not appear to ameliorate PTSD symptoms. (Hien, et al., 2009)

Treatment for Posttraumatic Stress (PTSD)

Given the scope and disabling nature of PTSD, much work has been done to identify effective treatment options. The mainstay of pharmacologic treatment in PTSD is administration of selective serotonin reuptake inhibitors. (Stein & McAllister, 2009) Studied to a lesser extent were monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and atypical antipsychotics, olanzapine and risperidone, which also demonstrated some efficacy in treatment of symptoms. (Stein & McAllister, 2009) Finally, some studies have reported on the use of antiepileptic medications, including carbamazepine, with good effect. (Van Etten ML, et. al., 1998)

There also appears to be a role for psychotherapy in the management of PTSD. Two of the most-studied modalities are trauma-focused cognitive behavioral therapy (TFCBT) and eye-movement desensitization and reprocessing (EMDR). In clinical trials, TFCBT and EMDR are both effective in the management of PTSD. (Bisson J & Andrew M, 2007) Furthermore, efficacy is roughly similar to pharmacologic therapy, and some studies even suggest that psychotherapy is more effective than pharmacotherapy. (Van Etten ML, et. al., 1998)

The Institute of Medicine (IOM) in the United States, however, convened a study committee to assess efficacy of PTSD treatments. Their findings, reported in 2007, concluded that the evidence was inadequate to determine efficacy in the treatment of PTSD with the alpha-adrenergic blocker prazosin, anticonvulsants, the novel antipsychotics olanzapine and risperidone, benzodiazepines, MAOIs phenelzine and brofaromine, SSRIs, other antidepressants, and other drugs (e.g., naltrexone, cycloserine, or inositol). One committee member did not concur with the committee's consensus on two conclusions, arguing that there was suggestive evidence for the efficacy of SSRIs and novel antipsychotic medications. For behavioral

treatments the Committee indicated there was sufficient evidence to conclude that exposure therapy was efficacious in the treatment of PTSD; however, the evidence was inadequate to determine the efficacy of EMDR, cognitive restructuring, coping skills training, and psychotherapies provided in a group format. Furthermore, despite the above therapies, PTSD is relatively refractory to treatment, with 30% of patients having symptoms despite treatment at 10 years, and the data implicating specific brain regions is internally consistent and growing. (Bresslau, et al., 2001a) (Breslau, et al., 1991) (Kehle, et al., 2011)

Repetitive Transcranial Magnetic Stimulation (rTMS)

FDA has cleared rTMS for major depressive disorder. rTMS is a noninvasive method to cause depolarization or hyperpolarization of neurons in the brain. It uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field; this can cause activity in specific or general parts of the brain with minimal discomfort, allowing the functioning and interconnections of the brain to be studied. Most rTMS treatment protocols are carried out with unified stimulation parameters, such as dorsolateral left prefrontal cortex (DLPFC) stimulation for patients with major depressive disorder using a10 Hz repetitive pulse at 120% of motor threshold (MT), 5 days a week for 6 weeks. (See **Table 1** below) A variety of TMS protocols have been tested as a treatment tool for various neurological and psychiatric disorders including migraine, stroke, Parkinson's disease, dystonia, tinnitus, depression, and auditory hallucination. Mayer et al. concludes that some participants may derive long-term benefit from the rTMS course. (Mayer, Aviram, Walter, Levkovitz, & Bloch, 2012) However, there is a lack of clinical trials to show the safety and efficacy of rTMS in persons with PTSD.

The rTMS system to be used in this study has been shown to have an excellent safety profile, with nearly all adverse events being minor. In a review (Janicak, et al., 2008) of three rTMS studies involving 325 patients, no serious adverse event was reported that was due to the rTMS treatment. During acute treatment, the most common adverse event was headache, reported in 58.2% of active and 55.1% of sham groups. Headache was assessed by the study investigator as "severe" in 4.2% of active TMS and 5.1% of sham groups. Transient headache, which resolves spontaneously or with mild analgesics, is the most common adverse effect of rTMS in adults. Site pain was reported by 35.8% in active TMS group and 3.8% in the sham group. Pain was reported as "severe" in 6.1% of active and none in the sham. All other adverse events were very infrequent across all groups. The eTMS protocol is conducted at 50% MT, unlike the standard rTMS 10 Hz protocol, which is conducted at 120% MT. Reduction of % MT intensity reduces site pain. Intensity is reduced when using eTMS protocols when a participant indicates discomfort at the starting intensity of 50% MT. No serious adverse event occurred during the pilot phase of a sister trial to this trial (MeRT-005).

Regarding psychiatric side effects, Rossi et al. report that in comparison with safety data for MDD, data for other psychiatric disorders are less complete; however, there is no evidence of a clinically different AE or SAE profile in other disorders, including where rTMS is applied for co-morbid depressive syndromes. (Rossi, et al., 2020) High-frequency rTMS has been reported to induce manic switch and delusions in patients with depression. (Sakkas, et al., 2003) However, while treatment emergent mania has been reported by Xia et al. for both low and high frequency rTMS in patients with uni- and bipolar depression following stimulation of the left

prefrontal cortex, the overall rate (13 cases) over 53 randomized controlled studies in depression appears to be not only low (0.84% versus 0.73% mania for active versus sham treatment, respectively), but even below natural switch rates in patients with bipolar disorders receiving mood stabilizers (2.3 – 3.45%). (Xia, et al., 2008) (Rossi, et al., 2020) Sub-manic symptoms of onset or worsening of insomnia, agitation, or anxiety are not uncommon among depressed patients receiving high-frequency rTMS in naturalistic settings. (Phillip, et al., 2015) Participants with MDD or bi-polar psychiatric disorders are excluded from the MERT-005-B study. While induced psychotic symptoms (Zwanzger reported one case of new delusional symptoms in a patient undergoing rTMS for MDD (Zwanzger, Robin, Keck, Rupprecht, & Padberg, 2002)), agitation, anxiety, insomnia and suicidal ideation have been reported (Janicak, et al., 2008) , Rossi et al. state that it is unknown whether such AEs are more frequent during rTMS compared to the natural course of the underlying psychiatric conditions. (Rossi, et al., 2020) They note that neither psychotic symptoms nor suicidal ideation have been described in normal subjects during or after rTMS and that there exists some evidence for an anti-suicidal effect of rTMS in MDD. (George, et al., 2014)

The 2020 safety recommendations are based almost entirely on large sham-controlled RCTs. The recommendation related to psychiatric AEs is that psychiatric patients undergoing rTMS should be "clearly informed about the risk of psychiatric side effects which are not uncommon but relatively minor in severity." Rossi et al. concluded that these psychiatric SAEs occurred at a rate between 1% and 5%, depending on the event type, but their occurrence did not clearly differ between the active and sham treatment groups. (Rossi, et al., 2020) The authors provided a table of the 7 RCTs that were included in their supplemental analyses. Only 6 of these trials compared rTMS to sham, while 1 was a head-to-head comparison of rTMS with intermittent theta-burst stimulation – iTBS. Additionally, 1 trial used dTMS (deep Transcranial Magnetic Stimulation) at 18 Hz. Of the remaining 5 trials that are closest comparators to the stimulation parameters of the eTMS protocol, all were conducted at 110% - 120% MT) as opposed to the eTMS protocol, which is conducted at a significantly lower intensity of 50% MT). Three of these trials were for MDD, 1 for negative symptoms of schizophrenia, and 1 for treatment resistant MDD. For these 5 trials psychiatric AE and SAE are summarized below in **Table 1**, as given in the supplemental materials to the 2020 safety recommendations. (Rossi, et al., 2020). These materials are consistent with the observation that when researching with psychiatric populations there will be psychiatric AEs and SAEs, but in this group of trials these do not appear to be related to active stimulation and appear to be, instead, a phenomenon related to the population characteristics.

Table 1
Psychiatric side-effects reported in RCTs relied upon for 2020 safety recommendations

Authors / indication	# subjects Active/Sham	AE Active # / %	AE Sham # / %	SAE Active # / %	SAE Sham # / %
O'Reardon/ MDD[1]	169/158	None	None	• Suicidality 1(0.6%) • Depression 1(0.6%) • Suicide gesture 0(0%) • >HAMD suicidality 1(0.6%)	• Suicidality 3(1.9%) • Depression 3(1.9%) • Suicide gesture 1(<1%) • >HAMD suicidality 10(6.3%)
Herwig / MDD[2]	62/65	None	None	None	None
George / MDD[3]	92/98	Worsening of depression/anxiety 6(7%)	Worsening of depression/anxiety 8(8%)	None	Paranoid ideation 1(1%)
Wobrock / Negative symptoms schizophrenia[4]	76/81	Psychotic ideation 1(1.3%)	Psychotic ideation 1(1.2%)	• Suicidality 1(1.3%) • Deterioration in symptoms 1(1.3%)	• Suicidality 2(2.4%) • Deterioration in symptoms 0(0%)
Yesavage / Tx resistant MDD[5]	81/83	None	None	Suicidal ideation 3(3.7%)	Suicidal ideation 4(4.8%)

Regarding non-psychiatric adverse events, severe adverse events associated with rTMS have rarely been reported and most adverse events reported were found to be mild. Seizure was the most serious adverse event. In 2009 Rossi et al. reported that high frequency rTMS has a possible 1.4% crude risk estimate in epileptic patients, and less than 1% in normals; reporting that over a 9-year period there were 4 cases of accidental seizures in studies using treatment parameters outside the 1998 safety guidelines – where 3 of the 4 events occurred in patients taking pro-epileptogenic medications or following sleep-deprivation, and where 1 of the 4 cases may have represented a non-epileptic event. (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009) One analysis (Loo, McFarquhar, & Mitchell, 2008) reported that as of 2008, there had been 12 case reports of seizures during rTMS in subjects who were healthy, depressed, or had a disorder not known to increase seizure risk. In all of these cases, stimulation was given near or above the suggested safety guidelines. (Wasserman, 1998)

Hundreds of thousands of TMS treatments have been conducted since the 2009 safety guidelines were published. (Rossi, et al., 2020) (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009) Rossi et al. report that at present the seizure risk is known to be extremely rare, but the precise risk is unknown. It was estimated by Lerner et al. (2019) via a survey of laboratories and clinics that conduct TMS. (Lerner, Wassermann, & Tamir, 2019) Lerner et al. agree that risk of seizure is extremely low, reporting from an

[1] (O'Reardon, et al., 2007)
[2] (Herwig, et al., 2007)
[3] (George, et al., 2010)
[4] (Wobrock, et al., 2015)
[5] (Yesavage, et al., 2018)

estimated 318,560 TMS sessions with various characteristics (low/high frequency, waveform and burst patterns, single/paired pulse versus rTMS, placement of coil, coil design, whether operating outside 2009 safety guidelines – referred to above as elevated protocol risk - and whether subjects had underlying conditions – referred to above as inherent subject factor risks). Of the 25 seizures described by Lerner et al. (2019) only 5 occurred associated with stimulation of the DLPFC during high frequency (>1 Hz) stimulation. Additionally, all 5 of these events occurred at frequencies at or above 15 Hz (1 at 15, 3 at 18 and 1 at 20 Hz). (eTMS-001 stimulation protocol has a ceiling of 13 Hz, but very rarely achieves even this frequency for individualized treatment protocols.) Seizure was most associated with stimulation of the motor cortex. Also, observed risk associated with use of figure-8 coils (which are used in the eTMS-001 protocol) was lower than for double cone or H-coils.[6].

Rossi et al. distinguish between theoretically possible types of TMS-induced seizures: (1) seizure during or seconds after trains of rTMS, and (2) temporally displaced seizures potentiated by generalized modulation of cortical excitability ("kindling effect"). The authors report that while the former has been observed that no evidence exists that kindling has ever occurred, i.e., it is theoretical only, stating that "… there is no solid evidence for kindling in humans in any situation." Also, worth noting, it is advised to be aware that a convulsive syncope may be misinterpreted as a seizure – which could be mediated by emotional stress or pain, dehydration, bradycardia or use of medications that cause orthostatic hypotension or reduce cardiac output. A myoclonic jerk observed during syncope is not usually characterized by the confusion and disorientation of a post-ictal state, nor are tongue-biting, incontinence, oral frothing or vomiting expected. Syncope may be managed by head-lowering, hydration, skin-cooling and emotional reassurance. (Rossi, et al., 2020)

Risk factors for TMS-provoked seizures were reviewed, and while Rossi et al. do not regard the presence of one, or even more than one, of these factors to be a contraindication to TMS, they recommend additional precautions for TMS subjects who display them, including potential postponement of the TMS session if multiple transient factors are present concurrently. It should be noted that Rossi et al. comment that these potentially seizure-lowering risk factors are theoretical – not having been seen in clinical practice. These include neuropsychiatric conditions bearing a higher risk for developing seizures, such as MDD (especially if intercurrent with dementia or recent stroke, underweight, current smoking, alcoholism, drug abuse, and concurrent use of cephalosporins and antiarrhythmics – especially propranolol) schizophrenia, autism, bipolar disorder and alcohol abuse. However, prior to every treatment, participant status is assessed – including vital signs, general health status, adverse events, recent sleep deprivation, alcohol consumption and medication changes. Additionally, Rossi et al. recommend neurophysiological monitoring for signs of increased cortical excitation (observation during stimulation for muscle twitching). (Rossi, et al., 2020)

[6] However, the relatively low number of sessions with these latter coil types coupled with the presence of underlying subject conditions made conclusions about coil type preliminary.

rTMS Safety and Efficacy with Concomitant Medications

In clinical practice, rTMS is generally administered in conjunction with ongoing medication and several studies have confirmed rTMS effectiveness used in tandem with antidepressants or as an initial boost at the outset of antidepressant treatment. (Hunter, et al., 2019;9;e01275) Experimental pharmaco-TMS-EEG studies in single or paired-pulse paradigms demonstrate effects of CNS drugs on measures of cortical excitability, connectivity, and plasticity (Ziemann, TMS and drugs, 2004); the therapeutic effects of rTMS are thought to be the result of long-term potentiation or long-term depression effects in brain circuits. (Kobayashi, et al., 2017) (Ziemann, et al., 2015) Thus, similar mechanisms of action are posited for rTMS and CNS medications. Recent publications have addressed the safety and efficacy issues associated with the use of concomitant medications during the course of rTMS treatment. (Hunter, et al., 2019;9;e01275)

A 2016 consensus indicates that TMS therapy can be administered both with and without antidepressant or other psychotropic medications. (Perera, et al., 2016) In 2018, McClintock et al. advised caution in administering rTMS to persons taking medications that may lower seizure threshold, or following a decrease or discontinuation of antiepileptics, benzodiazepines or other anticonvulsants. (McClintock, et al., 2018) Partially contradicting the McClintock caution (specifically the blanket caution for medications that lower threshold), the 2009 safety guidelines (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009), revised in 2020 (Rossi, et al., 2020), represent a sea-change regarding views on the concurrent use of psychoactive concomitant medications and medications known to lower seizure threshold. Whereas the 2009 safety guidelines advised caution in the application of TMS in persons taking medications known to lower seizure threshold, the consensus group states that **"the currently available data showing low seizure rate no longer support this recommendation."** They refer to this as a "theoretical risk" that has not been substantiated. Instead, the group recommends documentation of concurrent intake of drugs and other potentially seizure threshold lowering factors (such as sleep deprivation, infection, alcohol consumption) during TMS application and systematic capture/reporting of side effect data. The authors state, "We recommend that vigilance is warranted if rTMS is applied in patients receiving concomitant pharmacotherapy with medication that has pro-convulsant properties, although no additional risk has been documented to date." (Rossi, et al., 2020)

Noting a paucity of efficacy data associating standard medication classes with rTMS treatment outcome, Hunter et al. explored the clinical relationship in depression studies of a wider range of concomitant medications to rTMS, including SSRI, SNRI, TCA, MAOI, atypical antidepressants, atypical antipsychotics, typical antipsychotics, anti-epileptics, benzodiazepine, quasi-benzodiazepines, psychostimulants, lithium, and 'other' (amlodipine, baclofen, buspirone, clonidine, ephedrine, prazosin, propranolol, tizanidine, and verapamil). (Hunter, et al., 2019;9;e01275) In the 181-patient sample over 30% were taking medications during acute rTMS treatment for depression in the following non-exclusive categories: SSRI, atypical antidepressants, atypical antipsychotics, anti-epileptics, benzodiazepines, and psychostimulants. Only benzodiazepines and psychostimulants were statistically significantly predictive of 2-week clinical outcome of rTMS - benzodiazepines depressed responsiveness and psychostimulants enhanced responsiveness. No other medication categories even approached statistical significance (p-values ranged from 0.47 to 0.92 for other categories). Considering a response

criterion of 50% improvement in the IDS-SR30 total score at week 6, the response rate was lower in benzodiazepine users versus non-users (16.4% vs. 35.5%, p = 0.008), and higher in psychostimulant users versus non-users (39.2% vs. 22.0%, p = 0.02). Supplemental analyses indicated that a broader group of GABA agonists which included benzodiazepines (but also eszopiclone and zolpidem – Lunesta and Ambien, respectively – which the authors dubbed 'quasi-benzodiazepines' or QBDZ) was associated with a poorer 6-week outcome.

rTMS safety and efficacy with accelerated treatment

Accelerated rTMS involves administering rTMS more than one session per day. The purpose of accelerated rTMS is to reduce treatment length and improve response time. Recently, FDA cleared an accelerated rTMS protocol for treatment of major depression. The Stanford Neuromodulation Therapy (SNT) protocol consists of five days of intermittent theta burst stimulation (iTBS) administered at 10 sessions per day (Cole, et al., 2022). Additional evidence suggests that improvement in depressive symptoms may be achieved using accelerated rTMS (Holtzheimer, et al., 2010) (Baeken, et al., 2013) (George, et al., 2014) (Modirrousta, Meek, & Wikstrom, 2018). The side effect profile for accelerated rTMS has been shown to be similar to once-daily rTMS, with the most common being headache (28.4%), fatigue (8.6%), and pain/discomfort at the stimulation site (8.3) (Caulfield, Fleischmann, George, & McTeague, 2022). In addition, literature suggests that accelerated rTMS has similar minimal risk of seizure compared to once-daily rTMS, and does not increase the number of serious adverse events. It has been shown that treatment duration, in number of days required, is a factor in compliance to clinical trial protocols (Jin, Sklar, Oh, & Li, 2008). Although the preponderance of existing data in support of Accelerated rTMS is directed at patients with Major depression, the safety and efficacy profiles of rTMS are similar between Major Depression and PTSD populations (Philip, Doherty, Faucher, Aiken, & Wout-Frank, 2022). By using twice-a-day sessions, the number of treatment days is reduced, lowering the burden on the participant, and increasing the likelihood of compliance to the protocol.

