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Pilot Sham-Controlled Acceptability Trial of Synchronized Transcranial Magnetic Stimulation for Substance Use-Disordered Veterans

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RUNNING HEAD: sTMS FOR SUBSTANCE USE DISORDERED VETERANS

Title: Pilot Sham-Controlled Acceptability Trial of Synchronized Transcranial Magnetic Stimulation for Substance Use-Disordered Veterans

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ABSTRACT

Introduction Substance use disorders (SUDs) take an enormous toll on United States Veterans and civilians alike. Existing empirically supported interventions vary by substance and demonstrate only moderate efficacy. Non-invasive brain stimulation represents an innovative new treatment for SUDs, yet aspects of traditional neurostimulation may hinder its implementation in SUD populations. Synchronized transcranial magnetic stimulation (sTMS) uses rotating rare earth magnets to deliver low-field stimulation synchronized to an individual's alpha peak frequency that is safe for at-home administration. The current study aims to assess the acceptability and feasibility of sTMS, as well as the safety of at-home sTMS administration for substance disordered Veterans.

Methods and analysis Sixty Veterans in substance treatment at the Providence VA will be randomized to receive six weeks of either active or sham sTMS treatment. Eligibility will be confirmed by meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for an alcohol, cocaine, or opioid use disorder at baseline. Daily supervised sTMS treatment will occur either in-clinic or at-home through video monitoring. Clinical and self-report assessments and drug/alcohol cue reactivity tasks will be completed at baseline, end of treatment and one-month follow up. Urine drug screening will be completed once per week during the treatment phase. Primary outcomes include treatment adherence/retention and treatment satisfaction to evaluate sTMS feasibility and acceptability in Veterans with SUDs. The safety of in-lab and at-home sTMS administration will be assessed via adverse event monitoring.

Ethics and dissemination Study procedures were approved in August 2021 with data collection beginning in September 2021. Data collection is planned to continue through December 2022. Pilot study results will be disseminated at national conferences and in peer-reviewed journals. Results will serve to inform the development of large-scale clinical trials of sTMS efficacy for substance-disordered Veterans.

Trail registration number clinicaltrials.gov identifier NCT04336293 (pre-results).

Strengths and limitations of this study

- Synchronized transcranial magnetic stimulation (sTMS) is a novel form of neuromodulation that has yet to be investigated for the treatment of substance use disorders (SUDs).
- This protocol implements a double-blind randomized sham-control design to evaluate the acceptability, feasibility, and safety of sTMS in Veterans with alcohol, cocaine, or opioid use disorders.
- This trial will measure the safety of at-home sTMS administration, and thus lay the foundation for future efficacy trials for a portable, patient operated, neurostimulation treatment for SUDs.
- Enrollment will be limited to sixty Veterans (20 participants each with alcohol, cocaine, and opioid use disorder respectively) and will therefore not produce a sample large enough to evaluate sTMS efficacy for substance related outcomes.
- Participants will not be randomized to at-home or in-clinic treatment administration, which creates the potential for patient self-selection biases and impairs active vs. sham treatment balancing across the treatment delivery locations.

INTRODUCTION

Substance use disorders (SUDs) disproportionately affect United States Veterans, with treatment costs exceeding $350M annually within the Veterans Health Administration (VHA) alone[1, 2]. However, empirically supported pharmacological and behavioral treatments vary by substance and display only moderate efficacy[3-5]. Therefore, alternative SUD treatments, such as non-invasive neurostimulation, warrant investigation.

Trials investigating the effect of the most common form of neurostimulation, repetitive transcranial magnetic stimulation (rTMS), in reducing substance specific cravings have produced varying degrees of success for those with alcohol, cocaine or opioid use disorders[6-10]. Mixed findings may be due to the nature of rTMS and how the device is calibrated for treatment[11, 12]. Standard rTMS involves device calibration to individual cortical excitability, yet precisely how substance use changes cortical excitability remains unclear[13]. Any such changes to neural reactivity in substance users could increase the risk of seizure through the application of too much energy[14]. Conversely, treatment non-response is possible if too little energy is delivered. To optimize the likelihood of treatment success, and increase safety for those with SUDs, the development of an intervention that can provide low level stimulation and enhance access though at-home use is critical. These concerns highlight synchronized transcranial magnetic stimulation (sTMS), which delivers non-invasive magnetic energy calibrated to a person's individualized alpha frequency (IAF) measured via electroencephalography (EEG), as a novel SUD treatment alternative[15].

Furthermore, spatial targeting within neurostimulation for SUDs continues to be heavily debated[16, 17]. In a review of TMS for the treatment of depression, Philip et al. (2018) found a lack of consensus regarding target site parameters, thus raising the question of whether precise spatial targeting is necessary for treatment success. sTMS operates through the application of energy to midline brain regions more broadly and has received preliminary support in the treatment of depression and posttraumatic stress disorder (PTSD), reinforcing the notion that spatial targeting may not be essential[19, 20]. The building evidence that TMS effects are not brain region specific opens the door to research accounting for frequency specificity, such as stimulation calibrated to an individualized frequency.

Treatment retention is another challenge for empirically supported SUD treatments[21]. Compared to traditional rTMS, which involves daily outpatient appointments over the course of many weeks, the sTMS device, manufactured by Wave Neuroscience Inc., can be operated by patients in their homes[22]. An investigation of the safety of at-home sTMS for SUDs could reduce burden among a clinical population that faces tremendous barriers to treatment success[23]. In sum, the factors listed above imply that sTMS may serve as a novel treatment for Veterans with substance use disorders.

Current Aims

Our primary objective is to conduct the first study to deliver sTMS to Veterans with alcohol, cocaine, or opioid use disorders. Two specific aims will be addressed. First, this study serves to assess the acceptability and feasibility of sTMS among Veterans with SUDs using the Wave Neuroscience device in a pilot sham-controlled trial. Secondly, we will evaluate the safety of in-lab and at-home sTMS administration for substance-disordered Veterans. Our hope is to lay the groundwork for larger scale clinical trials that will evaluate the efficacy of sTMS to help those with addiction, particularly through the establishment of at-home neurostimulation treatment.

METHODS AND ANALYSIS

Sample Size Calculation

At least 20 subjects will be enrolled for each of the three substances focused on in this study (alcohol, cocaine, opioids) for a total N of 60. A previous study focused on different sTMS parameters for SUD utilized a sample size of ~N=20 [24]. The sample size for this pilot-controlled

study is based on estimations focused on the amount of information required to inform next steps in trial design, rather than on statistically significant calculations for a primary safety or efficacy endpoint. By employing a comparable sample size for each substance, we anticipate having sufficient power to detect significant differences between baseline and endpoint. This sample size is adequate to determine the appropriate sample size for subsequent trials.

Participants

Individuals will be eligible to participate if they (1) are Veterans affiliated with VA Providence, Providence, Rhode Island; (2) meet the DSM-V criteria for SUD; and (3) are 18-70 years of age (inclusive) (see table 1 for full list of inclusion criteria).

Participants will be excluded if they (1) have greater than a mild TBI; (2) have a current or significant past neurological disorder including seizure, primary or secondary CNS tremor, stroke, or cerebral aneurysm; (3) have a severe psychiatric disorder that requires immediate clinical attention (e.g., psychosis, suicidal ideation with intent and plan); and/or (4) have implanted devices activated or controlled by physiologic signals (e.g., cardiac pacemakers, implanted medication pumps, etc.). Participants must also (5) not have an implanted device or metal in the brain, cervical spinal cord, or upper thoracic spinal cord (see table 1 for full list of exclusion criteria).

Table 1. Participant inclusion and exclusion criteria for study

Inclusion	Exclusion
(1) outpatients 18-70 years of age (inclusive) at time of screening	(1) any history of TBI with a severity greater than mild. This will be defined by meeting any of the following criteria: a) history of losing consciousness due to head injury for greater than 10 minutes b) history of losing consciousness due to a head injury with documented evidence of brain injury (including brain atrophy) c) history of have three or more concussions within the span of one year.
(2) meet DSM-V criteria for SUD at time of baseline visit criteria determined by the Structured Clinical Interview for DSM-V (SCID-5) which is a structured clinical interview used to confirm SUD diagnosis	(2) current (or past if appropriate) significant neurological disorder, or lifetime history of a) seizure disorder b) primary or secondary CNS tumors c) stroke or d) cerebral aneurysm
(3) veterans will not be excluded for comorbid substance use (i.e., additional substance use beyond alcohol, cocaine, or opiates), but data will be collected on use patterns so that these behaviors may be balanced across conditions and/or controlled for statistically	(3) implanted devices activated or controlled by physiologic signals, such as cardiac pacemakers, implanted medication pumps, and intra cardiac lines. Participants must also not have an implanted device (deep brain stimulation) or metal in the following areas: brain, cervical spinal cord, or upper thoracic spinal cord.
(4) abstinent from alcohol for at least 3 days prior to baseline sTMS procedures abstinent from benzodiazepines if meeting criteria for benzodiazepine use disorder	(4) have metal objects lodged in their body, such as shrapnel, bullets, or bullet fragments, or magnetically activated dental implants.
(5) be on a stable psychotropic medication regimen for at least 6 weeks prior to baseline, or no psychotropic medication at all (for at least 6 weeks prior to baseline), and be willing to maintain the current regimen and dosing for the duration of the study (unless medically necessary to make changes). If there is a psychotropic medication change during the 6 weeks of sTMS treatment, the participants will notify the study team.	(5) significant alcohol withdrawal symptoms at baseline
(6) if of childbearing potential, agree to use an	

acceptable method of birth control for the duration of the study treatment period	(6) >1 month of abstinence from alcohol prior to baseline
(7) be willing and able to comply with all study related procedures and visits	(7) are pregnant or lactating, or planning to become pregnant within three months after baseline
(8) be capable of independently reading and understanding patient information materials and giving written informed consent	(8) legally mandated substance abuse treatment
(9) currently assigned a VA mental health treatment coordinator and willing to remain in care throughout the study	(9) inability to obtain EEG of sufficient quality and duration that can be processed for use to calibrate the study device
(10) be willing to provide two verifiable emergency contacts	(10) unstable medical illness, or, in the opinion of the investigator, significant absence of appropriate medical care
	(11) current Axis 1 primary psychotic disorder, or bipolar I disorder
	(12) have active suicidal intent or plan, or in the investigative team's opinion, is likely to attempt suicide within the next six months criteria determined by the Structured Clinical Interview for DSM-5 (SCID-5), which asks specifically about suicidal ideation (both passive and active), suicide plans, and previous suicide attempts
	(13) demonstrate the presence of any other condition or circumstance that, in the opinion of the investigative team, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments

Procedures

Recruitment and screening

Up to 60 participants who meet criteria for a DSM-V SUD will be recruited to complete this study (see figure 1), with 20 identifying alcohol as their drug of choice, 20 identifying cocaine as their drug of choice, and 20 identifying opiates are their drug of choice. Veterans will be recruited through the Collaborative Addiction and Recovery Services program at VA Providence. Potential participants may call in response to advertisements for the study or will be referred by clinicians (by giving patients the study ad). Research assistants will assess preliminary demographic eligibility criteria upon phone screen. Those who meet preliminary eligibility criteria will be invited to the lab for a baseline visit. After providing written informed consent, psychiatric interview and self-report measures will be used to confirm eligibility with regard to diagnosis, past psychotropic treatment history, current health history, and current symptom severity (see table 2 for full list of assessments). There is a requirement for maintenance on a stable regimen of psychotropic medications (if applicable) for 6 weeks prior to baseline and during participation in sTMS treatment.

[Figure 1 here]

Baseline

Participants meeting initial phone screen eligibility will be invited to a baseline visit. Research staff will review and obtain written informed consent for either at-home administration or in-lab administration prior to the initiation of study procedures.

Psychiatric interviews and self-report measures will confirm eligibility regarding SUD diagnosis, past psychiatric treatment history, current health history and current symptom severity. Demographic and clinical data include gender, age, substance use (quantity and frequency), and co-morbid symptomatology which will be collected to quantify change due to sTMS, or as factors that may influence the effect and tolerability of sTMS. Participants will complete a Timeline Follow Back (TLFB) to confirm substance use over the past 30 days [25]. The Quick Structured Clinical Interview for DSM-5 Disorders (Quick SCID-5)[26] will assess diagnostic criteria for alcohol, cocaine or opioid use disorder.

Laboratory assessments will quantify substance use and include a urine drug screen (USD), ethyl glucuronide (EtG) test and the following liver functioning tests: GGT (u/l), SGOT/AST (u/l), SGPT/ALT (u/l), Total Bilirubin (mg/dl). Prior research shows that response to neurostimulation may be related to genetic or epigenetic differences between people. Accordingly, an additional blood sample will be collected, with DNA extracted and assessed using genome wide and epigenome wide analyses to investigate genetic and epigenetic differences in the context of treatment response.

Drug/alcohol cue reactivity will be measured via a task presented using E-Prime 3 software (Psychology Software Tools, Inc., 2017)[27] following work by the Hanlon group in the area of cue reactivity and TMS. The computer task consists of six 96-second blocks. The first three blocks contain neutral images (e.g., glass of water, cooking utensils, people eating dinner). The last three blocks contain images of drug- or alcohol-related stimuli customized for each group (e.g., crack pipe for cocaine users, liquor bottles for alcohol users). Prior to starting the task and at the end of each block, participants will record their substance cravings on a paper assessment.

Participants will undergo a 10-minute resting state EEG after which deidentified data will be shared with the sTMS device manufacturer, Wave Neuroscience, for analyses. These analyses will capture participants' individualized alpha frequency (IAF), a marker of inter-individual differences in EEG rhythms, which will indicate the optimal magnetic field frequency for treatment.