Electroencephalogram (EEG) personalized Transcranial Magnetic Stimulation (eTMS)

The Sponsor of eTMS-PTSD-001 has developed a personalized biometrics-guided protocol known as Electroencephalogram (EEG) personalized Transcranial Magnetic Stimulation (eTMS). The protocol has also been referred to as MeRT. The eTMS protocol is tailored specifically to each person's EEG intrinsic alpha frequency (IAF). If an IAF from the EEG cannot be found, the participant will be excluded from the study.

The location of stimulation will be fixed at Fz (Frontal Midline as per the 10/20 system). Electroencephalogram (EEG) is a gross measure of brain electrical activity from the scalp. Amplitude of a given activity reflects the degree of neuronal synchronization underneath the recording lead. The relative magnitude distribution among different frequency bands reflects the brain status, whether in sleep, relaxation, or vigilance. In addition to epileptic spikes found in seizure patients, individuals with different mental disorders often have different patterns in their EEG profile. The eTMS treatment protocol is based on the physics principle of resonance and is intended to restore the physiological rhythm.

While most rTMS protocols call for stimulation at 120% of motor threshold (MT), eTMS stimulation intensity is generally set at 50% or less of motor threshold - and will be set at 50% MT in the trial. If a participant reports discomfort, intensity will be reduced according to a written protocol. Sponsor's protocols follow the medical consensus on maximum safe exposure as indicated in the safety review by Rossi et al. (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009). See **Table 2**, below, comparing the characteristics of eTMS treatment with recommended protocols for cleared rTMS devices.

Preliminary Data

Stimulation will be at a fixed location at the midline on the frontal cortex (Fz). The prefrontal cortex, which is close to the Fz location, is a common stimulation site for rTMS treatment, and has shown to have no increase in any adverse event. The rTMS treatment parameters for the devices that were cleared at the time of initiation of this trial by FDA for treatment of Major Depressive Disorder (MDD) target this region (Tonica/MagVenture MagVita, Neuronetics NeuroStar, Brainsway DTMS, and MagStim Rapid2). The site is relatively far from the occipital lobe, cerebellum, and other regions that might affect vision or autonomic function. The Sponsor has treated over 5,000 patients off-label at the Fz position without a serious adverse event. Adverse events such as seizure or site pain are at, or below, those reported in rTMS studies. More than 20 510(k) clearances of *de novo* petitions have been granted by FDA for rTMS systems since that time, including a *de novo* and a clearance for Obsessive Compulsive Disorder. (See **Table 2** below) These clearances have largely been for a variety of changes to the initial devices (addition or deletion of accessories or software, or coil capabilities) or their treatment protocols (mostly reductions in intertrain intervals or the introduction of a novel rhythm capability called intermittent Theta burst stimulation), although several new manufacturers also have received clearances.

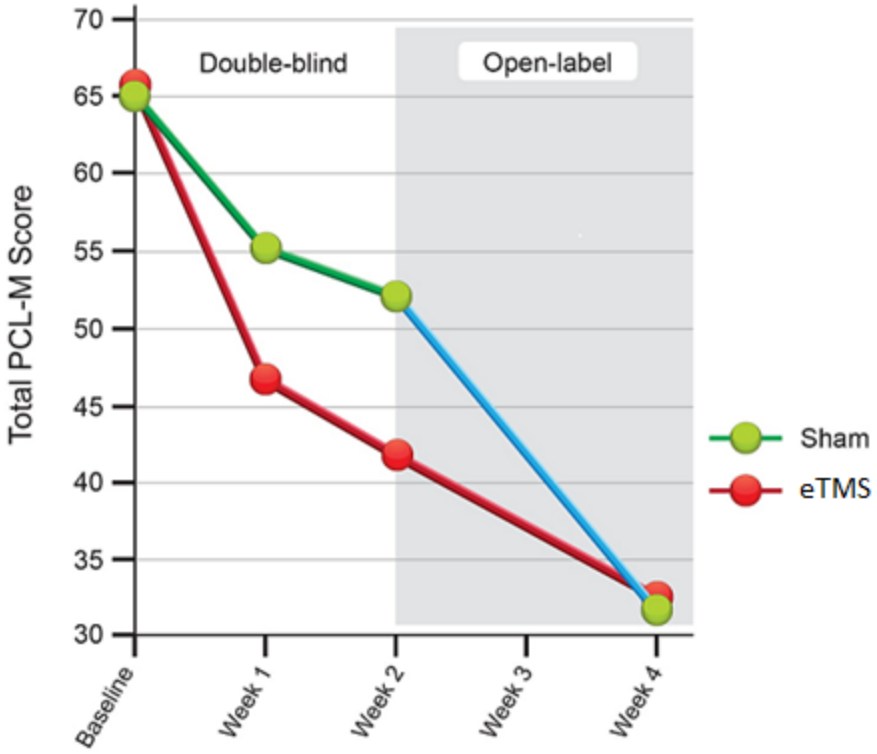
In a prospective, open-label trial, Sponsor's predecessor corporation successfully identified and treated 21 patients with PTSD, using quantitative EEG/ECG-guided transcranial magnetic stimulation. Analysis showed that 100% of patients who completed a 2 week or longer course of treatment responded with an average 61% reduction in symptom severity as measured by PCL-M (Taghva, et al., 2015). Most participants who experienced, at the screening visit, sleeping difficulty, memory loss, attention deficit, or headache reported significant improvement in these symptoms following MeRT treatment.

A randomized, double-blind sham-controlled trial of veterans with PTSD was conducted by Sponsor's predecessor. Data from the preliminary dataset are available. Eighty-six (86) participants were randomized to MeRT or Sham MeRT. After completion of phase 1, the randomized, blinded portion of the study, participants continued to be treated, unblinded, with active MeRT for an additional two weeks in phase 2. The Per Protocol (PP) data analysis set consisted of 80 participants; 6 (3 Sham MeRT-treated, 3 MeRT-treated) were removed from the intent to treat analysis population for protocol deviations, such as incomplete study treatment or data collection, or medical issues. All removals were determined prior to unblinding the decision makers. As displayed in **Figure 1**, below, the MeRT-treated group showed a statistically significantly higher therapeutic effect than the Sham-treated group in the double-blind phase. Symptom reduction as measured by mean percentage PCL-M score reduction of 46% in the

MeRT-treated group was significantly greater than 30% reduction in the Sham MeRT-treated group at week 2 (2-tailed t-test; p = 0.017). The proportion of participants who had a 30% or greater reduction from the Screening Visit to week 2 was significantly different in the MeRT-treated versus Sham MeRT-treated group (74.5% versus 40%, respectively, 2-tailed z-test of proportions p=0.007).

In the unblinded phase, both groups continued to show clinical improvement. The PCL-M reductions, and percentage reductions in the two groups were almost identical at week 4 (Sham=31.7, MeRT=32.5, and Sham=63.9%, MeRT=66.8%; respectively). The average PCL-M score percentage reduction over the 4-week treatment for the aggregate of both groups was 65.4%.

Figure 1: PTSD Symptom Reduction following eTMS versus Sham eTMS



STUDY OBJECTIVE

The primary objective of the eTMS-PTSD-001 trial is to evaluate the safety and efficacy of electroencephalogram (EEG) personalized transcranial magnetic stimulation (eTMS) for the treatment of Post-Traumatic Stress Disorder (PTSD).

STUDY DESIGN

eTMS-PTSD-001 comprises two stages. Stage 1 is an open-label safety pilot study with a recruitment goal of 30 subjects, with 26 completers. Stage 1 is intended to evaluate the safety aspects of eTMS in the target population. A maximum of 400 individuals will be screened in order to achieve the recruitment goal. The total number of days from the first participant enrolled to the last enrolled participant treated will be approximately 7 months. Following Stage 1, a recommendation will be made by the DSMB as to whether the safety results warrant proceeding to Stage 2. Stage 2 is a prospective randomized, double-blind, sham-controlled trial of eTMS, with an open-label period for sham-assigned participants following the randomized portion. The recruitment goal for Stage 2 is 140 subjects, with 126 completers (90%). Participants will be either Veterans or First Responders (e.g., emergency medical service provider, firefighter, or any other emergency response personnel), between 22-65 years of age. Participants may be male or female of any racial/ethnic background who meet the eligibility criteria. Participants will be recruited from the general public, and from veterans and first responder organizations.

Stage 1

Stage 1 consists of an open-label safety pilot study. The primary outcome for Stage 1 will be the incidence, severity, relatedness, type, subsequent treatment/intervention required, and resolution status of adverse events during the study. A total of 30 participants will be recruited for this stage.

Following Stage 1 completion, the Data and Safety Monitoring Board (DSMB) will meet to recommend whether to continue to Stage 2. Upon approval from the DSMB, a supplementary IDE will be submitted to FDA for approval to proceed to Stage 2.

Stage 2

Stage 2 is intended to establish the efficacy and safety of eTMS for treatment of PTSD in the target population. The primary outcome of the trial for Stage 2 is reduction in symptoms of PTSD as calculated by arithmetic reduction in the PCL-5 assessment. A total of 140 participants will be randomized for this Stage.

All subjects who finish BL assessments and meet inclusion/exclusion criteria will be randomized into one of two groups, "Active eTMS" and "Sham eTMS", in a 1:1 ratio, stratified by clinic. Stage 2 will consist of a randomized period and an open-label period. During the randomized period, the Active eTMS group will receive Active eTMS and the Sham eTMS group will receive Sham eTMS twice per day, with 20 total treatments delivered in a 2 or 3-week period. Following the randomized period of the study, all Sham eTMS subjects will have the option of participating in the open-label portion of the study. Those who choose to participate in open-label treatment will receive 20 Active eTMS sessions, twice per day, which must be completed in a period of 21 calendar days.

All groups will undergo an assessment of symptoms at baseline, before Week 6 (F1), and then again at the end of Week 10 (F2). The primary efficacy endpoint, and outcome time point, is

change in Post-Traumatic Stress Disorder symptoms between the Baseline (BL) and the first follow-up (F1). The primary efficacy outcome will be measured using the PCL-5. Safety outcomes will be measured by recording adverse events, incidence and type.

PARTICIPANT POPULATION

The enrollment goal for the combined two stages of the study is 170 participants of any gender or ethnic background, age 22-65 years, with Post-Traumatic Stress Disorder. Thirty (30) participants will be part of Stage 1 and be provided with open-label treatment to evaluate safety of eTMS in this population. 140 participants will be part of Stage 2, randomized to either active or sham eTMS, in a 1:1 allocation ratio, stratified by recruitment site. Participants randomized to sham eTMS in Stage 2 will receive an additional series of open-label active eTMS following the randomized portion of Stage 2.

Inclusion Criteria

Participants must meet all following inclusion criteria to qualify for enrollment into the study:

1. Willing and able to consent to participate in the study via signed Informed Consent
2. Age 22 – 65 years
3. Provisional diagnosis of PTSD according to Veterans Administration PCL-5 rubric fulfillment AND cutpoint score of 31 or above
4. Positive identification as either a Veteran, or First Responder (e.g., emergency medical service provider, firefighter, or any other emergency response personnel)

Exclusion Criteria

Participants will be excluded from study participation if one or more of the following exclusion criteria apply:

1. Uncontrolled medical, psychological or neurological conditions including, but not limited to:
    a. Uncontrolled psychosis or mania
    b. Uncontrolled seizure disorder or EEG abnormalities that indicate risk of seizure, i.e., epileptiform discharges during the EEG recording
    c. Uncontrolled cardiac, pulmonary, or endocrine disorder (e.g., diabetes)
    d. Acute pain or illness
    e. Active, untreated addiction to prescription drugs, alcohol or illicit substances* (not including THC/CBD, which is available in many states under medical prescription or for recreational use)
    f. Clinically significant medical condition or abnormality that in the Investigator's judgment might pose a potential safety risk to the subject or limit the interpretation of the trial results
2. Pregnant, or female unwilling to use effective birth control during the course of the trial (unless cleared for participation by an obstetrician/gynecologist)
3. Presence of aneurysm clips or coils, cochlear or ocular implant, cortical epidural stimulator, deep brain stimulator, pacemaker or defibrillator, retained intracranial metal

foreign body (bullets, shrapnel – excluding titanium and oral implants), steel stents or shunts, active vagal nerve stimulator, ventriculoperitoneal (VP) shunt
4. Past exposure to metal fragments, permanent piercings, and/or other possible metal sources in the head and neck
5. Unwilling or unable to adhere to the study treatment, data collection schedule, or study procedures, or any condition, that in the judgment of the Investigator might prevent the participant from completing the study
6. Inability to calculate the EEG intrinsic alpha frequency at Baseline
7. Current participation in any interventional research protocol
8. History of any type of ECT or rTMS
9. History of intracranial lesion or increased intracranial pressure
10. History of ischemic or hemorrhagic stroke
11. History of other neurologic conditions with associated cerebral damage
12. Family history of epilepsy or seizure in a first degree relative
13. An elevated risk of suicide or violence to others
14. A personal history of epilepsy or seizure
15. Clinically significant medical illness, psychopathology, or other condition, that in the judgment of the Investigator might pose a potential safety risk to the participant or limit the interpretation of study results

Suicidality and Harm to Others

High suicide risk individuals will be ineligible as well as those with clinically significant psychopathology or other psychiatric disorders that may pose a safety threat to the participant. The U.S. Army Medical Command (United States Army Medical Command, 2014) screens individuals discharged from emergency departments and inpatient units. MEDCOM uses the Columbia Suicide Severity Rating Scale (C-SSRS) with triage points. The 6-item scale identifies ascending levels of risk, as subsequent items from 1 to 6 are endorsed as having occurred within the past month. Item 6 is related to actual preparatory activities, and it asks for additional time frame specificity, such as 1 week, 1 month, 3 months, and 1 year.

We will implement a suicide risk reduction plan for individuals found ineligible to participate in eTMS-PTSD-001 by virtue of suicidal ideation above a certain risk level. It is anticipated that some potential participants will have a measure of suicide risk, but these are some of the individuals for whom MeRT should be tested for benefit. It is therefore inappropriate to declare all persons with suicidal ideation ineligible. A triage plan tailored to the eTMS-PTSD-001will be implemented that considers the competing considerations of allowing enrollment of individuals with some measure of suicidal ideation yet excluding individuals at higher levels of risk, who require immediate intervention.

At the BL Visit, potential participants will be administered the C-SSRS. The C-SSRS incorporates findings from suicide literature and has prospective data that validates the scale's ability to identify risk probability ranges for potential future suicidal behaviors. The first 5 items of the scale divides responses according to whether the participant endorses an item within the past month or at a more remote time in the past. Items 1 and 2 refer to passive suicidal ideation

without intent or plan. Item 3 refers to whether a method has been considered, but intent is absent.

Individuals who endorse items 4 or 5 within the past month, i.e., intent without plan, or intent with plan, respectively, will be ineligible to participate in eTMS-PTSD-001. Item 6, referring to actual preparatory or attempt activities, asks for a time frame for those activities. If an individual endorses item 6 within the past 6 months for preparatory activities that did not constitute an attempt, they also will be ineligible. If the individual endorses item 6 with an attempt occurring at any time in the past, they will be ineligible.

When an individual is found to be ineligible secondary to responses suggesting likelihood of self-harm, or expression of homicidal feelings toward inappropriate targets (e.g., if active military personnel express homicidal feelings toward individuals who are not enemies of the United States), screening will be terminated. All individuals deemed ineligible due to suicidal ideation, whether deemed at imminent risk or not, will be given resource information that explains where resources and assistance may be obtained. Individuals deemed ineligible on the basis of suicide risk or homicidal ideation are permanently ineligible for the trial.

When an individual is screened and meets the exclusion criteria for suicidal risk or expresses inappropriate homicidal intent, the Medical Monitor, Site PI or his/her medically qualified designee will be contacted. If the Medical Monitor, Site PI/designee deems the individual to be at imminent risk, an emergency medical service or the police will be called to transport that individual to the nearest civilian hospital, or to the appropriate military hospital as appropriate to military status. If the individual is not deemed to be at imminent risk, the individual will be advised to call or present to the closest Emergency Department, call 911, or the appropriate crisis hotline.

STUDY TREATMENTS

Equipment

All equipment used to evaluate and treat participants in the trial are either FDA-cleared or are exempt from clearance and listed with FDA. The MagPro family of magnetic stimulators are manufactured by Tonica Electronik, A/S, a sister company of MagVenture. Specific application of the device can be arranged by selection of multiple coil configurations, varied in stimulation area (<1" to >10"), rate (single pulse to <30/sec for the R30 stimulator used in the eTMS-PTSD-001 trial), and output intensity (up to 3.9 tesla) depending on the triggering program and type of coils.

For Stage 1 and for the open-label portion of Stage 2 of the eTMS-PTSD-001 trial, a standard figure 8 stimulation coil is used. The coil is held against the head by a mechanical arm.

For Stage 2 randomized portion, a special setup will be used to maintain participant blinding while ensuring that no magnetic field stimulation is administered.

During EEG recording procedures and treatment procedures, the participant and technician will be on opposite sides of a temporary barrier that will allow the technician to keep eyes on both the participant and the equipment at the same time. All necessary cabling will be run in order to allow the stimulator along with all equipment controls and displays to be located on the technician's side of the barrier.

The coil (which will be on the participant's side of the barrier along with its positioning arm) will be positioned against the participant's head. The coil will be connected to the technician-side stimulator for active eTMS treatments but will not be connected to the stimulator for sham eTMS study treatments. A different coil will be connected to the stimulator for sham eTMS treatments and will be placed in a basket close by so that the participant will hear the discharge at their assigned eTMS stimulation frequency. The technician will initiate and end treatment sessions and will observe the stimulator for any error codes.

During the treatment, active-assigned participants will experience repetitive tapping over the stimulus area. Some may feel uncomfortable with the physical sensation on the scalp, or with the clicking noise made by the coil. If a participant experiences discomfort, the stimulus intensity may be reduced, and sponge mufflers may be given to block the noise. The subjective experience during sham eTMS treatment includes hearing a clicking noise from the active coil, which is attached to the stimulator, but hidden from view.

The MagPro R30 is FDA 510k-cleared (K061645), as are the additional members of the MagPro family (including the MagPro X100 (K091940)) under 21 CFR §882.1870 as Evoked Response Electrical Stimulators. The cleared indication is to stimulate peripheral nerves for diagnostic purposes; however, all components are also included in a cleared system (MagVita TMS System) where the clearance is for rTMS. The Cool-B65 coils are FDA-cleared under K071821. The MagVita TMS System, which uses the MagPro Stimulator family (MagPro R30, MagPro X100, and more recently MagPro R20), is cleared by FDA for Major Depressive Disorder (K150641).

Efficacy of eTMS treatment depends on the accuracy of EEG resonant frequency calculation. A standard quantitative EEG analysis routine will be carried out. A 19-channel EEG, placed according to international 10-20 montage, will be acquired using the WR19 System (manufacturer, Zeto, Inc., K17275). The device is a full-montage standard electroencephalograph indicated for use in a health care facility or clinical research environment to acquire, transmit, display and store primarily EEG signals. The Zeto also incorporates ECG capability.

Study treatment is implemented with stimulus parameters determined by the Sponsor's proprietary algorithm using input from EEG and ECG recordings that will be uploaded to its servers via internet. The stimulus parameters will be downloaded via internet to the MagVita device after EEG processing and individualized treatment parameter determination.

Data will be digitized at 500 points/sec during the A/D conversion and stored on computer hard disk. Once completed, the data will be uploaded to servers hosting Sponsor's proprietary algorithms for analysis. Raw data will be filtered to reject artifacts before quantitative analysis. A minimal period of 60-second artifact-free, resting EEG is necessary for analysis. An FFT routine with a 2,048-point window will be used to calculate the power density of each frequency for each channel to yield spectra with 0.125 Hz frequency resolution. A dominant EEG frequency in the band of 8 - 13 will be detected automatically from the power spectra. This highly individualized EEG resonant frequency will then be used to program the MagVita to deliver the required eTMS pulses. If minimal requirements for clean data are not met, then a new EEG will be requested by Sponsor's software.

Blinding

This study is randomized, double-blind, and sham-controlled. It is not triple-blind, i.e., the treating technician/coordinator will know the participant's study assignment. Participants, Investigators and assessors will be blind to treatment assignment. Specifically, no primary or secondary outcome data will be collected by, or seen by, the unblinded technician/coordinator. Additionally, exploratory outcomes will be self-administered with electronic data capture, and also will not be seen or collected by unblinded personnel. The technician/coordinator will have reduced contact with participants in comparison to Sponsor's previous eTMS clinical trials, due to increased remote data collection (also leading to reduced dwell time at the clinic), and barrier separation from technicians during as much of the EEG/ECG and treatment procedures as is physically possible.

Blinding challenges arise from visual, aural, and proprioceptive sources. Unless the connection of the coil assembly to the stimulator is hidden from the participant, the participant will know if the coil used is or is not properly engaged with the stimulator. The discharging coil head produces a clicking sound at the frequency of discharge that is audible to the participant. Additionally, the discharge of the coil head on the forehead is accompanied by a tapping sensation, sometimes strong enough to produce discomfort. The Test Phase of this trial relies on a combination of visual barriers and exclusion of persons who have in the past received any form of rTMS treatment to accomplish blinding of the participant.

Visual blinding is accomplished by concealing the stimulator end of the coil assembly. Two coils are attached to the stimulator, but only one of them is engaged properly with the stimulator so as to produce magnetic discharges at the coil head. The other is merely taped or tied in place for stability. The engaged coil is held to the forehead of active-assigned participants and the unengaged coil is held to the forehead of sham-assigned participants. The coil to be used with the participant is threaded through a barrier sufficient to hide whether the stimulator connection part of the assembly is engaged with the stimulator or merely tied down nearby.

When the active coil is held to the active-assigned participant's head, the participant experiences a clicking noise emanating from the coil in the vicinity of their forehead. When the sham coil is held to the sham-assigned participant's head, the participant experiences a clicking noise emanating from the active coil behind the barrier in the vicinity of the stimulator. Therefore, regardless of which coil is held to the participant's head, the participant experiences a clicking noise originating from the active coil. rTMS naïve individuals do not have any experience that would indicate whether the sound should be heard at the forehead or in the vicinity of the stimulator; therefore, both groups would be expected to conclude that they are receiving active treatment. Active treatment also causes a tapping sensation on the participant's forehead due to contraction of the muscles in the forehead. This sensation will be absent for participants in the sham eTMS assigned group. The participants in this trial are naïve to rTMS and eTMS treatment so that they will have no point of comparison regarding this sensation. The treating technicians are unavoidably unblinded.

The issue of blinding technology for rTMS trials with equipment using observable coils is sparse, and studies conducted using differing blinding strategies have conflicting efficacy outcomes, making it difficult to determine a winning study design. A recent clearance by FDA for rTMS to treat MDD (K173620) was based on a trial where both the participants and the treating technicians were unblinded – only the assessment staff were blinded to treatment assignment. (Blumberger & et. al., 2018) It underscores the difficulty of selecting a blinding strategy that FDA has accepted assessor-only blinded studies.

Study Treatment Parameters

The stimulus parameters for the algorithmically determined, individualized, active eTMS treatment will be downloaded to the MagVita for all participants.

Stimulation frequency for treatment will be individualized according to each participant's EEG. Stimulus rate is determined by the individual's intrinsic alpha EEG frequency. This biometric measure is highly variable from person to person. Active eTMS delivers an algorithmically determined resonant frequency via repetitive electromagnetic stimulation. The stimulus frequency range is constrained to vary between 8 and 13 Hz, thus the upper frequency range of eTMS stimulation is within the range of conventional rTMS already cleared by FDA, which is between 10 and 18 Hz. The frequency range more likely to precipitate seizure is the higher end of the range, not the lower end.

Stimulation intensity is chosen according to the participant's motor threshold. The eTMS treatment delivers subthreshold magnetic stimulation at 50% of motor threshold. Because the

intensity is subthreshold, it does not cause neuronal depolarization. FDA-cleared recommended rTMS intensity is supra-threshold, thus designed to cause neuronal depolarization, and is cleared to be used at 150% of the eTMS recommended intensity, i.e., 120% of motor threshold. Motor threshold is determined by the treatment technician before the first treatment visit according to a standardized procedure outlined in the study Manual of Procedures (MoP). MT determination is performed before the first treatment of each 5-week treatment period (i.e., Blinded and Open-label).

The stimulation dose is 5-seconds of repetitive stimulation, with an intertrain interval of 20 seconds, for a session duration of 15 minutes. The treatment regimen is 20 sessions performed twice per day over a 3-week period. If all 20 treatment sessions are not conducted in the allotted 21 calendar day period, additional treatments will not be conducted.

Open Label Treatment

In the randomized, blinded, Stage 2 of the trial, post-trial access to the active study treatment will be provided. For both ethical and recruitment purposes, there will be up to 20 additional treatments of open-label active eTMS treatment offered to participants who are part of the Sham eTMS Group who complete 75% of their assigned blinded treatment (15 treatments), unless the site PI in consultation with the Medical Monitor deem active treatment not to be in the best interests of the participant or of the study personnel (e.g., if the participant begins medications that lower seizure threshold, or experiences an adverse event such as a negative health or psychological event that would have excluded them from the blinded study).

Basis of Study Treatment Parameter Selection

Treatment with rTMS (repetitive transcranial magnetic stimulation) requires the specification of many treatment parameters. Within-session parameters that must be specified include stimulus waveform (square wave, triangle wave, sine wave), coil geometry (depth-focality tradeoff), field intensity, frequency of stimulation during the pulse train, duration of the pulse train, duration of the quiet period, number of pulse train-quiet period cycles in the treatment session. Course-of-treatment parameters that must be specified include the number of treatment sessions and the spacing of sessions.

As is the case with many forms of medical treatment, understanding of the mechanism of rTMS action is incomplete. A review by Leuchter, et al. (Leuchter, Cook, Jin, & Phillips, 2013) considered the mechanism of action in rTMS treatment of depression. The authors concluded that benefits of rTMS were tied to enhanced neuroplasticity and the resetting of corticothalamic pathways. While this assessment may provide a conceptual basis for an understanding, it does not provide quantitative specification of treatment parameters. This being the case, our best recourse was to review the prior clinical literature.

The greatest body of prior experience is in the treatment of depression. Most rTMS treatments for depression were carried out with standardized stimulation parameters, typically left dorsolateral prefrontal cortex using 10 Hz stimulation at 120% of motor threshold. The early cleared rTMS devices used this standard 10 Hz protocol – largely 37.5-minute sessions, 5 days

per week for 6 weeks, with 10 pulses per second in 4 second trains, with an intertrain interval of 26 seconds. This resulted in 3,000 pulses per session. One cleared device used 18 Hz stimulation at 120% of motor threshold 5 days per week for 4 weeks, with 18 pulses per second in 2 second trains, with an intertrain interval of 20 seconds – resulting in 1980 pulses per session. The number of total pulses per 15-minute session for this study is dependent upon the treatment pulse frequency. At a pulse frequency of 8 Hz, the total number of pulses is 1,340 per session. At 13 Hz, the total number of pulses increases to 2,340 per session.

Research has been directed to investigating individualized treatment parameters based on the pre-treatment EEG. This has been done in the treatment of schizophrenia (Jin, et al., 2006), (Jin, et al., 2012) and treatment of depression. (Jin & Phillips, 2014) Recent publications suggest that clinical response is highly sensitive to small differences between the treatment frequency and the intrinsic alpha frequency. Specifically, it has been observed, in clinical trials of rTMS for Major Depressive Disorder that neurostimulation appears to be more efficacious when the stimulation frequency is closest to the subject's IAF - with a quadratic relationship between clinical outcome and proximity of the 10 Hz stimulation that was delivered to the subject's IAF frequency. (Roelofs, et al., 2020) (Corlier, et al., 2019) The eTMS-PTSD-001 trial extends this work; it utilizes the pre-treatment EEG to specify treatment frequency at the intrinsic alpha frequency..

Comparison of eTMS Study Active Treatment Exposure with FDA-Cleared rTMS Treatments

Table 1, below, shows a side-by-side comparison of eTMS active treatment parameters and exposures with treatment regimens already recommended for use by FDA. The 4 earliest-cleared rTMS devices (those devices already cleared when the protocol for the eTMS-PTSD-001 trial was written): Neuronetics NeuroStar, Brainsway DTMS, MagStim Rapid2, and Tonica/MagVenture MagVita, along with accompanying 510k submission numbers, appear on rows 2 through 6. All but the Brainsway device were cleared for use with the standard 10 Hz protocol. Total number of pulses per session for eTMS are fewer than protocols for cleared standard 10 Hz treatment protocols (1440 pulses at 8Hz to 2340 pulses at 13Hz for eTMS, versus 3000 pulses at 10Hz for other protocols). The Brainsway DTMS System is an outlier from the other three devices in that its protocol uses fewer pulses per train, but at the higher frequency of 18Hz (instead of 40 pulse trains at 10 pulses per second for 4 seconds for the 10 Hz standard protocol, the Brainsway device protocol delivers 36 pulse trains at 18 pulses per second for 2 seconds). eTMS treatment uses a 20 second rest interval between pulse trains (similar to the 26 second rest intervals used in the standard 10 Hz protocols and 20 second rest intervals used in the Brainsway 18 Hz protocol).

The four cleared rTMS stimulation systems described above use rapidly alternating, or pulsed, magnetic fields to induce electrical currents in regions of the cerebral cortex by bringing a magnetic coil into contact with the head. These cleared devices use standardized treatment frequency and placement of stimulation. All are cleared for use in the prefrontal cortex. These systems are recommended for use at 150% higher amplitude of stimulation than used in the eTMS treatment protocols - 120% of motor threshold (i.e., suprathreshold stimulation) - versus 50% of motor threshold (i.e., subthreshold stimulation) for eTMS treatment protocols.

Comparative treatment regimens in terms of total number of sessions and length of total

treatment regimen are significantly less for eTMS versus standard 10 Hz protocols. eTMS uses 2 sessions/day, 5 days per week, for a total of 20 treatment sessions over a period of 3 weeks (allowing for missed treatment days). Tonica/MagVenture MagVita, Neuronetics NeuroStar, and MagStim Rapid2 use 5 sessions per week at 1 treatment per day, but continue for 6 weeks, for a total of 30 treatment sessions. Total exposure for eTMS is less than recommended treatment with already cleared rTMS devices in terms of intensity and total pulses for an entire course of treatment. Brainsway DTMS uses 20 sessions at 18 Hz over 4 weeks, but then includes a maintenance regimen of biweekly sessions for an additional 12 weeks.

Recently, there have been multiple 510k clearances (18) for rTMS treatment, and a successful *de novo* submission for rTMS adjunct treatment of Obsessive-Compulsive Disorder (OCD). Some of these clearances represent changes in the intertrain interval to create shorter treatment sessions (labeling changes allowing a reduction of the intertrain interval to as little as 11 seconds for devices that previously had protocols with fixed 26 second intertrain intervals). Two marketing approvals represent a fundamentally different stimulation rhythm profile called theta-burst TMS, one of which is intermittent Theta burst stimulation (iTBS). See (Huang, 2005); (Blumberger & et. al., 2018) Thus, during the past 4 years, manufacturers have begun to experiment with changes to some elements of the treatment protocol parameter space. FDA has responded by allowing marketing of devices using more varied frequencies, intertrain intervals, and treatment schedule regimens. The Blumberger et. al. study was pivotal to FDA clearance (K173620) of an iTBS protocol for the treatment of depression in 2018. (Caulfield K. A., 2020) However, as of 16 March 2020, personalized treatment protocols for rTMS based on patient-specific electrophysiological measures, have not been cleared or approved for any indication.