Assessment Goal	Measure/Study Procedure	Time-point	Mode
Diagnostic and Screening	Phone Screen (to determine eligibility)	Pre-B	Interview
	Screening, Demographics, Medical Review	B	Self-report
	Structured Clinical Interview for DMS-V	B	Interview
	EEG	B	Clinician-Administered
SUD	Time-Line Follow-back	B, W, PT1 PT2	Interview
	Alcohol Urge Questionnaire (AUQ), Cocaine Urge Questionnaire (CUQ), or Opioid Urge Questionnaire (OUQ)	B, W, PT1, PT2	Self-report
PTSD	Clinician-Administered PTSD Scale (CAPS)	B, PT1, PT2	Interview

	PTSD Checklist for DSM-5 (PCL-5)	B, PT1, PT2	Self-report
	The Life Events Checklist (LEC)	B	Self-report
Depression	Inventory of Depressive Symptomatology Self-Report (IDS- SR)	B, PT1, PT2	Self-report
Affect	Positive and Negative Affect Schedule (PANAS)	B, PT1, PT2	Self-report
Anxiety	State-Trait Anxiety Inventory (STAI)	B, PT1, PT2	Self-report
Quality of Life	Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	B, PT1, PT2	Self-report
	Social and Occupational Functioning Assessment Scale (SOFAS)	B, PT1, PT2	Self-report
Sleep	Pittsburgh Sleep Quality Index (PSQI)	B, W, PT1, PT2	Self-report
General	Clinical Global Impressions– Severity (CGI-s)	B, PT1, PT2	Interview
	CGI – Improvement (CGI-i)	B, PT1, PT2	Interview
Treatment Satisfaction	Adapted Satisfaction with Treatment Form	PT1, PT2	Self-report
Blinding Questionnaire	Treatment Blinding Questionnaire	PT1	Self-report
Specimen Collection	Urine Toxicology Screen	B, W, PT1, PT2	Laboratory
	Blood Draw	B	Laboratory
	DNA Collection	B	Laboratory

Randomization and Blinding

Participants will be randomized into either active sTMS or sham sTMS treatment groups. Treatment will be delivered in a double-blind fashion so that neither participants nor research staff will be aware of study condition. The sham sTMS device has an external appearance, weight, sound and operation indistinguishable from the active sTMS device with a non-magnetic rotating metal shaft replacing the rotating neodymium magnets to reduce the potential for unblinding. Participants will self-select into either at-home or in-lab sTMS administration procedures.

Treatment phase

sTMS Device

The study will use the Wave Neuroscience sTMS device which consists of three main elements: (1) Headset; (2) Patient Passport Module (PPM); and (3) Base Station. The PPM is a USB flash drive containing an encrypted file with the IAF device parameter as well as a code to specify whether the PPM is destined for an active or sham device. If an active PPM is inserted into a sham device or vice versa, the display on the base station will show "invalid PPM."

At home administration

Treatment sessions will be completed in participants' homes using a portable sTMS device. Acting under the supervision of a TMS-credentialed physician, trained research staff will observe all 30 in-home treatments (5 per week) through video technology to ensure that participants are awake and using the device correctly. Treatment emergent side effects associated with stimulation (during treatments) and emerging between treatment sessions will be queried on each treatment day and recorded into participants' medical charts.

In lab administration

Trained research staff will be present for all sTMS sessions at VA Providence. During the sTMS session, study staff will ensure that participants are awake and using the device correctly. Treatment emergent side effects will be queried and recorded on each treatment day. Appropriate medical coverage is available at all times.

Common treatment procedures

sTMS will be delivered following Wave Neuroscience guidelines using the device user manual. Each participant's IAF will be displayed on the device LCD screen once the PPM is plugged in. Before initiating treatment sessions, study staff will confirm that the IAF parameters displayed on the device LCD screen match the IAF provided by Wave Neuroscience. If the values do not match, treatment will not be administered. Participants will be instructed to remove jewelry above their shoulders and anything from their mouth (e.g., gum) that could generate facial muscle activity. They will then secure the sTMS device to their heads, lay down in a semi-reclined position and turn the magnetic adjustment knobs. After pressing the start button, the device will rotate the magnets for 30 minutes, at which point rotation ceases and the session ends. Sessions may be paused or canceled at any time, however once canceled, or completed, the device is programmed such that a new session cannot be started for 10 hours. This prevents subjects from excessively using the device while not under the direct supervision of study staff.

Weekly in-person visits will occur across the treatment phase (six weekly visits total). Participants will complete a TLFB, brief self-reports and provide a urine drug screen. Additional measures will be taken by research staff to protect against COVID-19 infection including pre-appointment COVID screening, PPE, etc.

Follow Up Assessments

Two post-treatment appointments will occur: an end of treatment (EOT) visit 72-hours after the final treatment session, and a one-month follow up. At both post-treatment visits participants will complete self-report questionnaires, the drug/cue reactivity task, a TLFB and a urine drug screen. At the EOT visit, participants will additionally be asked to complete a treatment satisfaction questionnaire and condition blinding questionnaire to ensure they were blinded to study condition.

Compensation

Participants will be offered compensation for completion of specific milestones in the study: $50 for completion of all baseline procedures, $100 upon completion of all 30 sTMS treatments, plus another $75 for completing the one-month follow up, totaling $225. Payment will be offered in the form of gift cards or electronic funds transfer.

Primary Outcomes

Aim 1: To demonstrate feasibility and acceptability of at-home and in-lab sTMS among Veterans with specific substance use disorders (i.e., alcohol, cocaine, opioids) in a pilot sham-controlled study. Thirty sTMS treatment sessions will occur with trained research staff monitoring in person or through video technology to verify that participants are awake and using the device properly. Feasibility will be evaluated by rates of recruitment, treatment adherence, retention, and completion of assessments (see table 3). Acceptability will be measured by retention and participant reports of acceptability and satisfaction (see table 3).

Table 3. Primary clinical and mechanistic outcomes

Clinical outcome	Measure
Aim 1: To demonstrate feasibility and acceptability of at-home sTMS among Veterans with specific substance use disorders (i.e. alcohol, cocaine, opioids) in a pilot sham-controlled study	
Feasibility Recruitment Retention Adherence	Rate of 2 or more patients per month 50% or higher study assessment completion rate Completion of at least 80% of sTMS treatment sessions
Acceptability	Treatment Satisfaction Questionnaire
Aim 2: To evaluate the safety of at-home sTMS among Veterans with substance use disorders.	
Safety	Monitor all adverse events that occur during the study using a combination of clinical interviews and spontaneous adverse event reports (coded using the Medical Dictionary of Regulatory activities), and through systematic self-report using SAFTEE. All adverse events will be assessed and described in terms of the relationship to the device, relationship to the procedure, severity of the event, subsequent treatment or intervention, and the resolution status. All reporting procedures will align with those listed in 21 CFR 812.150

Although we anticipate the sample will not be large enough to provide adequate statistical power to test for differences between sTMS and sham stimulation, we anticipate collecting feasibility data and will generate confidence intervals around all observed effect sizes.

Aim 2: To evaluate the safety of in-lab and at-home sTMS among Veterans with substance use disorders. Safety of at-home sTMS administration for Veterans with alcohol, cocaine and opioid use disorder will be assessed through adverse event monitoring. Daily safety questions will probe potential treatment related side effects and changes in substance use. Medications will be

monitored through self-report and electronic medical record review. Adverse events will immediately be reported to the principal investigator.