Table 2: Comparison of eTMS vs. rTMS Cleared Devices' Treatment Protocols

510K/ DEN#	DEVICE	COMPANY	CLEARANCE DATE	REGULATION/ PRODUCT CODE	INDICATION	MAGNETIC FIELD INTENSITY (%MT)	FREQUENCY (HZ)	TRAIN DURATION (SEC)	INTER- TRAIN INTERVAL (SEC)	# TRAINS	PULSES PER SESSION	SESSION DURATION (MIN)	TREATMENT SCHEDULE	TOTAL PULSES PER TREATMENT PROTOCOL
IDE	**eTMS** TRIAL USES MAGVITA TMS THERAPY SYSTEM DEVICE CLEARED IN K150641	TONICA ELEKTRONIK A/S	N/A	882.5805 / OBP	PTSD	80	8 - 13	5	20	36	1440@8HZ - 2340@13HZ	15	5/WK FOR 20 total sessions over 5 WKS	38,800@8HZ - 46,800@13HZ
DEN07003, K061053, K083538, K130233	NEUROSTAR TMS THERAPY SYSTEM MODEL 1.1	NEURONETICS INC.	10/7/2008, 3/23/2011, 12/16/2008, 4/30/2013	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K122288	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	1/7/2013	882.5805 / OBP	MDD	120	18	2	20	55	1980	20.2	5/WK FOR 4 WKS; THEN BIWEEKLY FOR 12 WKS	39600 +11880
K133408	NEUROSTAR TMS THERAPY SYSTEM	NEURONETICS INC.	3/28/2014	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K143531	RAPID2 THERAPY SYSTEM	MAGSTIM COMPANY LTD.	5/8/2015	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K150641	MAGVITA TMS THERAPY SYSTEM	TONICA ELEKTRONIK A/S	7/31/2015	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K160309	NEUROSOFT TMS	TELEEMG LLC	12/22/2016	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K160703	NEUROSTAR TMS THERAPY SYSTEM	NEURONETICS INC.	6/10/2016	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
K161519	NEUROSTAR TMS THERAPY SYSTEM 3.0	NEURONETICS INC.	9/11/2016	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
K162935	RAPID2 THERAPY SYSTEM	MAGSTIM COMPANY LTD.	3/10/2017	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K170114	MAGVITA TMS THERAPY - W/MAGPRO R20	TONICA ELEKTRONIK A/S	5/1/2017	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K171051	HORIZON THERAPY SYSTEM	MAGSTIM COMPANY LTD.	9/13/2017	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K171481	MAGVITA TMS THERAPY SYSTEM	TONICA ELEKTRONIK A/S	6/16/2017	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
K171902	NEXSTIM NAVIGATED BRAIN THERAPY (NBT) SYSTEM 2	NEXSTIM PLC	11/10/2017	882.5805 / OBP*	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K171967	MAGVITA TMS THERAPY SYSTEM	TONICA ELEKTRONIK A/S	7/25/2017	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K172667	MAGVITA TMS THERAPY - W/MAGPRO R20	TONICA ELEKTRONIK A/S	10/5/2017	882.5805 / OBP	MDD	120	10	4	26	75	3000	37.5	5/WK FOR 6 WKS	90000
K173441	NEUROSOFT TMS (ALSO CLOUD TMS)	TELEEMG LLC	12/13/2017	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
K173540	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	5/3/2018	882.5805 / OBP	MDD	120	18	2	20	55	1980	20.2	5/WK FOR 4 WKS; THEN BIWEEKLY FOR 12 WKS	39600 +11880
K173620	MAGVITA TMS THERAPY SYSTEM W/THETA BURST STIMULATION	TONICA ELEKTRONIK A/S	8/14/2018	882.5805 / OBP	MDD	120	iTBS*	2	8	20	600	3 MIN 9 SEC	5/WK FOR 5 WKS	15000
K180313	APOLLO TMS THERAPY SYSTEM	MAG & MORE GMBH	5/4/2018	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000

510K/ DEN#	DEVICE	COMPANY	CLEARANCE DATE	REGULATION/ PRODUCT CODE	INDICATION	MAGNETIC FIELD INTENSITY (%MT)	FREQUENCY (HZ)	TRAIN DURATION (SEC)	INTER- TRAIN INTERVAL (SEC)	# TRAINS	PULSES PER SESSION	SESSION DURATION (MIN)	TREATMENT SCHEDULE	TOTAL PULSES PER TREATMENT PROTOCOL
IDE	**eTMS** TRIAL USES MAGVITA TMS THERAPY SYSTEM DEVICE CLEARED IN K150641	TONICA ELEKTRONIK A/S	N/A	882.5805 / OBP	PTSD	80	8 - 13	5	20	36	1440@8HZ - 2340@13HZ	15	5/WK FOR 20 total sessions over 5 WKS	38,800@8HZ - 46,800@13HZ
K180907	HORIZON TMS THERAPY SYSTEM	MAGSTIM COMPANY LTD.	8/3/2018	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
DEN170078	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	8/16/2018	882.5802 / QCI	OCD	120	20	2	20	50	2000	18.3	5/WK FOR 5 WKS; THEN 4/WK FOR 1 WK	50000 + 8000
K1833303	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	2/5/2019	882.5802 / QCI	OCD	120	20	2	20	50	2000	18.3	5/WK FOR 5 WKS; THEN 4/WK FOR 1 WK	50000 + 8000
K182700	NEXSTIM NAVIGATED BRAIN THERAPY (NBT) SYSTEM 2	NEXSTIM PLC	3/22/2019	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
K182853	HORIZON TMS THERAPY SYSTEM	MAGSTIM COMPANY LTD.	3/15/2019	882.5805 / OBP	MDD	120	10	4	11 - 26	75	3000	18.8 - 37.5	5/WK FOR 6 WKS	90000
							iTBS*	2	8	20	600	3.09	5/WK FOR 5 WKS	15000
K183376	HORIZON TMS THERAPY SYSTEM WITH NAVIGATION	MAGSTIM COMPANY LTD	4/3/2019	882.5805 / OBP	MDD	120	10	4	11- 26	75	3000	18.8- 37.5	5/WK FOR 6 WKS	90000
							ITBS*	2	8	20	600	3.09	5/WK FOR 5 WKS	15000

* Parameters for intermittent Theta-burst pattern: Each 2-second train consists of bursts of 3 pulses @ 50Hz (i.e., where the pulses occur every 20 msec) repeated @ 5Hz (i.e., 1 burst of 3 pulses every 200 msec), which totals 15 pulses every second, and 30 pulses in each 2-second train. There are 20 2-second trains per treatment session which totals 600 pulses per treatment session. Intertrain intervals are 8 seconds. K173620 reports total session duration at 3 minutes, 9 seconds, i.e., 189 seconds. K182853 misstates the session length given in K173620 (its predicate device) as 3.09 minutes, and the submitter of K182853 reports its own session length, and later the session length for K183376, as 3.09 minutes. We concluded that the minor differences between the devices for the two different manufacturers may be accounted for by differences in the pulse width or other subtle timing decisions that implement the pattern of pulses, bursts, and rest periods. The Table above lists session lengths for each device as it is reported in the 510K submission summary table by the original submitter.

Note: All device protocols listed stimulate the pre-frontal cortex

Table 3: MagVita Device* Characteristics versus other Cleared rTMS Devices

510K/ DEN#	DEVICE	COMPANY	CLEARANCE DATE	WAVEFORM	PULSE WIDTH (µSEC)	FREQUENCY (PULSES/SEC)	AVAILABLE AMPLITUDES IN STD. MT UNITS	COIL	CONFIGURATION
K150641*	**MAGVITA TMS THERAPY SYSTEM**	TONICA ELEKTRONIK A/S	7/31/2015	BIPHASIC SINUSOID	290	**R30 MODEL: 0.1-30** R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
DEN07003, K061053, K083538, K130233	NEUROSTAR TMS THERAPY SYSTEM MODEL 1.1	NEURONETICS INC.	10/7/2008, 3/23/2011, 12/16/2008, 4/30/2013	BIPHASIC SINUSOID	185	0.1-30	0.22-1.6	FIGURE 8	FERRO-MAGNETIC CORE
K122288	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	1/7/2013	NOT REPORTED	370	0.02-30	0.6-1.4	H-COIL	AIR CORE
K133408	NEUROSTAR TMS THERAPY SYSTEM	NEURONETICS INC.	3/28/2014	BIPHASIC SINUSOID	185	0.1-30	0.22-1.6	FIGURE 8	FERRO-MAGNETIC CORE
K143531	RAPID2 THERAPY SYSTEM	MAGSTIM COMPANY LTD.	5/8/2015	BIPHASIC	300	0.1-30	0.28-1.9	FIGURE 8	AIR CORE
K160309	NEUROSOFT TMS	TELEEMG LLC	12/22/2016	BIPHASIC SINUSOID	280	0.1-30 STAND-ALONE 0.1-100 WITH PC	0-2.38**	FIGURE 8	AIR CORE
K160703	NEUROSTAR TMS THERAPY SYSTEM	NEURONETICS INC.	6/10/2016	BIPHASIC SINUSOID	185	0.1-30	0.22-1.6	FIGURE 8	FERRO-MAGNETIC CORE
K161519	NEUROSTAR TMS THERAPY SYSTEM 3.0	NEURONETICS INC.	9/11/2016	BIPHASIC SINUSOID	185	0.1-30	0.22-1.6	FIGURE 8	IRON CORE
K162935	RAPID2 THERAPY SYSTEM	MAGSTIM COMPANY LTD.	3/10/2017	BIPHASIC	300 OR 330*	0.1-30	0.28-1.9	FIGURE 8	AIR CORE
K170114	MAGVITA TMS THERAPY - W/MAGPRO R20	TONICA ELEKTRONIK A/S	5/1/2017	BIPHASIC SINUSOID	290	R30 MODEL: 0.1-30 R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
K171051	HORIZON THERAPY SYSTEM	MAGSTIM COMPANY LTD.	9/13/2017	BIPHASIC	330	1-20	0.28-1.9	FIGURE 8	AIR CORE
K171481	MAGVITA TMS THERAPY SYSTEM	TONICA ELEKTRONIK A/S	6/16/2017	BIPHASIC SINUSOID	290	R30 MODEL: 0.1-30 R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
K171902	NEXSTIM NAVIGATED BRAIN THERAPY (NBT) SYSTEM 2	NEXSTIM PLC	11/10/2017	BIPHASIC	230	0.1-50	0-2.5	FIGURE 8	AIR CORE
K171967	MAGVITA TMS THERAPY SYSTEM	TONICA ELEKTRONIK A/S	7/25/2017	BIPHASIC SINUSOID	290	R30 MODEL: 0.1-30 R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
K172667	MAGVITA TMS THERAPY - W/MAGPRO R20	TONICA ELEKTRONIK A/S	10/5/2017	BIPHASIC SINUSOID	290	0.1-20	0-1.7	FIGURE 8	AIR CORE
K173441	NEUROSOFT TMS (ALSO CLOUD TMS)	TELEEMG LLC	12/13/2017	BIPHASIC SINUSOID	280	0.1-30 STAND-ALONE 0.1-100 WITH PC	0-2.38**	FIGURE 8	AIR CORE
K173540	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	5/3/2018	BIPHASIC	369	0.1-50	0.6-1.4	H COIL	AIR CORE
K173620	MAGVITA TMS THERAPY SYSTEM W/THETA BURST STIMULATION	TONICA ELEKTRONIK A/S	8/14/2018	BIPHASIC SINUSOID	290	R30 MODEL: 0.1-30 R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
K180313	APOLLO TMS THERAPY SYSTEM	MAG & MORE GMBH	5/4/2018	NOT REPORTED	167	0-100	0-2	FIGURE 8	AIR CORE
K180907	HORIZON TMS THERAPY SYSTEM	MAGSTIM COMPANY LTD.	8/3/2018	BIPHASIC	300, 330, OR 340***	1-20	0.28-1.9	FIGURE 8	AIR CORE
DEN170078	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	8/16/2018	NOT REPORTED	324	1-50	0.6-1.4	H COIL	AIR CORE
K1833303	BRAINSWAY DEEP TMS SYSTEM	BRAINSWAY LTD	2/5/2019	NOT REPORTED	324	0.1-50	0.6-1.4	H COIL	AIR CORE

510K/ DEN#	DEVICE	COMPANY	CLEARANCE DATE	WAVEFORM	PULSE WIDTH (µSEC)	FREQUENCY (PULSES/SEC)	AVAILABLE AMPLITUDES IN STD. MT UNITS	COIL	CONFIGURATION
K150641*	**MAGVITA TMS THERAPY SYSTEM**	TONICA ELEKTRONIK A/S	7/31/2015	BIPHASIC SINUSOID	290	**R30 MODEL: 0.1-30** R100 MODEL: 0.1-100	0-1.7	FIGURE 8	AIR CORE
K182700	NEXSTIM NAVIGATED BRAIN THERAPY (NBT) SYSTEM 2	NEXSTIM PLC	3/22/2019	BIPHASIC	230	0.1-50	0-2.5	FIGURE 8	AIR CORE
K182853	HORIZON TMS THERAPY SYSTEM	MAGSTIM COMPANY LTD.	3/15/2019	BIPHASIC	300, 330, OR 340***	1-20	0.28-1.9	FIGURE 8	AIR CORE

* The MagVita R30 model device is used in the MERT-005-B trial.
** Upper limit depends on choice of coil (range = 1.89 to 2.38)
*** Depending on choice of coil.

Changes in Treatment

Treatment personalization is based on 500 per second sampling rate EEGs. Every participant's Screening EEG will be used to establish the initial stimulus parameters. A final EEG/ECG will be conducted on the last treatment day or during the F1 period (D+10 through D+21).

STUDY PROCEDURES

IRB Approval

Prior to recruitment activities for the study, written approval of the protocol informed consent process, and any other approvals required by the overseeing IRB will be obtained from the Institutional Review Board (IRB). It is anticipated that multiple strategies for recruitment may be used, i.e., flyers, outreach to health care providers, direct advertising via radio or internet. All recruitment materials required to be approved by the IRB will be submitted and approved by the overseeing IRB prior to deployment.

Recruitment Considerations and Incentives

All recruitment activities involving active military participants will be compliant with DoDI 3216.02 regarding coercion and perceived coercion. DoDI 3216.02 specifies rules whereby coercion and the appearance of coercion is mitigated. Only civilian personnel trained in recruitment (i.e., Study Site Coordinators) will be allowed to offer information to potential participants. In addition, no military or civilian personnel with potential supervisory influence over a subordinate participant will be allowed in the room when the potential participant is being recruited. The Study Site PI will brief command leadership on the restrictions put on superiors by DoDI 3216.02 and emphasize that coercion or influence will not be tolerated.

All participants may opt-in to free-of-charge recruitment incentive background supportive treatment (BST). During the Stage 1 period, participants will be offered 5 weeks of BST. During the Stage 2 period, participants will be offered 10 weeks of BST. BST may include massage therapy, exercise through a gym membership or personal trainer, or counseling visits. Data will be collected detailing the BST and other concomitant treatments received. This information may be used in exploratory analyses or as co-variates to investigate the potential influence of concomitant treatment on eTMS treatment effects.

Screening Participants

A Screening Form will be kept for all individuals approaching study personnel for possible participation in the study who wish to be screened. The Screening will take place during a telephone call or on-line meeting. During screening, the potential participant will be walked through and will electronically sign the Informed Consent. The screener will provide the potential participant with information regarding the study, including the commitment to the study protocol and the treatment sessions that will be required. A quiz to assess understanding of the burdens, risks and benefits of participation will be used to ensure that actual consent is being obtained. In the event they do not consent to participate, their Screening Form will be de-identified and placed with other screening failure forms. The Screening Form is a recruitment tool and not a CRF. It will not be entered into the trial database.

Consent Process

When a potential participant is screened, the study consent form will be reviewed with the potential participant and the study methods, risks and benefits, and requirements will be explained. Informed consent will then be obtained, and electronically signed by the participant during the Screening. A copy of the signed consent form will be provided to the potential study participant. This process and its documentation will be conducted in a manner consistent with law, regulation and best practice and according to IRB rules. No study procedures or data collection activities will be conducted prior to obtaining informed consent. The consent process will be conducted by qualified study data collection personnel. With regard to consenting of active military duty participants, the study data collection personnel are civilians, and in accordance with coercion mitigation requirements of DoDI 3216.02(e)(1)(b) and (c), are not in the chain of command for any potential active-duty military participants in this clinical trial. No service member superior, or equivalent civilian, will be present during the consent process.

The consent process involves feedback from the potential participant in the form of questions/items of discussion that demonstrate participant understanding of the study procedures, and ethical and scientific design. These items touch on (1) voluntariness/freedom to withdraw, (2) the importance of the participant accurately reporting metal or biomedical devices on or in their body, (3) the safety issue connected with having a history of seizures, (4) any prohibition on beginning use of certain drugs during the study, (5) the number of treatments to be undergone, and (6) a discomfort and a common side effect. In the Stage 2 randomized, sham-controlled portion of the trial, the consent process also will include complete transparency about their

chances of being randomized to a Sham treatment, after which they will be offered open-label Active treatment if they are still qualified to receive it for safety reasons and if they have participated in receiving 75% of the Sham treatments to which they were assigned. If an item is not comprehended by the participant, the consent process requires a discussion of the item until the person obtaining consent is confident that the potential participant understands it. The person obtaining consent is asked to endorse and document key aspects of the process, i.e., (1) that the study was discussed – including, but not limited to, all potential risks, benefits, discomforts, and participant responsibilities, (2) that the participant read the entire ICF at his/her own pace, (3) that the participant was given the opportunity to ask questions, (4) that the consent process was conducted prior to initiation of any study procedures or data collection, and (5) that the participant was given a copy of the signed and dated ICF.

Certificate of Confidentiality

A Certificate of Confidentiality (CoC) protects the privacy of research participants by prohibiting disclosure of identifiable, sensitive research information to anyone no connected to the research except when the participant consents or in a few other specific situations (potential harm to themselves or others). A CoC may be obtained through the National Institute of Health (NIH). Since this study comprises assessments of potential illicit opioid drug use, a CoC will be obtained before the study begins. All participants in the study will receive a CoC as part of their Informed Consent process. All trial personnel will be trained and tested to ensure they comply with the tenets of the CoC regarding every participant.

Withdrawal from Study

Participants have the right to withdraw from the study at any time, for any reason. The Investigator may withdraw a participant from the trial for the safety of the participant, other participants, or study personnel. The Investigator may similarly suspend or terminate only a participant's treatment protocol and may re-initiate a suspended treatment protocol. Participants who withdraw, or are withdrawn, from the study will be asked to complete Early Termination assessments. Participants for whom the treatment protocol only is suspended or terminated, are regarded as ongoing participants in the study, and will be asked to complete all data collection visits and data collection procedures regardless of treatment status.

The IRB may terminate the trial. The Food and Drug Administration may terminate the trial under an IDE. The study Sponsor may terminate the trial for the following reasons:

- Occurrence of unacceptable risk to the participants enrolled in the study
- Upon recommendation of the Data and Safety Monitoring Board to terminate the trial for futility or for safety reasons
- A business decision on the part of Sponsor to suspend or discontinue testing, evaluation, or development of the product

Participants who are withdrawn, or whose treatment protocols are suspended or terminated due to adverse events will be followed until resolution or stabilization of the adverse event, or until

30 days following the final study treatment received, whichever is sooner, unless it is not possible to do so.

Assignment of Participant Identification

Each study recruitment site will be assigned a unique identifying code. A unique participant identification number and participant character code identifier will be assigned to every potential participant who gives consent at the Screening Visit and provides any data at the Baseline Visit. Every participant will be uniquely identified by these three identifiers. All identifiers will be recorded on all study data collected. A file linking the study identifiers to the participant's name will be secured at the study site in a locked cabinet in a secure location. The Principal Investigator will receive a copy of the linkage document periodically (e.g., weekly), and will store it in a locked cabinet in a secure location.

To maintain confidentiality, the participant's name will not be recorded on any study document that will be in the participant's study paper files, or on any input to the study electronic database. Any consent forms or paper copies thereof, will be filed separately from other study forms and will not bear the participant's numerical or character identifiers.

The MagVita device input field requirements, and study identifiers will be harmonized. Photographs/avatars or other identifiers will be used as part of the setup screens to ensure that the individualized study treatment protocol calculated for the individual is what the stimulator outputs to the engaged coil to ensure the safety of participants assigned to active eTMS.

Baseline Visit and Eligibility Determination

Potential participants will undergo assessments and EEG recording during a Baseline Visit (BL), which occurs on-site following the Screening Visit (SC). Eligibility is determined after all BL procedures have been conducted, results have been reviewed, and the EEG has been reviewed for neurological and EEG quality exclusionary conditions. A neurologist or neurosurgeon with adequate training and experience in reading EEGs will review EEG quality. If a potential neurological exclusionary condition is noted by Sponsor, i.e., general or focal slowing or ictal spikes, it will be brought to the attention of a medically qualified Investigator or member of the IDE Sponsor's staff, who will be consulted to confirm eligibility status.

If a potential participant is a female of child-bearing potential (i.e., not 2 years post-menopausal, and not sterile by tubal ligation or hysterectomy), a urine pregnancy test will be conducted. Unless the test is negative, the individual is not eligible to participate. The site Investigator or Clinic Coordinator will provide the result of the test to the potential participant. If the result is positive or indeterminate, the individual will be advised to confirm with a health care provider. A copy of the test package insert will be provided to each individual and the possibility of both false negative and false positive results noted. If it is determined at a later date, after the screening period has expired, that the potential participant is not pregnant, then the screening process can be repeated in totality, and if she is eligible, she may be enrolled.

Eligibility is not confirmed until an eligibility checklist and any supporting materials needed have been reviewed by the site Investigator, and s/he has confirmed, in writing that enrollment may proceed. No participant will be enrolled without such written confirmation.

Continued eligibility related to safety factors will be checked before conducting active eTMS treatment in the open-label extension for those participants who opt-in.

Additional Considerations for Stage 2 Randomized Controlled Trial

Randomization

Participants in Stage 2 will be assigned randomly to one of the two treatment groups (Active eTMS treatment vs Sham eTMS treatment). The treatment allocation will be in a 1:1 ratio, using permuted variable blocks of size 2, 4, and 6.

Participants will be randomized at the beginning of the first treatment visit. This will occur after giving informed consent at SC; after eligibility is determined from data collected at the BL Visit; after all data necessary to determine eligibility is reviewed and documented on the Eligibility data collection form; and **after written confirmation to proceed is provided by the site Investigator**. Participants will be randomized at the last possible moment (just prior to the first treatment) in order to avoid randomizing an eligible potential participant who thereafter changes his or her mind about participation before the first study treatment can be delivered, or who is not well enough to be treated on that occasion.

The study intends to use a commercial randomization system that supports interactive web response that is capable of supporting blinded studies and providing stratification according to the eTMS-PTSD-001 randomized study design. If multiple sites are used in the Stage 2 RCT, the randomization schema will be stratified by site.

Unblinding

The randomization assignment information will be kept in a separate file by the PI. It will not be accessible to the study investigators before the study is completed or terminated unless unblinding is needed for an individual participant for safety reasons. The site Investigator may request unblinding for safety reasons The study will be organized so that unblinding for safety purposes may be done at any time should an emergency arise. In most cases, the unblinding will be part of managing a SAE, and will be reported with the SAE to the IRB. The unblinded participant will be withdrawn from the randomized treatment protocol. In all cases, any breaking of the blind must be followed by a written narrative of the event within 5 days. Every attempt will be made to collect full follow-up data from participants withdrawn from the treatment protocol.

The study leadership will convene a for-cause DSMB meeting to review adverse events leading to unblinding that require immediate and real-time attention by that body. The Study Chair and Principal Investigator will have full access to the unblinded subject specific adverse event reports.

Prior and Concomitant Medications/Neuromodulation Treatments

All prior and concomitant medications, and neuromodulation treatments must be listed in the participant's study record and recorded in the study database. Participants will be questioned at F1 and before each treatment visit in Stage 1 and Stage 2, including the open-label period concerning any new or changed medications or neuromodulation treatments.

For each medication taken, a minimum of the following information will be collected:

- Medication name
- Indication for which the medication was given
- Dose, route, and frequency of administration
- Date started
- Date stopped

Participants should stay on their usual medication regimens at stable doses during the entire course of the trial. This includes OTC medications. Questions regarding the use of concomitant medications should be addressed to the medically qualified Investigator who will consult with the Study PI and Study Chair regarding any methodological implications.

Prohibited Concomitant Neuromodulation

No neuromodulation treatment other than study treatment is permitted until all treatments are concluded (both randomized and open-label), or the F1 data collection is completed, whichever comes later. This includes, but is not limited to, stellate ganglion block, tMS, rTMS, neurofeedback, electroconvulsive therapy (ECT), cranial electrotherapy stimulation (CES), Trigeminal Nerve Stimulation (TNS; including treatment with the Monarch eTNS device), or transcranial electric stimulation (tES), which includes (transcranial Direct Current Stimulation - tDCS, transcranial Alternating Current Stimulation – tACS, and transcranial Random Noise Stimulation, tRNS). Only one neuromodulatory treatment is exclusionary in the Stage 1 study if used any time in the past – ECT. Only two neuromodulatory treatments are exclusionary in the Stage 2 RCT, if used at any time in the past: ECT, and any form of rTMS (examples include, but are not limited to eTMS or MeRT). History of ECT is exclusionary due to its potential for long-term/permanent effects, and history of any type of rTMS is exclusionary due to the difficulty of blinding participants who are not naïve to the experience of rTMS.

No exclusionary or prohibited concurrent neuromodulation treatment may be introduced until (1) all treatments to be done are concluded (i.e., all treatments in Stage 1, and all blinded treatments plus open-label treatments in Stage 2), and the study main analysis data collection is complete (F1), whichever comes last. If introduction of such a treatment is necessary for emergency medical use (e.g., ECT) the site Investigator will inform the Study Chair and Principal

Investigator as soon as it is discovered. If the introduction of such a treatment is introduced for emergency medical use, the Study Chair and Principal Investigator will be notified within 48 hours of the site Investigator's discovery of its introduction.

Data Collection

Schedules

Tables 4, 5 and 6, below, (schedules of activities) show the time windows for data collection and study procedures.

TABLE 4: STAGE 1 SCHEDULE OF ACTIVITIES

	Enrollment		Pilot Study eTMS in Clinic		Follow-Up (F) Evaluation
Procedures	**SC**	**BL**	**Day 1**	**Days 2 through 21**	**(F1)**
Acceptable windows	SD-28 to SD-2	SD-28 to SD-1	SD+1	SD+2 to SD+21	SD+10 to SD+21
Phone Screen	X				
Informed Consent	X				
MMSE, TMSs		X			
Demographics		X			
DHQ, BPI		X			X
LEC-5, OSU-THI-ID		X			
Medical History/Physical, CGI		X			X
Braincheck		X	X		X
VR-36, PCL-5		X			X
PHQ-SADS, AUDIT, DAST-10, OCS, PSQI		X			X
CSSRS		X			X
Concomitant Treatments, Medications, Illicit Drug and Alcohol use		X	X	X	X
SEQ/AEs		X	X	X	X
EEG		X			X
MT			X		
eTMS			X	X	

Notes:

1. All eTMS treatments in Stage 1 are open-label active stimulation
2. Safety stage (Stage 1) study days are labeled SD to differentiate them from randomized stage (Stage 2) study days, labeled RD and from the open-label (Stage 2) days, labeled OD

TABLE 5: STAGE 2 SCHEDULE OF ACTIVITIES

	Enrollment		Randomized Study Treatment in Clinic		Follow-Up (F) Evaluations		
Procedures	**SC**	**BL**	**Day 1**	**Days 2 through 35**	**(F1)**	**(F2)**	**(F3)**
Acceptable windows	RD-28 to RD-2	RD-28 to RD-1	RD+1	RD+2 to RD+21	RD+10 to RD+21	RD+71 to RD+77	RD+176 to RD+196
Phone Screen	X						
Informed Consent	X						
MMSE, TMSs		X					
Demographics		X					
DHQ, BPI		X			X		
LEC-5, OSU-TBI-ID		X					
Medical History/Physical, CGI		X			X	X	X
Braincheck		X	X		X		
VR-36, PCL-5		X			X	X	X
PHQ-SADS, AUDIT, DAST-10, OCS, PSQI		X			X		
CSSRS		X			X	X	X
Concomitant Treatments, Medications, Illicit Drug and Alcohol Use		X	X	X	X	X	X
SEQ/AEs		X	X	X	X	X	X
EEG		X			X		
MT			X				
eTMS: (Active/Sham)			X	X			

Notes:

1. The F1 EEG may serve as the treatment-setting EEG for Open Label if conducted within 15 days of beginning OL treatment

TABLE 6: STAGE 2 OPEN-LABEL SCHEDULE OF ACTIVITIES

	Open-label eligibility	Open-Label Active eTMS in Clinic	
Procedures	**EL**	**Day 1**	**Days 2 through 21**
Acceptable windows	Within 60 days of F1 completion	OD+1	OD+2 to OD+21
Open Label Eligibility Review	X		
Concomitant Treatments and Medications, MED, OCS		X	X
SEQ/AEs		X	X
EEG	X[3]		
MT		X	
eTMS		X	X

Notes:

1. All Stage 2 Sham-assigned participants who complete 75% of assigned study treatments during the randomized period may opt-in for up to 20 open label active eTMS treatments. They must continue to be safe to receive eTMS treatment as determined from data collected at the F1 data collection visit and prior to the first open label treatment.
2. The eligibility determination for open-label treatment (reviewed and signed by the Investigator) shall be made within 60 days of the completion of the F1 data collection in the randomized period.
3. The F1 EEG may serve as the treatment-setting EEG for the Open Label period if treatment begins within 15 days of the collection of the F1 EEG. Otherwise, conduct another EEG within 15 days of the first Open Label treatment

Data to be collected

The data to be collected include, according to the schedule in the Schedules of Activities, above, include:

- DSM-5 PTSD Checklist (PCL-5)
- Veterans RAND 36-Item Health Survey(VR-36)
- TMS Screening Form (TMSs)
- Mini Mental Status Exam (MMSE)
- Columbia Suicide Severity Rating Scale (CSSRS)
- Ohio State University Traumatic Brain Injury Identification Method (OSU-TBI-ID)
- Drug History Questionnaire (DHQ)
- Life Events Checklist for DSM-5 (LEC-5)
- Clinical Global Impression (CGI)
- Computerized Neuropsychological Battery (Braincheck)
- Somatic Symptom, Anxiety, Depression Screen (PHQ-SADS)
- Alcohol Use Disorders ID Test (AUDIT)
- Morphine Equivalent Dose (MED)
- Opiate Craving Scale (OCS)
- Drug Abuse Screening Test (DAST-10)
- Pittsburgh Sleep Quality Index (PSQI)
- Side Effects Questionnaire (SEQ)
- EEG/ECG
- Brief Pain Inventory (BPI)
- Blinding Assessment
- Body Temperature
- Blood Pressure
- Concomitant treatments: background supportive, physical, and neuromodulatory
- Concomitant medications
- Concomitant illicit drug use
- Concomitant alcohol use
- Adverse Events
- Demographics/Military/First Responder
- Medical/Psychiatric History
- Pregnancy

PCL-5: The PCL-5 is a measure of severity of PTSD symptoms. . The PTSD Checklist-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 has a variety of purposes including monitoring symptom change during and after treatment, screening individuals for PTSD, and making a provisional PTSD diagnosis. Each item ranges from 0 to 4 (0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, 4=extremely), and a total score ranging from 0 to 80. It takes approximately 5 – 10 minutes to complete. It can be administered in 3 formats: without Criterion A (TE exposure), with a brief Criterion A assessment, or with the Life Events Checklist for DSM-5 (LEC-5) and extended Criterion A assessment. When used for provisional diagnosis, instead of for severity measurement, the DSM-5 diagnostic rubric is followed to assure distribution across the symptom clusters, but when other diagnostic measures

provide the diagnosis (i.e., the CAPS-5), a simple summation of severity scores across the 20 items may be used to determine probable PTSD. Initial research indicates that a cut off score of between 31 and 33 signals probable PTSD. (U.S. Department of Veterans Affairs, 2022) (Spoont, et al., 2013) A provisional PTSD diagnosis can be made by treating each item rated as 2 = "Moderately" or higher as a symptom endorsed, then following the DSM-5 diagnostic rule which requires at least: 1 B item (questions 1-5), 1 C item (questions 6-7), 2 D items (questions 8-14), 2 E items (questions 15-20). In order to avoid enrolling persons who do not have PTSD, criteria for the diagnostic rubric must be fulfilled AND a minimum PCL-5 score of 31 will be required. Evidence for the PCL for DSM-IV suggests that a 5-10 point change represents reliable change and a 10-20 point change represents clinically significant change. It is recommended to use 10 points of change as a minimum threshold for determining whether the improvement is clinically meaningful. Change score characteristics are currently being determined regarding reliable and clinically meaningful change. The VA recommends following the DSM-IV recommendations. The PCL-5 is the primary efficacy outcome for Stage 2 of this trial. Morrison et. al., in the first study on the PCL-5's psychometric properties for first responders in the United States, studied a sample of 133 first responders, including firefighters/EMT (76.7%) and police (23.3%). The mean total PCL-5 score was 38.73 (SD = 18.68, range 0-72). (Morrison, Su, Keck, & Beidel, 2021)

Veterans RAND 36-Item Health Survey (VR-36): The VR-36 is a self-report questionnaire surveying health-related quality of life and consists of 36 items. It was developed specifically for Veterans based on the Medical Outcomes Study RAND SF-36. (Measuring Health Preference, 2023) Items represent eight (8) domains, including: general health, mental health, energy, social functioning, physical functioning, bodily pain, disability (role limitations) due to physical problems, and disability (role limitations) due to emotional problems. Each of the subscales is scored on a range of 0-100, with higher scores indicating better function. Two summary scores, physical functioning (physical component score, VR-36 PCS) and mental functioning (mental component score, VR-36 MCS) are also generated. PCS and MCS summary scores are calculated using a t-score transformation that is normed to a general U.S. population, such that scores >= 50 indicate better-than-average functioning, and scores < 50 indicate diminished functioning. For both, standard deviation is 10 and MCID is 7. Norms updated per Selim (2009) for the general population use cutoffs of 51.4 (PCS) and 49.0 (MCS). Veteran norms based on a VA sample are: MCS=35.2 and PCS = 43.6.

MMSE: The MMSE is a rapid screen for cognitive function that is widely used among populations at risk for cognitive dysfunction due to age or neurologic condition. It will be given as part of the physical examination to evaluate for neurological disorders that may affect capacity for treatment consent or increased risk for side effects that would require closer monitoring. Administration takes approximately 5-10 minutes. Total scores range from 0-30, with higher scores indicative of better function.

C-SSRS: The C-SSRS will be used to identify persons deemed to be at too elevated of a risk of suicide to be included in the study and whether they need assistance. The Columbia Suicide Severity Rating Scale is a semi-structured interview to identify suicidal ideation and behavior. Assessment of suicidal behavior ranges from preparatory acts to suicide attempt (distinguished

from aborted and interrupted attempts). Four constructs are measured: severity of suicidal ideation, intensity of suicidal ideation subscale, suicidal behavior subscale, and lethality subscale (assesses actual attempts). (Evidence-based Synthesis Program (ESP) Center, Portland VA Medical Center, 2015) In 2012 the U.S. Food and Drug Administration issued a draft guidance (United States Food and Drug Administration, 2012) indicating that the Columbia Protocol met the Agency's benchmark for measuring suicidal ideation and behavior in clinical trials. (The Columbia Protocol: About the Protocol, 2016).

OSU-TBI-ID: The OSU-TBI-ID is a 3 to 5-minute structured interview to elicit a person's lifetime history of traumatic brain injury (TBI). Metrics reported from the interview include Worst Injury (1-none, 2-mild TBI without loss of consciousness (LOC), 3-mild TBI with LOC, 4-moderate TBI, 5-severe TBI). Scores >=3 will be used to document self-reported history of TBI.