Other Outcomes

The clinical interview assessment of substance use symptoms will include the Clinical Global Impressions-Severity (CGI-S)[28] to quantify the severity of the participant's mental illness at the time of assessment; Social Occupational Functioning Assessment Scale (SOFAS) [29] to quantify the participant's level of social functioning in daily life at the time of assessment; and CGI-Improvement (CGI-I) assessment to quantify the level of improvement in participants' illness from baseline to the time of assessment.

The following self-report questionnaires will be administered in order to quantify measures of PTSD, depression, quality of life, affect and sleep to assess how these constructs may be related to substance use, craving and sTMS treatment feasibility: Clinician-Administered PTSD Scale (CAPS),[30] PTSD Checklist for DMS-V (PCL-5),[31] the Life Events Checklist (LEC),[32] Inventory of Depression Symptomatology Self-Report (IDS-SR) [33, 34], Positive and Negative Affect Schedule (PANAS) [35], State-Trait Anxiety Inventory (STAI),[36] Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[37] Pittsburg Sleep Quality Index (PSQI),[38] Adaptation Satisfaction with treatment Form, and Treatment Blinding Questionnaire.

Data Analysis Plan

Data management and confidentiality.

Only research staff who have undergone the relevant responsible research conduct and handling of private and confidential information training will handle study data. These data will only be used for research purposes. A unique identification number for each participant will be used on all assessments in lieu of any identifying information. Additionally, analyses will be completed on de-identified data.

Missing data.

Missing data (i.e., participants lost to follow-up) will be handled using full information maximum likelihood estimation for statistical models in our primary analyses. This type of approach can easily be implemented in model-based software packages, such as MPlus. Moreover, all available cases will contribute to the computation of the maximum likelihood estimates, providing the most likely results based on the observed data. Additionally, exploratory and sensitivity analyses will be conducted to characterize patterns of missingness and determine whether systematic similarities exist for participants who were lost to follow-up.

Aim 1: Feasibility and acceptability.

Adequate feasibility of the intervention will be indicated by a recruitment rate of 2 or more patients per month and retention rates of 50% or higher completed assessments based on previous sTMS trials [19] and empirical evidence from 3-month treatment programs [39]. Additionally, acceptable rates of treatment adherence will be completion of at least 80% of the treatment sessions as defined by a previous study that showed an effect of sTMS on depression[18].

Aim 2: Safety of in-lab and at-home sTMS.

In order to evaluate safety, we will meticulously monitor all adverse events that occur during the study. Adverse events will be captured using a combination of clinician interviews and spontaneous adverse event reports (coded using the current version of the Medical Dictionary for Regulatory Activities), and through systematic self-report using the SAFTEE[40]. All adverse events will be assessed and described in terms of the relationship to the device, relationship to the procedure, severity of the event, subsequent treatment or intervention, and the resolution

status. Medications will be followed at each study visit and corroborated with the VA electronic medical record. Any adverse events (AE) that occur while participants are using the sTMS device at-home will be captured by trained research staff who will observe all 30 at-home treatment sessions via video technology. All reported AEs will be logged and reported to the principal investigator.

Patient and Public Involvement

As part of this pilot trial, participants will provide important feedback on feasibility and safety through communication with research staff, as well as a treatment satisfaction questionnaire that assesses the burden of the intervention. Participants and members of the public were not involved in the design of study procedures. We will use feedback to inform efficacy trials.

ETHICS AND DISSEMINATION

Ethics

All study procedures were approved by the institutional review board and research and development committee at VA Providence. Serious and unexpected adverse events will be reported to the IRB within 24 hours while potentially adverse events will be reported during annual continuing reviews. The sTMS device has received a significant risk determination for at-home use by the Food and Drug Administration. As such, an independent data safety monitoring board composed of individuals not affiliated with the study will convene on at least a quarterly basis to review all relevant data pertaining to participant safety.

To address the risk of worsening SUD symptoms, substance use will be monitored with prescribed cutoffs in substance use assessments acting as indicators that symptoms may be worsening. Participants deemed at risk will be withdrawn and referred to the Providence VA Collaborative Addiction and Recovery Services clinic. Participants endorsing significant withdrawal symptoms will be instructed to seek immediate medical treatment. The PI will discontinue the trial if (1) participants experience any serious adverse events found to be attributable to sTMS; (2) two participants experience clinically meaningful deterioration in suicidal ideation or (3) any participant attempts suicide.

Dissemination

This study will lay the groundwork for large scale clinical trials that will evaluate the efficacy of sTMS as a treatment for SUD. The results of this pilot sham-controlled trial will be disseminated to maximize the impact of preliminary findings. The principal investigator will share de-identified datasets, statistics, and results collected from this proposal by depositing these data at the National Library of Medicine PubMed Central website repository as this is a VA supported data repository. Planned manuscripts include a primary outcomes paper(s) describing sTMS treatment feasibility for Veterans with substance use disorders (i.e., alcohol, cocaine, opioids). Results of this study will be presented at national conferences such as Research Society on Alcoholism and College on Problems of Drug Dependence.

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Contributors

JJ and JEM drafted the initial proposal, with input from NSP, RMS and LB. MJQ, JCL and CBB drafted the manuscript, which all authors reviewed and revised.

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Disclaimer
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Competing interests None declared.

Patient and public involvement. Patients and/or public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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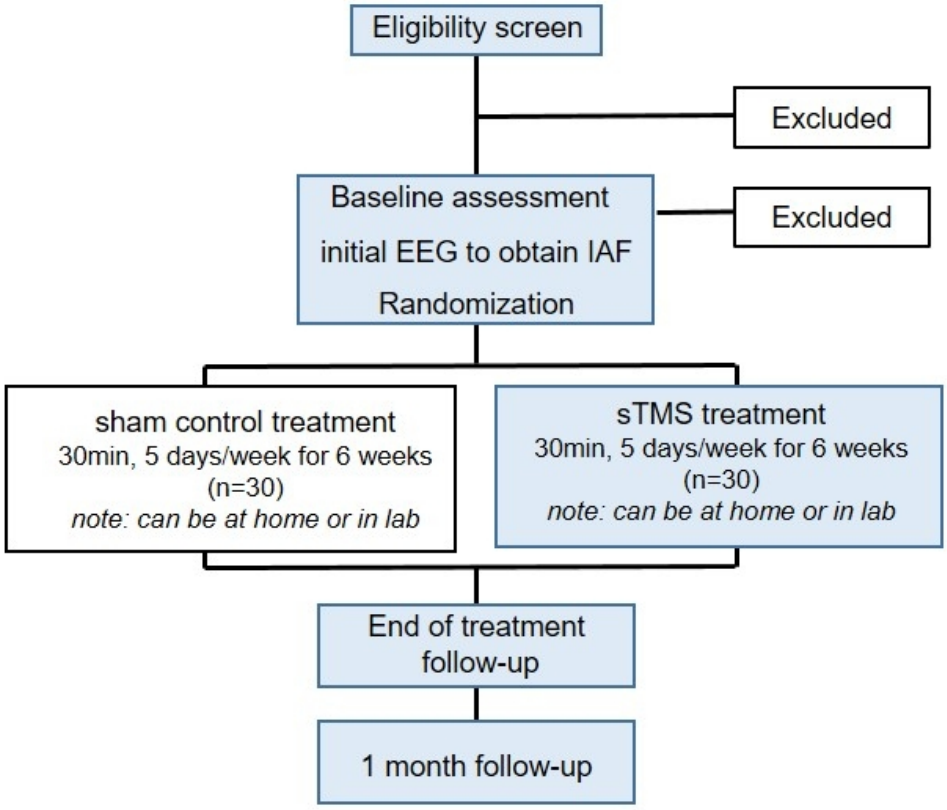

Figure 1. Participant flow diagram (n=60). EEG, electroencephalogram; IAF, individualized alpha frequency; sTMS, synchronized transcranial magnetic stimulation. This includes individuals from all 3 substance groups (alcohol, cocaine and opioids).

Figure 1. Participant flow diagram (n=60). EEG, electroencephalogram; IAF, individualized alpha frequency; sTMS, synchronized transcranial magnetic stimulation. This includes individuals from all 3 substance groups (alcohol, cocaine and opioids).

107x115mm (150 x 150 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Present in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Yes
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Yes
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	No
Funding	4	Sources and types of financial, material, and other support	Yes
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Yes
	5b	Name and contact information for the trial sponsor	Yes
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Yes
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Yes

	6b	Explanation for choice of comparators	Yes
Objectives	7	Specific objectives or hypotheses	Yes
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Yes
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Yes
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Yes
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Yes
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Yes
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Yes
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Yes
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Yes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Yes

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Yes
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Yes
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Yes
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Yes
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Yes
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Yes
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Yes
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Yes
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Yes
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Yes
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	No
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Yes
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Yes
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Yes
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Yes
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Protocol for the Pilot Sham-Controlled Acceptability Trial of Synchronized Transcranial Magnetic Stimulation for Substance Use-Disordered Veterans

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RUNNING HEAD: sTMS FOR SUBSTANCE USE DISORDERED VETERANS

Title: Protocol for the Pilot Sham-Controlled Acceptability Trial of Synchronized Transcranial Magnetic Stimulation for Substance Use-Disordered Veterans

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ABSTRACT

Introduction Substance use disorders (SUDs) take an enormous toll on United States Veterans and civilians alike. Existing empirically supported interventions vary by substance and demonstrate only moderate efficacy. Non-invasive brain stimulation represents an innovative treatment for SUDs, yet aspects of traditional neurostimulation may hinder its implementation in SUD populations. Synchronized transcranial magnetic stimulation (sTMS) uses rotating rare earth magnets to deliver low-field stimulation synchronized to an individual's alpha peak frequency that is safe for at-home administration. The current trial aims to assess the acceptability and feasibility of sTMS, as well as the safety of at-home sTMS administration for substance disordered Veterans.

Methods and analysis Sixty Veterans in substance treatment at the Providence VA will be randomized to receive six weeks of active or sham sTMS treatment. Eligibility will be confirmed by meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for an alcohol, cocaine, or opioid use disorder. Daily supervised sTMS treatment will occur either in-clinic or at-home through video monitoring. Clinical and self-report assessments will be completed at baseline, end of treatment and one-month follow up. Urine drug screening will occur once per week during the treatment phase. Primary outcomes include treatment adherence/retention and satisfaction to evaluate sTMS feasibility and acceptability in Veterans with SUDs. The safety of at-home sTMS administration will be assessed via adverse event monitoring.

Ethics and dissemination The sTMS device received a significant risk determination for at-home use by the Food and Drug Administration in July 2021. Ethics approval was obtained in August 2021 from the Providence VA institutional review board and research and development committee. Data collection began in September 2021 and is planned to continue through December 2023. Findings will be disseminated at national conferences and in peer-reviewed journals. Results will serve to inform the development of large-scale clinical trials of sTMS efficacy for substance-disordered Veterans.

Trail registration number clinicaltrials.gov identifier NCT04336293 (pre-results).

Strengths and limitations of this study

- Synchronized transcranial magnetic stimulation (sTMS) is a novel form of neuromodulation that has yet to be investigated for the treatment of substance use disorders (SUDs).
- This protocol implements a double-blind randomized sham-control design to evaluate the acceptability, feasibility, and safety of sTMS in Veterans with alcohol, cocaine, or opioid use disorders.
- This trial will measure the safety of at-home sTMS administration, and thus lay the foundation for future efficacy trials for a portable, patient operated, neurostimulation treatment for SUDs.
- Enrollment will be limited to sixty Veterans (20 participants each with alcohol, cocaine, and opioid use disorder respectively) and will therefore not produce a sample large enough to evaluate sTMS efficacy for substance related outcomes.
- Participants will not be randomized to at-home or in-clinic treatment administration, which creates the potential for patient self-selection biases and impairs active vs. sham treatment balancing across the treatment delivery locations.

INTRODUCTION

Substance use disorders (SUDs) disproportionately affect United States Veterans, with treatment costs exceeding $350M annually within the Veterans Health Administration (VHA) alone[1, 2]. However, empirically supported pharmacological and behavioral treatments vary by substance and display only moderate efficacy[3-5]. Therefore, alternative SUD treatments, such as non-invasive neurostimulation, warrant investigation.

Trials investigating the effect of the most common form of neurostimulation, repetitive transcranial magnetic stimulation (rTMS), in reducing substance specific cravings have produced varying degrees of success for those with alcohol, cocaine or opioid use disorders[6-10]. Mixed findings may be due to the nature of rTMS and how the device is calibrated for treatment[11, 12]. Standard rTMS involves device calibration to individual cortical excitability, yet precisely how substance use changes cortical excitability remains unclear[13]. Any such changes to neural reactivity in substance users could increase the risk of seizure through the application of too much energy[14]. Conversely, treatment non-response is possible if too little energy is delivered. To optimize the likelihood of treatment success, and increase safety for those with SUDs, the development of an intervention that can provide low level stimulation and enhance access though at-home use is critical. These concerns highlight synchronized transcranial magnetic stimulation (sTMS), which delivers non-invasive magnetic energy calibrated to a person's individualized alpha frequency (IAF) measured via electroencephalography (EEG), as a novel SUD treatment alternative[15].

Furthermore, spatial targeting within neurostimulation for SUDs continues to be heavily debated[16, 17]. In a review of TMS for the treatment of depression, Philip et al. (2018) found a lack of consensus regarding target site parameters, thus raising the question of whether precise spatial targeting is necessary for treatment success [18]. sTMS operates through the application of energy to midline brain regions more broadly and has received preliminary support in the treatment of depression and posttraumatic stress disorder (PTSD), reinforcing the notion that spatial targeting may not be essential[19, 20]. The building evidence that TMS effects are not brain region specific opens the door to research accounting for frequency specificity, such as stimulation calibrated to an individualized frequency.

Treatment retention is another challenge for empirically supported SUD treatments[21]. Compared to traditional rTMS, which involves daily outpatient appointments over the course of many weeks, the sTMS device, manufactured by Wave Neuroscience Inc., can be operated by patients in their homes[22]. An investigation of the safety of at-home sTMS for SUDs could reduce burden among a clinical population that faces tremendous barriers to treatment success[23]. In sum, the factors listed above imply that sTMS may serve as a novel treatment for Veterans with substance use disorders.