DHQ: The Drug History Questionnaire (DHQ) is a standardized, reliable screening interview that assesses lifetime and current drug use. Fourteen (14) drug classes are covered: alcohol, cannabis, stimulants/cocaine, stimulants/methamphetamine, stimulants/amphetamines, depressants/benzodiazepines, depressants/ sedative-hypnotics, narcotics/ heroin, narcotics/street or illicit methadone, narcotics/other opioids, hallucinogens, inhalants, steroids, illegal prescription use. Administration time is 5 minutes. For each class, the subject is asked whether they have ever used this type of drug, frequency of use in the last 6 months, total duration of use, year last used, and route (IV) of administration.

LEC-5: The Life Events Checklist is recommended by the Veterans Affairs National Center for PTSD as the prior inquiry to the CAPS-5. (U.S. Department of Veterans Affairs, 2020) It is preceded by the LEC-5 Standard Self-Report, which identifies lifetime exposure to 17 types of traumatic events (TEs), and how the respondent was involved (e.g., experienced, witnessed, learned of). This is used as a guide to the more in depth LEC-5 Checklist interview, in which the TEs are revisited, age at exposure, how exposed, whether it involved a threat to life or a serious injury, and the number of times it occurred. (Weathers, et al., 2020)

CGI: The CGI is a clinician-rated instrument that evaluates symptom severity (CGI-S), whether and what direction treatment response takes (CGI-I), and relative efficacy vs. side effects of treatment (CGI-E). The CGI-S provides a rating of mental illness severity on a 7-point Likert scale (1- normal, 2- borderline, 3- mildly ill, 4- moderately ill, 5- markedly ill, 6- severely ill, 7- extremely ill). The CGI-I describes change in mental illness with respect to baseline and due to treatment on a 7-point Likert scale (1- very much improved, 2- much improved 3- minimally improved, 4- no change, 5- minimally worse, 6- much worse, 7- very much worse). The CGI-E indicates a combination of therapeutic effect (marked improvement, moderate improvement, minimal improvement, unchanged or worse) and severity of side effects experienced (none, not functionally significant, functionally significant, outweighs therapeutic effect) on a 16-point scale.

Braincheck: Braincheck is a computerized, repeatable, neurocognitive test battery composed of well-known neuropsychological tests. It includes immediate and delayed recognition tests, tests of visual search speed, scanning, processing speed, mental flexibility, and executive functioning. Specific tests include trail marking, digit-symbol substitution tests, Stroop color, and word tests. Administration takes 15 minutes on average.

PHQ-SADS: The PHQ-SADS is a combination of the PHQ-9, PHQ-15, GAD-7 and the first five items of the PHQ panic module. It was developed based on observations of commonly occurring comorbidity between depression, anxiety, and somatization. Respondents are asked to consider the frequency of symptoms experienced over the past two weeks (PHQ-9 and GAD-7) or four weeks (PHQ-15). Administration takes approximately 10 minutes. Scores are based on thresholds for the individual component scales: scores of 5 (mild), 10 (moderate) and 15 (severe or moderately severe).

AUDIT: The AUDIT is a 10-item self-report questionnaire that provides information about habits surrounding alcohol use, including alcohol consumption, drinking behavior and alcohol-related problems. Each question is scored from 0-4 points. Administration time is 5 minutes. The total score ranges from 0-40, with higher scores being more concerning for unsafe drinking habits. A total score of 8 or more identifies individuals at risk for alcohol use disorder.

MED: The Morphine-Equivalent Dose is a value that represents the potency of an opioid dose relative to morphine. It is intended to be used as a method of tracking changes in opioid use. The assessment is intended for determining daily dosage, and includes 10 different opioids (Codeine, Fentanyl, Hydrocodone, Hydromorphone, Methadone, Morphine, Oxycodone, Oxymorphone, Tapentado, and Tramadol). Measurements are made in milligrams. A conversion factor is used (Von Korff, et al., 2011), and amounts are summed, resulting in a final amount (in milligrams) of morphine the subject ingested. Levels of >120 MED per day increases risks for overdose by 1.98 (Ciesielski, et al., 2016).

OCS: The Opiate Craving Scale is a 5-item self reported assessment that estimates the cravings an individual has for opiate drugs. This scale was adapted for opiates from The Penn Alcohol Craving Scale (PACS) (Flannery, 1999). Each item measures the severity of cravings on a 6 point scale, for a maximum score of 36. The instrument can be modified to measure weekly or daily cravings. In the present study, the daily instrument will be used.

DAST-10: The DAST-10 is a 10-item, self-report instrument to identify problem drug use. One point is scored for each item on the screen, with total score range from 0-10. Administration time is about 10 minutes.

PSQI: The Pittsburgh Sleep Quality Inventory is a self-administered questionnaire developed to discriminate between "good sleepers" and "poor sleepers." The PSQI is the most commonly used screening tool for sleep dysfunction. The instrument assesses sleep quality disturbances over a 1-month time interval. Nineteen individual items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Scores are summed for a global PSQI score. (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) (University of Pittsburgh, 2020) Best evidence synthesis shows strong reliability and validity, and moderate structural validity in a variety of sample populations, suggesting that it fulfills its intended utility. (Mollayeva, et al., 2016).

SEQ: The SEQ is a checklist to evaluate for side effects of eTMS therapy. Expected adverse reactions will be prompted for. For each item, individuals are asked to indicate whether they are experiencing the symptom. Response options are: None, Slightly, Moderate, Severe.

SAFETY

Adverse Events

An adverse event (AE) log will be kept. There will be data collection of AEs at all follow-up visits (F1, F2, F3) as well as recording of AEs reported to the treating personnel, or other medical personnel at the treatment site, at each treatment visit and AEs that are otherwise spontaneously reported. The Side Effects Questionnaire (SEQ) will be used to ensure full reporting of adverse effects of the study treatment and procedures. When an AE is noted by the Study Coordinator/Technician it will be escalated to the Site Investigator, or their medically qualified designee as appropriate, and in all cases for an SAE. All AEs and SAEs will be reported to the Data and Safety Monitoring Board. As noted above in the section on Unblinding, the PI will keep a log of unblinded adverse event data that may be used to call a for-cause DSMB meeting to conduct a safety review. AEs will be reported to the FDA and the IRB on the schedules determined by these oversight bodies, according to instructions for reporting differing types, severity, and relatedness, of AEs.

An adverse event (AE) is defined as any untoward medical occurrence in a participant treated with an investigational product and does not necessarily have to have a causal relationship with the treatment under investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Anticipated adverse device effects for purposes of both Stage 1 and Stage 2, in order of most common to least likely to occur, include:

- Headache and neck pain
  - Sponsor's clinical use history ~15%.
  - rTMS: Headache ~23%, Neck pain ~12% of rTMS cases in general. (Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006)
  - Generally related to muscle tension.
  - Responds well to analgesics
  - Generally, resolves within the first week of therapy.
  - Short-term only. No long-term implications.
- Application site pain/discomfort
  - Sponsor's clinical use history ~5%
  - Generally, results from pressure placed against the scalp as opposed to stimulation.
  - Generally, resolves within the first week of therapy.
  - Short term only. No long-term implications.
- Eye pain
  - Sponsor's clinical use history ~5%
  - Pressure may be felt in the back of the eyes during therapy, but this does not last more than a few seconds following the pulse train.
  - Short-term. Resolves in the first 1-2 days of therapy.

    - No long-term implications.
- Treatment emergent mania/hypomania
    - Sponsor's clinical use history ~5%.
    - Hypomania is much more common than mania. Often a secondary effect to improved symptoms.
    - Short term. Resolves in the first week of therapy.
    - No long-term implications.
- Anxiety/depression
    - Sponsor's clinical use history showed slight anxiety in ~5% of patients - generally occurring in patients responding positively to therapy as awareness of their own behavior develops.
    - rTMS: Very rare in general. Observed when stimulation of RPFC and LPFC (Pascual-Leone, Catalá, & Pascual-Leone, Lateralized effect of rapid-rate transcranial magnetic stimulation of the prefrontal cortex on mood, 1996) (George, et al., 1996) which is not used in the present trial.
    - Short term. Resolves within the second week of therapy.
    - No long-term implications.
- Cognitive changes
    - Sponsor's clinical use history ~5% report an alteration to cognition, associated with fatigue following therapy.
    - rTMS: No evidence of long-term adverse effect on cognitive, perceptual, or motor functions in general (Pascual-Leone, et al., 1993) (Wassermann E. M., 1998)
    - Short-term. Resolves in the second week of therapy.
    - No long-term implications.
- Insomnia
    - Sponsor's clinical use history ~3%.
    - Some patients nap following treatment, which disrupts sleep. Some report a shorter period of sleep initially with an early wake up.
    - Short term. Resolves within the first week of therapy.
    - No long-term implications.
- Dizziness
    - Sponsor's clinical use history ~3%.
    - Patients may feel very relaxed during therapy, and experience mild light headedness when standing afterward.
    - Resolves by asking subject to remain seated and stand slowly, or by giving patient water to drink.
    - Short-term. Resolves in the first 1-2 days of therapy.
    - No long-term implications.
- Auditory effects
    - Sponsor's clinical use history ~3%.

    - rTMS: Effects on hearing are very rare. Transient rise in auditory threshold or tinnitus in a small number of cases in general (Pascual-Leone, et al., 1992) (Pascual-Leone, et al., 1993) (Loo, et al., 2001) (Boutros, Gueorguieva, & Hoffman, 2002) (Anderson, et al., 2006).
        - Reports of treatments from different protocols, coils, and equipment are that sound during rTMS may exceed 140 dB (Rossi, et al., 2020); however, the MERT-005-B protocol includes subthreshold intensity and produces a maximum of 77 dB at 5 centimeters from the coil. This is well within the OSHA recommended safety levels.
    - Ticking sound is annoying to some patients. Resolves with ear plugs.
    - Short-term. Resolves in the first week.
    - No long-term implications.
- Muscle twitching
    - Sponsor's clinical use history < 1%
    - May result from rTMS pulses activating scalp muscles.
    - Short term. Resolves within the first week of therapy.
    - No long-term implications
- Dental pain/jaw pain
    - Sponsor's clinical use history < 1%
    - Occurs due to clenching of teeth during treatment. Resolves by requesting the subject relax their jaw.
    - Short-term. Resolves within the first 2-3 days of therapy.
    - No long-term implications.
- Seizure
    - Sponsor's clinical use history – zero occurrences.
    - rTMS: Extremely rare. < 1/10,000 in general (Wassermann & Lisanby, 2004) (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009).
        - Most recent estimates for high frequency rTMS: (Lerner, Wassermann, & Tamir, 2019) (Rossi, et al., 2020)
            - When no elevated inherent subject factor risks: .00/1000 (from 76,181 sessions)
            - When elevated inherent subject factor risk: .58/1000 (from 5215 sessions)
            - When elevated protocol risk only[7]: .00/1000 (from 1029 sessions)
        - Generally, a single episode; very short term.
        - No long-term implications.

A Serious Adverse Event (SAE) is defined (21 CFR 312.32(a)) as an adverse event that, in the view of the Investigator or the sponsor:

[7] Elevated protocol risk is associated with operating outside the recommended safety guidelines. See Rossi et al. (Rossi, S; Hallett, M; Rossini, P M; Alvaro, P; and The Safety of TMS Consensus Group, 2009).

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalizations
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect
- Is, according to appropriate medical judgment, another important medical event that jeopardizes a participant, and may require medical/surgical intervention to prevent one of the outcomes listed above

An unanticipated adverse device event (UADE) is defined, in 21 CFR 812.3(s) as any serious ("serious" as defined above and in 21 CFR 312.32(a)) adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol and/or Instructions For Use (IFU), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the participant.

All adverse events that do not meet any of the criteria for SAEs or UADEs should be regarded as non-serious adverse events.

Progression of disease reflects lack of therapeutic efficacy and should not be treated as serious adverse events. However, other events or complications meeting the criteria for serious adverse events should be considered as a serious adverse event and should be reported to the IRB regardless of presumed relationship to the investigational treatment.

Adverse Event Assessment

All adverse events (AE), including the following, will be assessed by the Investigator or his or her medically qualified designee, and recorded on the study Adverse Event form according to the protocol and the Manual of Procedures:

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- Medical condition which occurs during the study, having been absent at screening
- Medical condition present at screening which appears to worsen during the study

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study treatment.

Severity will be assessed using the following definitions:

- Mild: Aware of sign or symptom, but easily tolerated
- Moderate: Discomfort sufficient to cause interference with usual activity
- Severe: Incapacitating, with inability to work or do usual activity

The relationship to Investigational Treatment will be assessed by the Investigator using the following criteria:

- Not Related — Evidence exists that the adverse event definitely has a cause other than the study treatment (e.g., pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
- Suspected — There is a reasonable possibility that the treatment caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the treatment and the adverse event. This is a lesser degree of certainty about causality than the conclusion that the adverse event was caused by the treatment. (21 CFR 312.32(a) A causal relationship requires a temporal relationship to exist between the adverse event onset and administration of study treatment.
- Definitely Related — Strong evidence exists that the study treatment caused the adverse event. There is a temporal relationship between the event onset and administration of the study treatment. There is strong therapeutic evidence that the event was caused by the study treatment. The participant's clinical state and concomitant therapies have been ruled out as a cause.

All participants who have been exposed to study treatment will be evaluated for adverse events. All adverse events will be evaluated beginning with onset, and evaluation will continue until resolution or recovery is observed or until the Investigator determines that the participant's condition is stable, whichever is earlier. The Investigator will take all appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the study Concomitant Medication form. If more than one distinct adverse event occurs, each event will be recorded separately.

Adverse Event Reporting

The study period during which adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the follow-up data collection. The study procedures initiation is defined as beginning at the BL Visit. Every treatment visit is accompanied by adverse event data collection and adverse event data will be collected at all follow-up data collection visits. This data collection will use a side-effects questionnaire in order to methodically detect expected side effects.

Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects

All Serious Adverse Events (SAE), Unanticipated Adverse Device Effects (UADE), and Serious Unanticipated Problems (UPIRTSO) that occur during the study, including death, must be reported within one working day by telephone to the IDE Sponsor, and followed up in writing

within 24 hours. The urgency for reporting SAE and UADE is four-fold: (1) to facilitate discussion and implementation, if necessary, by Sponsor and the Investigator of appropriate follow-up measures; (2) to facilitate reporting of unanticipated problems involving risk to human participants to the IRB; (3) to facilitate Sponsor's rapid dissemination of information regarding AEs to other Investigators/sites in a multi-center study; and (4) to enable Sponsor to fulfill reporting requirements to the appropriate regulatory authority. Sponsor and the study PI will cooperate in supplying all necessary information to FDA.

Within the following 48 hours, the site Investigator must provide further information on the SAE, UADE, or UPIRTSO in the form of a written narrative. This should include a copy of the completed study Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to both Sponsor and the study PI.

Under FDA regulations, the IRB and the Sponsor must receive a report of any UADE (which includes serious UP, i.e., UPIRTSO) no later than 10 working days after the site Investigator learns of the effect. (21 CFR 812.150(a)(1). Sponsor is required to immediately conduct an investigation of all UADE and serious UP of which it is notified, under 21 CFR 812.46(b). If Sponsor determines a UADE or serious UP presents an unreasonable risk to participants, it must terminate any part of the investigation presenting that risk within 5 working days of making the determination, and not later than 15 days from first receiving notification of the effect. Sponsor must, under 21 CFR 812.150(7)(b)(1), report the results of that evaluation to the IRB and FDA, and all participating investigators within 10 working days of first receiving notice of the effect. All reporting operating procedures of the IRB will be followed.

Technical and Protocol Risk Mitigation

Risk of seizure is not zero but is mitigated by the trial design. Trial eligibility criteria are intended to minimize seizure risk, i.e., abnormal focal or general slowing, or ictal spikes, during the EEG recording will exclude a candidate from participation. All stimulation during this study will be sub-threshold. This will be guaranteed at BL by placing the coil over the motor cortex, finding the minimum stimulation energy to cause a thumb twitch, reducing the energy by 20% from that point, and then retesting to ensure no thumb twitch exists. Motor threshold is known to be stable over the time period used in the clinical trial. Sub-threshold stimulation ensures that eTMS therapy does not actively stimulate neurons, which minimizes any chance of seizure or other adverse event. Note that conventional cleared rTMS therapy uses stimulation at 120% of motor threshold. As per the 2020 safety rTMS safety guidelines (Rossi, et al., 2020), participants will be monitored for signs of cortical excitation by observation during stimulation of their hands for signs of twitching, and participants will be instructed to report any sensations of twitching. Finally, operators will have SOPs containing instructions as to what to do in the event of a seizure and will be trained for this eventuality.

Generally, risks from equipment misuse, contamination, accidental damage, or failure are controlled by a number of strategies. These include (1) expert installation and periodic inspection of all devices, (2) training, certification, and periodic re-certification of personnel who

use and maintain the equipment, (3) written standard operating procedures (SOPs), and (4) documentation of compliance with SOPs. Specific risk mitigations are detailed below.

Risks from personnel error are mitigated. Only trained, certified and periodically re-certified, personnel may use the stimulator and other equipment. Each stimulator operator is assigned a unique personal identifier and password, and an audit trail will track time of use and identity of user. Operators will be intensively trained to determine motor threshold. Stimulation frequency is controlled over the internet from the IDE Sponsor's facility. The operator has no discretion to view, or change, the frequency.