Current Aims

Our primary objective is to conduct the first study to deliver sTMS to Veterans with alcohol, cocaine, or opioid use disorders. Two specific aims will be addressed. First, this study serves to assess the acceptability and feasibility of sTMS among Veterans with SUDs using the Wave Neuroscience device in a pilot sham-controlled trial. Secondly, we will evaluate the safety of in-lab and at-home sTMS administration for substance-disordered Veterans. Our hope is to lay the groundwork for larger scale clinical trials that will evaluate the efficacy of sTMS to help those with addiction, particularly through the establishment of at-home neurostimulation treatment.

METHODS AND ANALYSIS

Sample Size Calculation

At least 20 subjects will be enrolled for each of the three substances focused on in this study (alcohol, cocaine, opioids) for a total N of 60. A previous study focused on different sTMS

parameters for SUD utilized a sample size of ~N=20 [24]. The sample size for this pilot-controlled study is based on estimations focused on the amount of information required to inform next steps in trial design, rather than on statistically significant calculations for a primary safety or efficacy endpoint. By employing a comparable sample size for each substance, we anticipate having sufficient power to detect significant differences between baseline and endpoint. This sample size is adequate to determine the appropriate sample size for subsequent trials.

Participants

Individuals will be eligible to participate if they (1) are Veterans affiliated with VA Providence, Providence, Rhode Island; (2) meet the DSM-V criteria for SUD; and (3) are 18-70 years of age (inclusive) (see table 1 for full list of inclusion criteria).

Participants will be excluded if they (1) have greater than a mild TBI; (2) have a current or significant past neurological disorder including seizure, primary or secondary CNS tremor, stroke, or cerebral aneurysm; (3) have a severe psychiatric disorder that requires immediate clinical attention (e.g., psychosis, suicidal ideation with intent and plan); and/or (4) have implanted devices activated or controlled by physiologic signals (e.g., cardiac pacemakers, implanted medication pumps, etc.). Participants must also (5) not have an implanted device or metal in the brain, cervical spinal cord, or upper thoracic spinal cord (see table 1 for full list of exclusion criteria).

Table 1. Participant inclusion and exclusion criteria for study

Inclusion	Exclusion
(1) outpatients 18-70 years of age (inclusive) at time of screening	(1) any history of TBI with a severity greater than mild. This will be defined by meeting any of the following criteria: a) history of losing consciousness due to head injury for greater than 10 minutes b) history of losing consciousness due to a head injury with documented evidence of brain injury (including brain atrophy) c) history of have three or more concussions within the span of one year.
(2) meet DSM-V criteria for SUD at time of baseline visit criteria determined by the Structured Clinical Interview for DSM-V (SCID-5) which is a structured clinical interview used to confirm SUD diagnosis	(2) current (or past if appropriate) significant neurological disorder, or lifetime history of a) seizure disorder b) primary or secondary CNS tumors c) stroke or d) cerebral aneurysm
(3) veterans will not be excluded for comorbid substance use (i.e., additional substance use beyond alcohol, cocaine, or opiates), but data will be collected on use patterns so that these behaviors may be balanced across conditions and/or controlled for statistically	(3) implanted devices activated or controlled by physiologic signals, such as cardiac pacemakers, implanted medication pumps, and intra cardiac lines. Participants must also not have an implanted device (deep brain stimulation) or metal in the following areas: brain, cervical spinal cord, or upper thoracic spinal cord.
(4) abstinent from alcohol for at least 3 days prior to baseline sTMS procedures abstinent from benzodiazepines if meeting criteria for benzodiazepine use disorder	(4) have metal objects lodged in their body, such as shrapnel, bullets, or bullet fragments, or magnetically activated dental implants.
(5) be on a stable psychotropic medication regimen for at least 6 weeks prior to baseline, or no psychotropic medication at all (for at least 6 weeks prior to baseline), and be willing to maintain the current regimen and dosing for the duration of the study (unless medically necessary to make changes). If there is a psychotropic medication change during the 6 weeks of sTMS treatment, the participants will notify the study team.	(5) significant alcohol withdrawal symptoms at baseline

(6) if of childbearing potential, agree to use an acceptable method of birth control for the duration of the study treatment period	(6) >1 month of abstinence from alcohol prior to baseline
(7) be willing and able to comply with all study related procedures and visits	(7) are pregnant or lactating, or planning to become pregnant within three months after baseline
(8) be capable of independently reading and understanding patient information materials and giving written informed consent	(8) legally mandated substance abuse treatment
(9) currently assigned a VA mental health treatment coordinator and willing to remain in care throughout the study	(9) inability to obtain EEG of sufficient quality and duration that can be processed for use to calibrate the study device
(10) be willing to provide two verifiable emergency contacts	(10) unstable medical illness, or, in the opinion of the investigator, significant absence of appropriate medical care
	(11) current Axis 1 primary psychotic disorder, or bipolar I disorder
	(12) have active suicidal intent or plan, or in the investigative team's opinion, is likely to attempt suicide within the next six months criteria determined by the Structured Clinical Interview for DSM-5 (SCID-5), which asks specifically about suicidal ideation (both passive and active), suicide plans, and previous suicide attempts
	(13) demonstrate the presence of any other condition or circumstance that, in the opinion of the investigative team, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments

Procedures

Recruitment and screening

Up to 60 participants who meet criteria for a DSM-V SUD will be recruited to complete this study (see figure 1), with 20 identifying alcohol as their drug of choice, 20 identifying cocaine as their drug of choice, and 20 identifying opiates are their drug of choice. Veterans will be recruited through the Collaborative Addiction and Recovery Services program at VA Providence. Potential participants may call in response to advertisements for the study or will be referred by clinicians (by giving patients the study ad). Research assistants will assess preliminary demographic eligibility criteria upon phone screen. Those who meet preliminary eligibility criteria will be invited to the lab for a baseline visit. After providing written informed consent, psychiatric interview and self-report measures will be used to confirm eligibility with regard to diagnosis, past psychotropic treatment history, current health history, and current symptom severity (see table 2 for full list of assessments). There is a requirement for maintenance on a stable regimen of psychotropic medications (if applicable) for 6 weeks prior to baseline and during participation in sTMS treatment.

[Figure 1 here]

Baseline

Participants meeting initial phone screen eligibility will be invited to a baseline visit. Research staff will review and obtain written informed consent for either at-home administration or in-lab administration prior to the initiation of study procedures.

Psychiatric interviews and self-report measures will confirm eligibility regarding SUD diagnosis, past psychiatric treatment history, current health history and current symptom severity. Demographic and clinical data include gender, age, substance use (quantity and frequency), and co-morbid symptomatology which will be collected to quantify change due to sTMS, or as factors that may influence the effect and tolerability of sTMS. Participants will complete a Timeline Follow Back (TLFB) to confirm substance use over the past 30 days [25]. The Quick Structured Clinical Interview for DSM-5 Disorders (Quick SCID-5)[26] will assess diagnostic criteria for alcohol, cocaine or opioid use disorder.