Risks of contamination transferred from one participant to another are mitigated with cleansing SOPs. All participant-contacting devices and surfaces will be cleaned after each use, and other surfaces that do not come into contact with the participant will be cleaned and decontaminated according to COVID-19 recommendations from public health authorities. Trainings, signoffs, and data collection procedures will be conducted using decontaminated computer equipment. Contact between study personnel and study participants will be consistent with current public health guidelines as they may change from time to time.

Risks from mechanical breakdowns and device damage are mitigated. The trial will have equipment moving and handling SOPs. Personnel will be trained in the handling and moving of this delicate and costly equipment. Carrying or lifting the stimulator is prohibited, cart maneuvering rules will be used, and cart casters will be locked. Operators will be trained in low strain procedures for handling the cable. In the eventuality of a cable connection break, the MagVita operation will automatically cease. Storage and environmental conditions for devices will be according to trial SOPs, including, but not limited to, thermal conditions and humidity conditions.

Electric shock risks from the stimulation equipment is minimized by its design. Sponsor has treated more than 5,000 patients using the MagVita device and has never experienced this adverse event. The MagVita device is an FDA cleared device. Sponsor has added strain relief to the junction of the cable and the coil housing in order to ensure maintenance of proper insulation. The PVC housing of the coil is at least 1/16th of an inch in thickness, which provides a sufficient barrier that the voltage of the coil could not be detected on the outside of the coil housing. The PVC plastic housing is approximately 10^{13} ohms in resistivity. Clinical trial eligibility criteria allow enrollment only of individuals capable of following study procedures. The screening testing includes significant data collection burden. Thus, the study population will be selected in such a way as to reduce the prospect of patient involvement in equipment damage.

Risks of overheating are mitigated. The MagVita device incorporates a thermal sensor in the coil that prohibits operation if the coil exceeds a predefined temperature of 41 degrees Celsius (106 degrees Fahrenheit). The MagVita device includes a software status panel where the temperature of the coil is continuously displayed. If the coil temperature exceeds 35 degrees Celsius, the temperature display field will turn yellow. The operator is trained to monitor this panel. There is an additional Intelligent Temperature Prediction algorithm, independent of the thermal sensor, which predicts the temperature based on number of pulses. This ITP algorithm predicts the near-term future status of the coil and will display the predicted excessive

temperature along with an exclamation mark to attract the attention of the operator. Sponsor has never had an adverse event in which a patient has been burned due to overheating of any part of the system. Sponsor has had events where the system alerted the operator that the coil had exceeded its cutoff temperature, and the system would not allow any further stimulation. The SOPs for the trial will include careful monitoring of the status panel. The participant also will be instructed to report any change in temperature to the operator.

Risk of hearing damage is mitigated. The MagVita device underwent human factors testing for the device generated noise. The eTMS treatment has a similar protocol to the MagVita protocol. The section entitled "Comparison of eTMS Study Active Treatment Exposure with FDA-Cleared rTMS Treatments," above, shows a table of comparisons of eTMS to cleared rTMS devices. The MagVita delivers 4 second trains every 30 seconds at a 10 Hz frequency, resulting in 3,000 pulses per treatment session. The eTMS protocol calls for 5 second trains of stimulation every 20 seconds, at a frequency between 8 and 13 Hz, resulting in between 1,440 and 2,340 pulses per treatment session. The sound of the MagVita device used under the eTMS protocol is lower than that for the cleared use of the MagVita device. The reason for this is that eTMS uses lower energy. eTMS is at 50% of motor threshold, whereas the MagVita cleared protocol stimulates at 120% of motor threshold. The MagVita coil produces 77 dB 5 centimeters from the source, when used at 50% of maximum energy that the MagVita can produce. Even if the participant's motor threshold were at the maximum that the device could produce, then 77 dB would be the most intense sound to which the participant would be subjected: a participant cannot be treated if his or her motor threshold cannot be determined, thus if the MT is at the maximum output of the device, and eTMS is conducted at 50% MT, then this establishes an upper limit of 77 dB of noise production. This is well within the OSHA standard for protection from acoustic trauma. (Dhamne, et al., 2014). Nevertheless, the sound can be annoying to some patients. Disposable earplugs will be provided to any participant who desires to use them. Operators also will offer earplugs at the beginning of each session. The 2020 safety guidelines cover the aural health of operators who are within less than 40 centimeters of the discharging coil, mandating that in these conditions either earplugs or earmuffs are used. (Rossi, et al., 2020) This mandate will be obeyed in the eTMS-PTSD-001trial.

Non-therapeutic effects of the stimulation equipment are mitigated with a combination of exclusion criteria, treatment room setup, and removing sensitive objects from proximity with the stimulator. The MagVita equipment magnetic field is the therapeutic element in eTMS treatment and is therefore required to be present. Its effects on other equipment, and especially participant implants must be mitigated or nullified. Treatment rooms will be set up to prevent the proximity of the MagVita device to sensitive equipment. Additionally, eligibility criteria for the trial exclude participants with implants that are sensitive to the strong magnetic field. These include: intracranial implants (e.g., aneurysm clips, shunts, stimulators, cochlear implants, stents, or electrodes) or any other metal object within or near the head, excluding the mouth, which cannot be safely removed, as well as implanted cardiac pacemakers, implantable cardioverter defibrillators (ICD), cervical or thoracic spinal cord stimulator, ventriculoperitoneal (VP) shunt, metal stents or shunts, medication dispensing devices, or any other active or non-active metal implants. There is a risk of permanent damage to any implanted battery-operated generator or lead/paddle. That damage could require revision surgery. Trial SOPs will include instructions regarding placement of wearable or removable devices or objects as well (for example, cell

phones, credit cards, ignition keys, jewelry, eyeglasses, and non-removable piercings). The informed consent process will stress the importance of giving a full and accurate history regarding the presence vulnerable or metal objects.

Emergency Action Plans

All sites will have specific emergency action plans to respond to seizure, cardiovascular events, elevation of risk of suicide or violent behavior, or a general injury. Plans and descriptions of resources will be included in the Manual of Procedures, which will include procedures for response and location of responding resources. Appropriate plans will be put into place for sites, as initiated to the study, depending on their intrinsic resources. All coordinators and technicians will be trained:

- to respond to seizure
- to react appropriately and anticipate violent behavior
- to recognize suicidal ideation
- to respond to general injury

In the event of a seizure, the response will be to (1) keep the airway clear, (2) provide room to safely move the participant, and (3) if not a medical treatment facility site, to call an ambulance.

No coordinator or technician will continue to be in a room alone with a participant who indicates an increased level of risk of violence, or who is identified by study staff as invoking fear of violence. Assistance will be identified that is within appropriately effective distance.

When a participant is considered at elevated risk of suicide or expresses inappropriate homicidal intent, the site Investigator or his/her medically qualified designee will be contacted. If the Investigator/designee deems the individual to be at imminent risk, an emergency medical service will be called to transport that individual to a prespecified medical facility, or the police will be called.

When a seizure occurs, the sponsor will report the occurrence details to the IRB and to FDA within 10 days from the seizure, to determine whether procedures need to be updated to optimize safety.

The following lists the relevant information for the Wright State clinical site with regards to emergency handling:

- The location where eTMS treatment is administered will be: Neuroscience Engineering Collaboration Building, Wright State University, 640 Colonel Glenn Highway, Dayton, OH 45435.
- There are no emergency services at the site. The emergency response would be to call the Soin Medical Center – Kettering Health, located 1.5 miles from the facility.
- An emergency defibrillator is located on site.
- All individuals administering eTMS will be trained and certified by the Sponsor.

- Each member of the team will be Seizure First Aid Certified through the Seizure Recognition and First Aid Certification from the Epilepsy Foundation. This program is supported by the Centers for Disease Control and Prevention.
- The facility does not have seizure monitoring available on-site. If a participant suffers a seizure, they will be transferred to a team of board certified and fellowship trained neurologists at the Soin Medical Center – Kettering Health.

STATISTICAL METHODS

STUDY OUTCOMES

Stage 1

Stage 1 of the eTMS-PTSD trial is intended to investigate the safety of the procedure in the target population. The primary outcome is safety. Adverse events will be recorded, and categorized based on incidence, relatedness, severity, type, subsequent treatment/intervention required, and resolution status.

Stage 2

Stage 2 of the trial is intended to investigate efficacy and safety of the procedure in the target population. The primary efficacy outcome is a measure of PTSD symptom severity. PTSD symptom reduction will be calculated as the arithmetic reduction in PCL-5 scores between BL and F1. See the above Data Collection section for a description of this assessment.

Safety will be characterized by adverse event incidence, relatedness, severity, type, subsequent treatment/intervention required, and resolution status.

SAMPLE SIZE CONSIDERATIONS FOR STAGE 1

A convenience sample size of thirty (30) will be treated in the safety pilot stage in order to detect common adverse effects or safety concerns.

SAMPLE SIZE CONSIDERATIONS FOR STAGE 2

Sample size assumptions:

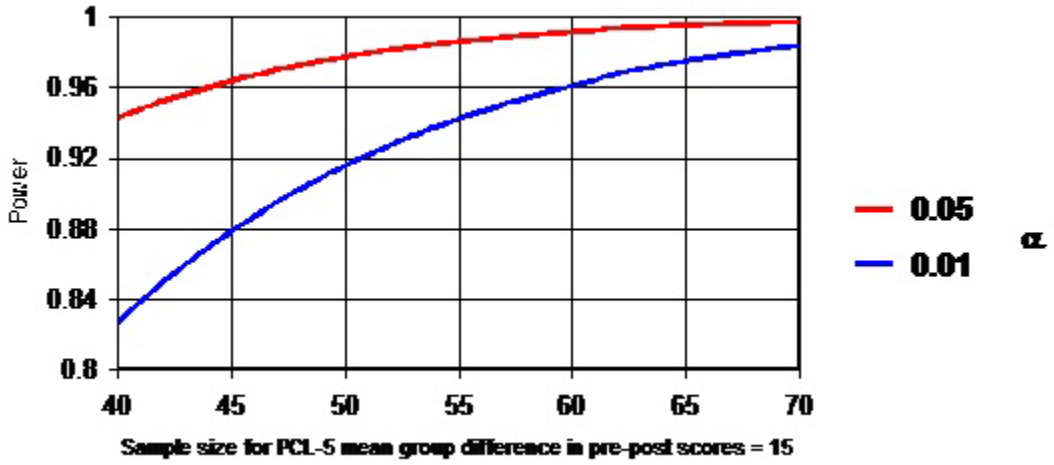
- Design variable is change in PCL-5 between BL and F1.
    - Mean in first responders = 38.73 (SD = 18.68) (Morrison, Su, Keck, & Beidel, 2021)
    - Primary outcome clinically important difference = 15 (10 – 20) (U.S. Department of Veterans Affairs, 2022)
- Planned estimated effect size +0.8 $SD_{difference}$, for a difference in Active eTMS versus Sham eTMS group mean pre-post PCL-5 scores = 15, with pooled $SD_{difference}$ = 18.68
- Assignment ratio =1:1 for Active eTMS vs. Sham eTMS
- 10% loss to followup

- Type 1 error = 0.05 (2-sided)
- Statistical power = .985
- Method of calculation – Sample size and power for given detectable difference between two mean difference scores using Student's t-test according to method of Dupont & Plummer

Sample size requirements:

- Total completers: 108 (90% - 54 per group) – See Figure 2 below
- Total to be randomized:120 (60 per group)

FIGURE 2: Primary efficacy outcome, PCL-5. Statistical power by number of completers per treatment group for Type 1 error 0.05 (.985) and 0.01 (.938)



DATA AND SAFETY MONITORING BOARD

A Data and Safety Monitoring Board (DSMB) comprised of at least 3 **independent** subject matter, medical, clinical trial methods, and biostatistics experts will be constituted to review the protocol, recruitment progress, site performance, study conduct, and safety data. The Board will request analyses, and will make recommendations regarding study continuation, amendment, or termination, as well as the advisability of adding up to 3 additional research sites.

Attendance at DSMB meetings by the Study Chair, the Principal Investigator and designated advisers to the DSMB is on a non-voting basis. Neither the Principal Investigator nor the Study Chair are involved with data collection or participant treatment at the clinical sites. The DSMB, according to its charter, will report its independent recommendations to the Principal Investigator and the Study Chair. The funders and the IDE Sponsor comprise the decisional authority, after

carefully considering all DSMB recommendations and the views expressed by the PI and Study Chair.

The DSMB will meet prior to study Stage 1 initiation, and immediately after data from Stage 1 is available, to make recommendations on continuing to Stage 2, and advised protocol changes. The Board may meet at any other time it deems necessary or prudent, or as requested by the study leadership, and will meet via internet at a minimum of every 6 months. The DSMB will conduct a planned interim review after approximately half of Stage 2 participants have completed F1 data collection.

The DSMB will conduct a planned interim group-sequential analysis with possible early stopping for benefit or early stopping for futility (lack of benefit). The interim analysis will be done when F1 data are available for approximately 50% of the anticipated completing participants. The boundary for possible early stopping for efficacy will be a two-sided p-value for the primary analysis ≤0.001; if the trial does not stop, the final analysis will be done using a criterion for statistical significance of a two-sided p-value ≤ 0.049. Possible early stopping for futility will be based on conditional power (CP) - the probability of finding a significant beneficial treatment effect (two-sided p ≤0.049) at the end of the study, given the current data and appropriate assumptions about the true treatment effect and $SD_{difference}$. The DSMB may recommend stopping for futility if CP is very low, for example 20% or lower, assuming a treatment difference of 15 for change in the PCL-5 score. Before stopping for either efficacy or futility, the DSMB will consider results for other endpoints.

STATISTICAL ANALYSIS PLAN FOR STAGE 1

Adverse events (AEs) will be summarized using MedDRA terms. AEs will be listed and summarized by system organ class, preferred term, incidence, severity and duration. Monthly safety summaries will be made for all study participants and listed by site and study treatment assignment and distributed to the Study Chair and Principal Investigator, who also will receive SAE reports in real-time. These listings will be produced for every DSMB meeting. The DSMB, the Study Chair and Principal Investigator will not be blinded to treatment assignment for any AE-related data.

STATISTICAL ANALYSIS PLAN FOR STAGE 2

Statistical Analysis Software

Statistical analyses will be performed using software such as the SAS® system, IBM SPSS, or EXCEL.

Analysis Populations

Two analysis populations are defined for Stage 2:

- The Intent-to-treat (ITT) analysis population includes all eligible and randomized participants

- The Per-Protocol (PP) analysis population includes all participants in the ITT population who (1) had all efficacy evaluations at the major study time points defining the primary outcome comparison, i.e., BL and F1, (2) who had no major protocol deviations, and (3) who received at least 75% of assigned blinded study treatments

Analysis of Safety

Adverse events (AEs) in Stage 2 will be summarized using MedDRA terms. AEs will be listed and summarized by system organ class, preferred term, incidence, severity and duration. Monthly safety summaries will be made for all study participants and listed by site and study treatment assignment and distributed to the Study Chair and Principal Investigator, who also will receive SAE reports in real-time. These listings will be produced for every DSMB meeting. The DSMB, the Study Chair and Principal Investigator will not be blinded to treatment assignment for any AE-related data.

Analysis of Efficacy

The tests of the primary and secondary efficacy outcomes will be hierarchical in order to constrain Type I error. If the test of the primary outcome shows a significant beneficial effect with a two-sided p-value ≤ 0.05, the secondary efficacy outcome analysis will be conducted at a two-sided alpha = 0.05 level. If alpha has been spent in DSMB efficacy monitoring, the alpha level apportioned to the primary results analyses will be accordingly reduced.

Primary outcome efficacy analysis

The primary efficacy outcome analysis will be conducted on the ITT population. The primary efficacy outcome measure is arithmetic change in PCL-5 score between BL and F1. The primary efficacy hypothesis is the superiority of eTMS treatment over sham eTMS treatment in participants with PTSD. Missing values will be imputed. The analysis of the primary outcome will be a linear regression of the change in PCL-5 total score between BL and F1, with independent variables being the BL PCL-5 total score and a dummy variable for the two treatment groups.

Missing F1 PCL-5 total scores will be addressed using multiple imputation. Missing PCL-5 total scores will be estimated (i.e., imputed) from a linear regression model to be determined from observations in which the F1 PCL-5 score is not missing; covariates considered for inclusion in the model will be the BL PCL-5 total score, a dummy variable for treatment group, and other potentially associated variables (e.g., age, gender, PTSD severity, military status, and number of treatments. The linear regression model will be chosen using the LASSO method with cross-validation, implemented in SAS PROC GLMSELECT. The set of variables to be considered for inclusion will be determined before the imputation is performed. After the form of the linear regression model is determined, at least 20 data sets will be created with the missing F1 PCL-5 values imputed, using the linear regression function and SAS PROC MI to introduce a random element. The described primary linear regression analysis (linear regression of change in PCL-5 score on BL score and a dummy variable for treatment group)

will be performed for each of the imputation datasets. SAS PROC MIANALYZE will then be used to combine the regression results from the previous step and form the final MI analysis results. Since there will be multiple imputed values for each missing F1 PCL-5 score, the analysis will account for variability in the missing values. This process assumes that missing values are missing at random (MAR), i.e., they may depend on values of other variables measured at the same time, but not on the non-missing values. The following sensitivity analyses will be conducted for missing PCL-5 total scores at F1: 1) analysis of non-missing F1 PCL-5 total scores; 2) analysis in which missing F1 PCL-5 total scores will be replaced with the best PCL-5 total score possible; and 3) analysis in which missing F1 PCL-5 total scores will be replaced with the worst PCL-5 total score possible.

Poolability over study sites will be separately assessed. In a separate analysis the association between the primary endpoint and the study site will be explored. Both the main effect of study site and the interaction between study site and treatment group will be explored.

Additional Analyses of the Primary Outcome

Exploratory responder analyses will be conducted. To determine whether a greater percentage of Active-treated participants respond to study treatment than Sham-treated participants, the binomial z-test will be used to compare the Active-treated group to the Sham-treated group at a number of percentage reductions in PCL-5 scores as candidate values of a successful treatment response. A range of percentage reduction values will be investigated as possible discriminating values to assist in designing future trials regarding sample size justification and power analysis, should a trial in future be designed with a responder analysis as the primary outcome or a secondary outcome.

Other participant reported outcomes analyses

Other participant reported outcomes, including assessment of blinding, will be analyzed according to their level of data (e.g., quantitative, rank order, or categorical) and validity of statistical assumptions required (e.g., homoscedasticity and normality).

Electrophysiological data analyses

Quantitative EEG data collected at BL and F1 will be stored on hard disk and analyzed offline. Raw data of each record will be visually inspected to reject significant artifact contamination. Selective data will be further analyzed by fast Fourier transform (FFT) routine to yield four consecutive frequency bands – delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13-35 Hz). Power density of each frequency band of each channel will be used to measure the EEG changes after treatment. Statistical analysis will include data reduction by initial factor analysis. Difference between treatment groups at each recording time will be tested by repeated measures and regression of number of treatments by channel. It is anticipated that successful treatment will result in reductions in low frequency rhythms and increases in peak alpha frequency and correspondent narrow-band density. These changes in EEG variables will be further correlated with clinical and cognitive data to explore the hypothesis that EEG parameters could be a biomarker for PTSD.

STUDY SITE MONITORING

Monitoring of the study sites will be conducted by a qualified and experienced Clinical Research Associate (CRA), with representation from the IDE Sponsor, the Study Principal Investigator and the Study Chair as needed. All monitoring will be conducted according to ICH/GCP guidelines. Monitoring visits will be conducted regularly, approximately every month at each site, to ensure that all aspects of the protocol are followed. All consent forms will be accounted for and all new consent forms accumulated since the previous site visit will be reviewed for regulatory compliance. A mix of electronic and paper study data collection forms (CRF) are the source documents. Paper forms will be used for any standard assessment that is not permitted to be collected electronically and will be used as a backup data collection method when there is an interruption in access to the electronic database. Paper data collection forms will be checked for consistency with the database and for compliance with study procedures for data collection form corrections.

Study materials, such as the Protocol, the Manual of Procedures (MoP), the study forms, IRB stamped consent forms, study logs, and study personnel certification records, will be reviewed to assure that all materials are current. The Principal Investigator and Study Chair will assume responsibility for external review of the Data Center.

CONFIDENTIALITY

Study participants will be assigned two unique identifiers (a unique Participant ID and a redundant identifier in the form of a non-identifying character Participant Alpha Code) that will be used to anonymize the participants in the electronic data capture system throughout the study. Personal identifiers will never be entered into the central electronic data capture system.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1984 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

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

A Certificate of Confidentiality will be obtained from the National Institutes of Health.

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

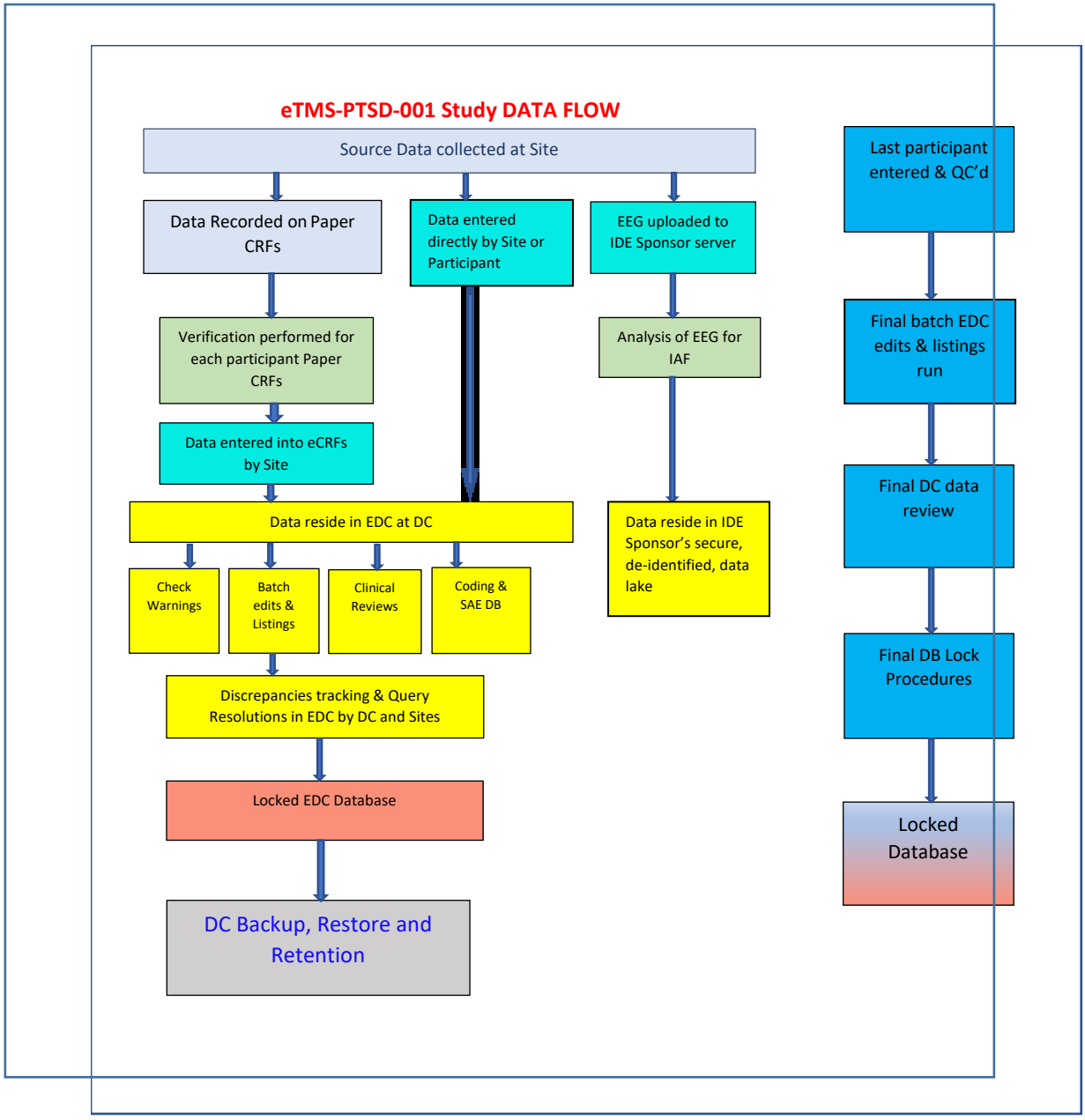
Participants will not have video or pictures taken while participating in the study. Their image, likeness, name or personal testimonies will not be used for any promotional or advertising purposes.

A clinical site master list with participant names, contact information, and study identifiers will be stored locally at each of the sites for that site only. Any paper or electronic files associated with these lists and information will be stored in a locked room in locked cabinets at the site with access only by authorized personnel or will be stored on password protected encrypted media. Any change in the ownership and location of these documents or files will be documented to allow the tracking of the stored records.

Data will be protected during transmission through SSL and two-factor authentication. Access to the study database will be restricted.

Study Data Flow

Figure 3: eTMS PTSD-001 Study Data Flow



Data Capture

The source data for this study are paper and electronic documents (standardized assessments and CRFs), as well as electronic data recordings of EEG/ECG. The paper study forms (CRF) are the primary data collection **templates** for the study. The forms will be implemented in the electronic data capture system (EDC). Participants and site staff will key source data into the EDC, depending on whether the data are collected via interview or self-administration. Authorized, uniquely credentialed study personnel will be given secure access to the system to review data as necessary for proper decision-making and signoffs.

Database and Environments

Data collection software are a combination of .net 7 using C#, and Microsoft SQL databases, with a front end leveraging angular framework. Testing, quality assurance, and production environments will run within the Microsoft Azure network, inclusive of Web services, APIs, and data storage. All data in storage is backed up twice daily and secured offsite.

Data Integrity

Error checking will be implemented in the EDC, including real-time range checking at entry, specification of required fields, skip pattern specification, and within-form internal consistency checks. Data will be checked for omissions in as real-time as possible, with explanation for missing data. Periodic cross-form consistency checks, and batch error-checking will be followed by data quality queries. Errors will be corrected in a manner that leaves a complete audit trail. The audit trail for any change will include information showing the original value, the new value, the date and time the change was made, who made the change, and a brief reason why the change was made.

When participants enter data, clinic personnel will check the entries for errors and omissions. Periodic checks and inspections will be conducted for data completeness and logical inconsistencies. Any discrepancies or needed clarifications will be resolved via Data Quality Query (DQQ), wherein study data collection personnel will be asked to resolve issues. Site monitoring, also, will include resolution of any issues not resolved by the periodic DQQs.

At the conclusion of each stage of the trial, a final round of quality checking will occur, and all issues that can be resolved, will be resolved. After the last participant visit is entered, data will be reviewed by a Study Monitor/Biostatistician, and a final batch EDC system edit run will be done to ensure all queries and discrepancies have been addressed. Issues that cannot be resolved will be described in a memo to file and attached to any analyses. The DC will notify the Study Chair, Principal Investigator and IDE Sponsor that it considers the database ready for lock. An approval signature by the Study Chair, Principal Investigator and Sponsor will be acquired prior to study database lock. The DC will perform final database lock procedures per SOP. Thereafter, the database will be locked for that stage. All final statistical analyses will be conducted on datasets extracted from the locked database.

Data Security

When paper forms are used as the primary data collection medium, these source documents will be housed at the clinical site under lock and key.

No data will be vulnerable to accidental or purposeful erasure. The data system will record the identity of personnel or participants accessing it. All entries and amendments will be time stamped. It will have security provisions to prevent unauthorized access. All records modified, added, or deleted follow a robust audit practice and can be reversed if necessary along with identifying who and when changes are made.

The EDC will have a secure, robust and scalable technology infrastructure validated according to 21 CFR 11. Study users will access the EDC with password protection. The EDC system will offer capacity for the study team to continuously review and monitor the data over the course of the clinical trial. The DC will maintain user accounts for the study EDC database access. All source code and documentation will be secured through SSL and use two-factor authentication.

Record Keeping, Handling, and Retention at the Sites

The investigators and authorized, trained site staff will maintain electronic or paper study documentation to ensure adherence to the protocol, regulations, Manual of Procedures (MoP), and any other study policies. Current study documentation may be maintained by the DC with internet access for study personnel.

The site investigators and study data collection staff will be responsible for completeness and accuracy of documented data and records to support study protocol adherence, review and audit. Enforcement will be carried out by regular internal audits and routine remote monitoring to verify that all processes are followed and required documentation is created and collected.

It is each clinical site Investigator's responsibility, by FDA regulation (21 CFR §812.140(d)), to retain essential study documents for at least 2 years after the study is completed. The Principal Investigator will notify each Investigator, in writing, of the date of completion of the study. If a site Investigator is not able to retain the records for the period of time required by regulation, or as otherwise instructed, then the Investigator will transfer the records to the PI according to the requirements of 21 CFR §812.140(e), under the regulations of 21 CFR Part 812. Notice of the transfer will be given to FDA not later than 10 working days after the transfer occurs – as per FDA regulation.

Data Transmission from Sites to Data Center

The Data Center (DC) will set up a secure file transfer system for data transmission for the study, provide the study personnel with access to upload data and files and will provide other study personnel with access to download data and files. Processes will be quality assured with test data prior to the first data transfer.

The DC will provide for encrypted and secure communications between the DC, research sites, and other study components. Encryption minimizes the likelihood of interception or modification of data during transmission. The DC's network infrastructure (internal and external systems) will be protected from the public Internet by various mechanisms including, but not limited to, firewalls (with restrictive policies in place), virtual private network (VPN) endpoints and software as well as antivirus and malware detection software. The protection system output will be collected and reviewed. For further protection against disaster or loss of data, all data will be backed up daily.

Data transmission starts with the electronic entry into the data system. Study personnel, and participants, will enter data into the electronic data capture system (described below).

Anonymized participant data will be received by the DC. All original transmissions will be stored electronically in a secure commercial server (i.e., the "DC server"). Any problems identified during the upload and transmission process will be reported back to the sites for correction or clarification. The process for addressing data discrepancies with sites will be determined in coordination with other study components during study set-up. The data transmitted to and stored on the DC server will be coded with the assigned participant identification number and alpha code; no personal identifiers will be associated with these data.

Data and Record Retention by the DC

All records created by or received by the DC, will be retained for as long as they are required to meet the contractual, legal, regulatory, administrative, financial and operational requirements of the DC, after which time they are transferred to the IDE Sponsor.

Data and Record Transfer

Raw EEG/ECG files will be transmitted automatically and securely via internet only to the IDE Sponsor for immediate processing to determine treatment parameters (i.e., frequency). The files will be identified only by study participant numbers.

The media used to transfer electronic files and study data will be discussed and documented in a study close-out plan that will be prepared as the study progresses. The necessary security measures will be taken for file/data security and integrity during preparing and transmitting these files.

The DC will provide a de-identified data set that integrates the final study data in the EDC system. The de-identified data set will be received by the IDE Sponsor, the study PI for purposes of biostatistical analyses, and the State of Ohio according to the funding RFP. Each data set will conform to the specifications of the receiver. Data transfer transmission will be encrypted and password protected.

Record Removal to IDE Sponsor's Facility

At the end of the study, all study data and materials requested by the IDE Sponsor will be sent, along with a packing document that identifies as specifically as possible, the contents of the shipment. Any paper files will be removed to the IDE Sponsor's facility, with notification to FDA under 21 CFR 812.140(e) within 10 working days of transfer. A memo detailing the transfer of responsibility for study documentation will be prepared by the DC and signed off by the Principal Investigator and IDE Sponsor prior to the shipment of material to the IDE Sponsor. The time of the end of the study will be formally declared in writing by the Principal Investigator, Study Chair, and the Data and Safety Monitoring Board (DSMB).

ETHICAL CONSIDERATIONS, INSTITUTIONAL REVIEW BOARD

This study will be conducted according to U.S. standards of Good Clinical Practice (GCP), applicable government regulations and institutional research policies and procedures.

This protocol, any amendments, Investigator curricula vitae, consent documents, and any other printed materials that will be given to study participants, will be submitted to an independent Institutional Review Board for formal approval of the study conduct.

All participants for this study will be provided a consent form describing this Study that contains sufficient information for participants to make an informed decision about their participation. The formal consent of a participant, using the currently IRB-approved consent form, must be obtained before that participant undergoes any Study procedure. The informed consent form must be signed by the participant, and the research personnel designated to obtain the consent. Only participants capable of understanding and consenting for themselves are eligible for this study.

A copy of the approval of the IRB concerning the conduct of the study will be given to the Study Chair, the Principal Investigator, the DC, and IDE Sponsor, and to each clinical site PI before commencement of this study.

FDA INVESTIGATIONAL DEVICE EXEMPTION

This clinical trial may be conducted under a United States Food and Drug Administration (FDA) Investigational Device Exemption (IDE), if so instructed by FDA.

TRIAL REGISTRATION

The study will be registered on ClinicalTrials.gov by IDE Sponsor in compliance with law. Sponsor will keep the listing current with all required information. When a study requires registration, FDA requires registration within 21 days of enrollment of the first participant. The study consent form will include a statement to the participant, as may be amended by IRB requirements, stating, "ClinicalTrials.gov is a Web site that provides information about clinical trials. A description of this clinical trial will be available on www.clinicaltrials.gov, as required

by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time."

REPORTING STANDARDS

Study results will be reported consistent with the CONSORT 2010 Statement, or any later revision. (CONsolidated Standards of Reporting Trials). (CONSORT Group, 2010)

PUBLICATION POLICIES

Authorship policies will conform to the International Committee of Medical Journal Editors (ICMJE) criteria. (International Committee of Medical Journal Editors, 2015) The ICMJE recommends that authorship be based on the following 4 criteria: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) drafting the work or revising it critically for important intellectual content; AND (3) final approval of the version to be published, AND (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors should meet all 4 criteria, and any Investigator meeting criterion 1 is to be given the opportunity to meet criteria 2 and 3.

The IDE Sponsor will, at a minimum, have the right to advance review publications and presentations before dissemination for the sole purpose of removing Sponsor's confidential information.

The individual clinical centers will not publish efficacy or safety data if those data were collected as part of a multicenter study. Main results of the trial will be published before other data from the study. Submission of data and analyses to the FDA may be done at any time after the database is quality checked and finalized; regulatory submissions will not be delayed pending publication.

DATA DISTRIBUTION AND USE

The anonymized primary database will be distributed to the IDE Sponsor and to the State of Ohio according to the terms of the Request for Proposal (State of Ohio (2021 RFP Number SRC0000002472, Index Number DMH009).

The linkage table of names with participant identifiers will be unavailable to the Investigators after the locked Study database is transmitted to the IDE Sponsor and the representative of the State of Ohio. Linkage tables received from the sites will be transmitted by the Study PI to the IDE Sponsor.

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