Laboratory assessments will quantify substance use and include a urine drug screen (USD), ethyl glucuronide (EtG) test and the following liver functioning tests: GGT (u/l), SGOT/AST (u/l), SGPT/ALT (u/l), Total Bilirubin (mg/dl). Prior research shows that response to neurostimulation may be related to genetic or epigenetic differences between people. Accordingly, an additional blood sample will be collected, with DNA extracted and assessed using genome wide and epigenome wide analyses to investigate genetic and epigenetic differences in the context of treatment response.

Drug/alcohol cue reactivity will be measured via a task presented using E-Prime 3 software (Psychology Software Tools, Inc., 2017)[27] following work by the Hanlon group in the area of cue reactivity and TMS. The computer task consists of six 96-second blocks. The first three blocks contain neutral images (e.g., glass of water, cooking utensils, people eating dinner). The last three blocks contain images of drug- or alcohol-related stimuli customized for each group (e.g., crack pipe for cocaine users, liquor bottles for alcohol users). Prior to starting the task and at the end of each block, participants will record their substance cravings on a paper assessment.

Participants will undergo a 10-minute resting state EEG after which deidentified data will be shared with the sTMS device manufacturer, Wave Neuroscience, for analyses. These analyses will capture participants' individualized alpha frequency (IAF), a marker of inter-individual differences in EEG rhythms, which will indicate the optimal magnetic field frequency for treatment.

Table 2. Measures by Time Point Assessed and Mode of Administration

Assessment Goal	Measure/Study Procedure	Time-point	Mode
Diagnostic and Screening	Phone Screen (to determine eligibility)	Pre-B	Interview
	Screening, Demographics, Medical Review	B	Self-report
	Structured Clinical Interview for DMS-V	B	Interview
	EEG	B	Clinician-Administered
SUD	Time-Line Follow-back	B, W, PT1 PT2	Interview

	Alcohol Urge Questionnaire (AUQ), Cocaine Urge Questionnaire (CUQ), or Opioid Urge Questionnaire (OUQ)	B, W, PT1, PT2	Self-report
PTSD	Clinician-Administered PTSD Scale (CAPS)	B, PT1, PT2	Interview
	PTSD Checklist for DSM-5 (PCL-5)	B, PT1, PT2	Self-report
	The Life Events Checklist (LEC)	B	Self-report
Depression	Inventory of Depressive Symptomatology Self-Report (IDS- SR)	B, PT1, PT2	Self-report
Affect	Positive and Negative Affect Schedule (PANAS)	B, PT1, PT2	Self-report
Anxiety	State-Trait Anxiety Inventory (STAI)	B, PT1, PT2	Self-report
Quality of Life	Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	B, PT1, PT2	Self-report
	Social and Occupational Functioning Assessment Scale (SOFAS)	B, PT1, PT2	Self-report
Sleep	Pittsburgh Sleep Quality Index (PSQI)	B, W, PT1, PT2	Self-report
General	Clinical Global Impressions– Severity (CGI-s)	B, PT1, PT2	Interview
	CGI – Improvement (CGI-i)	B, PT1, PT2	Interview
Treatment Satisfaction	Adapted Satisfaction with Treatment Form	PT1, PT2	Self-report
Blinding Questionnaire	Treatment Blinding Questionnaire	PT1	Self-report
Specimen Collection	Urine Toxicology Screen	B, W, PT1, PT2	Laboratory
	Blood Draw	B	Laboratory
	DNA Collection	B	Laboratory

Randomization and Blinding

Participants will be randomized into either active sTMS or sham sTMS treatment groups. Treatment will be delivered in a double-blind fashion so that neither participants nor research staff will be aware of study condition. The sham sTMS device has an external appearance, weight, sound and operation indistinguishable from the active sTMS device with a non-magnetic rotating

metal shaft replacing the rotating neodymium magnets to reduce the potential for unblinding. Participants will self-select into either at-home or in-lab sTMS administration procedures.

Treatment phase

sTMS Device

The study will use the Wave Neuroscience sTMS device which consists of three main elements: (1) Headset; (2) Patient Passport Module (PPM); and (3) Base Station. The PPM is a USB flash drive containing an encrypted file with the IAF device parameter as well as a code to specify whether the PPM is destined for an active or sham device. If an active PPM is inserted into a sham device or vice versa, the display on the base station will show "invalid PPM."

At home administration

Treatment sessions will be completed in participants' homes using a portable sTMS device. Acting under the supervision of a TMS-credentialed physician, trained research staff will observe all 30 in-home treatments (5 per week) through video technology to ensure that participants are awake and using the device correctly. Treatment emergent side effects associated with stimulation (during treatments) and emerging between treatment sessions will be queried on each treatment day and recorded into participants' medical charts.

In lab administration

Trained research staff will be present for all sTMS sessions at VA Providence. During the sTMS session, study staff will ensure that participants are awake and using the device correctly. Treatment emergent side effects will be queried and recorded on each treatment day. Appropriate medical coverage is available at all times.

Common treatment procedures

sTMS will be delivered following Wave Neuroscience guidelines using the device user manual. Each participant's IAF will be displayed on the device LCD screen once the PPM is plugged in. Before initiating treatment sessions, study staff will confirm that the IAF parameters displayed on the device LCD screen match the IAF provided by Wave Neuroscience. If the values do not match, treatment will not be administered. Participants will be instructed to remove jewelry above their shoulders and anything from their mouth (e.g., gum) that could generate facial muscle activity. They will then secure the sTMS device to their heads, lay down in a semi-reclined position and turn the magnetic adjustment knobs. After pressing the start button, the device will rotate the magnets for 30 minutes, at which point rotation ceases and the session ends. Sessions may be paused or canceled at any time, however once canceled, or completed, the device is programmed such that a new session cannot be started for 10 hours. This prevents subjects from excessively using the device while not under the direct supervision of study staff.

Weekly in-person visits will occur across the treatment phase (six weekly visits total). Participants will complete a TLFB, brief self-reports and provide a urine drug screen. Additional measures will be taken by research staff to protect against COVID-19 infection including pre-appointment COVID screening, PPE, etc.

Follow Up Assessments

Two post-treatment appointments will occur: an end of treatment (EOT) visit 72-hours after the final treatment session, and a one-month follow up. At both post-treatment visits participants will complete self-report questionnaires, the drug/cue reactivity task, a TLFB and a urine drug screen. At the EOT visit, participants will additionally be asked to complete a treatment satisfaction questionnaire and condition blinding questionnaire to ensure they were blinded to study condition.

Compensation

Participants will be offered compensation for completion of specific milestones in the study: $50 for completion of all baseline procedures, $100 upon completion of all 30 sTMS treatments, plus another $75 for completing the one-month follow up, totaling $225. Payment will be offered in the form of gift cards or electronic funds transfer.

Primary Outcomes

Aim 1: To demonstrate feasibility and acceptability of at-home and in-lab sTMS among Veterans with specific substance use disorders (i.e., alcohol, cocaine, opioids) in a pilot sham-controlled study. Thirty sTMS treatment sessions will occur with trained research staff monitoring in person or through video technology to verify that participants are awake and using the device properly. Feasibility will be evaluated by rates of recruitment, treatment adherence, retention, and completion of assessments (see table 3). Acceptability will be measured by retention and participant reports of acceptability and satisfaction (see table 3).

Table 3. Primary clinical and mechanistic outcomes

Clinical outcome	Measure
Aim 1: To demonstrate feasibility and acceptability of at-home sTMS among Veterans with specific substance use disorders (i.e. alcohol, cocaine, opioids) in a pilot sham-controlled study	
Feasibility Recruitment Retention Adherence	Rate of 2 or more patients per month 50% or higher study assessment completion rate Completion of at least 80% of sTMS treatment sessions
Acceptability	Treatment Satisfaction Questionnaire
Aim 2: To evaluate the safety of at-home sTMS among Veterans with substance use disorders.	
Safety	Monitor all adverse events that occur during the study using a combination of clinical interviews and spontaneous adverse event reports (coded using the Medical Dictionary of Regulatory activities), and through systematic self-report using SAFTEE. All adverse events will be assessed and described in terms of the relationship to the device, relationship to the procedure, severity of the event, subsequent treatment or intervention, and the resolution status. All reporting procedures will align with those listed in 21 CFR 812.150

Although we anticipate the sample will not be large enough to provide adequate statistical power to test for differences between sTMS and sham stimulation, we anticipate collecting feasibility data and will generate confidence intervals around all observed effect sizes.

Aim 2: To evaluate the safety of in-lab and at-home sTMS among Veterans with substance use disorders. Safety of at-home sTMS administration for Veterans with alcohol, cocaine and opioid use disorder will be assessed through adverse event monitoring. Daily safety questions will probe potential treatment related side effects and changes in substance use. Medications will be monitored through self-report and electronic medical record review. Adverse events will immediately be reported to the principal investigator.

Other Outcomes

The clinical interview assessment of substance use symptoms will include the Clinical Global Impressions-Severity (CGI-S)[28] to quantify the severity of the participant's mental illness at the time of assessment; Social Occupational Functioning Assessment Scale (SOFAS) [29] to quantify the participant's level of social functioning in daily life at the time of assessment; and CGI-Improvement (CGI-I) assessment to quantify the level of improvement in participants' illness from baseline to the time of assessment.

The following self-report questionnaires will be administered in order to quantify measures of PTSD, depression, quality of life, affect and sleep to assess how these constructs may be related to substance use, craving and sTMS treatment feasibility: Clinician-Administered PTSD Scale (CAPS),[30] PTSD Checklist for DMS-V (PCL-5),[31] the Life Events Checklist (LEC),[32] Inventory of Depression Symptomatology Self-Report (IDS-SR) [33, 34], Positive and Negative Affect Schedule (PANAS) [35], State-Trait Anxiety Inventory (STAI),[36] Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[37] Pittsburg Sleep Quality Index (PSQI),[38] Adaptation Satisfaction with treatment Form, and Treatment Blinding Questionnaire.

Data Analysis Plan

Data management and confidentiality.

Only research staff who have undergone the relevant responsible research conduct and handling of private and confidential information training will handle study data. These data will only be used for research purposes. A unique identification number for each participant will be used on all assessments in lieu of any identifying information. Additionally, analyses will be completed on de-identified data.

Data management and confidentiality.

Missing data (i.e., participants lost to follow-up) will be handled using full information maximum likelihood estimation for statistical models in our primary analyses. This type of approach can easily be implemented in model-based software packages, such as MPlus. Moreover, all available cases will contribute to the computation of the maximum likelihood estimates, providing the most likely results based on the observed data. Additionally, exploratory and sensitivity analyses will be conducted to characterize patterns of missingness and determine whether systematic similarities exist for participants who were lost to follow-up.

Aim 1: Feasibility and acceptability.

Adequate feasibility of the intervention will be indicated by a recruitment rate of 2 or more patients per month and retention rates of 50% or higher completed assessments based on previous sTMS trials [19] and empirical evidence from 3-month treatment programs [39]. Additionally, acceptable rates of treatment adherence will be completion of at least 80% of the treatment sessions as defined by a previous study that showed an effect of sTMS on depression[18].

Aim 2: Safety of in-lab and at-home sTMS.

In order to evaluate safety, we will meticulously monitor all adverse events that occur during the study. Adverse events will be captured using a combination of clinician interviews and spontaneous adverse event reports (coded using the current version of the Medical Dictionary for Regulatory Activities), and through systematic self-report using the SAFTEE[40]. All adverse events will be assessed and described in terms of the relationship to the device, relationship to the procedure, severity of the event, subsequent treatment or intervention, and the resolution status. Medications will be followed at each study visit and corroborated with the VA electronic medical record. Any adverse events (AE) that occur while participants are using the sTMS device at-home will be captured by trained research staff who will observe all 30 at-home treatment sessions via video technology. All reported AEs will be logged and reported to the principal investigator.

Patient and Public Involvement

As part of this pilot trial, participants will provide important feedback on feasibility and safety through communication with research staff, as well as a treatment satisfaction questionnaire that assesses the burden of the intervention. Participants and members of the public were not involved in the design of study procedures. We will use feedback to inform efficacy trials.

ETHICS AND DISSEMINATION

Ethics

All study procedures were approved by the Providence VA institutional review board (IRB) and research and development committee. Serious and unexpected adverse events will be reported to the IRB within 24 hours while potentially adverse events will be reported during annual continuing reviews. The sTMS device has received a significant risk determination for at-home use by the Food and Drug Administration. As such, an independent data safety monitoring board composed of individuals not affiliated with the study will convene on at least a quarterly basis to review all relevant data pertaining to participant safety.

To address the risk of worsening SUD symptoms, substance use will be monitored with prescribed cutoffs in substance use assessments acting as indicators that symptoms may be worsening. Participants deemed at risk will be withdrawn and referred to the Providence VA Collaborative Addiction and Recovery Services clinic. Participants endorsing significant withdrawal symptoms will be instructed to seek immediate medical treatment. The PI will discontinue the trial if (1) participants experience any serious adverse events found to be attributable to sTMS; (2) two participants experience clinically meaningful deterioration in suicidal ideation or (3) any participant attempts suicide.

Dissemination

This study will lay the groundwork for large scale clinical trials that will evaluate the efficacy of sTMS as a treatment for SUD. The results of this pilot sham-controlled trial will be disseminated to maximize the impact of preliminary findings. The principal investigator will share de-identified datasets, statistics, and results collected from this proposal by depositing these data at the National Library of Medicine PubMed Central website repository as this is a VA supported data repository. Planned manuscripts include a primary outcomes paper(s) describing sTMS treatment feasibility for Veterans with substance use disorders (i.e., alcohol, cocaine, opioids). Results of this study will be presented at national conferences such as Research Society on Alcoholism and College on Problems of Drug Dependence.

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Contributors

JJ and JEM drafted the initial proposal, with input from NSP, RMS and LB. MJQ, JCL and CBB drafted the manuscript, which all authors reviewed and revised.

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Disclaimer

The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. Neither the funders nor Wave Neuroscience were involved in the decision to conduct the study or study procedures.

Competing interests None declared.

Patient consent for publication Not required.

Figure 1. Participant flow diagram (n=60). EEG, electroencephalogram; IAF, individualized alpha frequency; sTMS, synchronized transcranial magnetic stimulation. This includes individuals from all 3 substance groups (alcohol, cocaine, and opioids).

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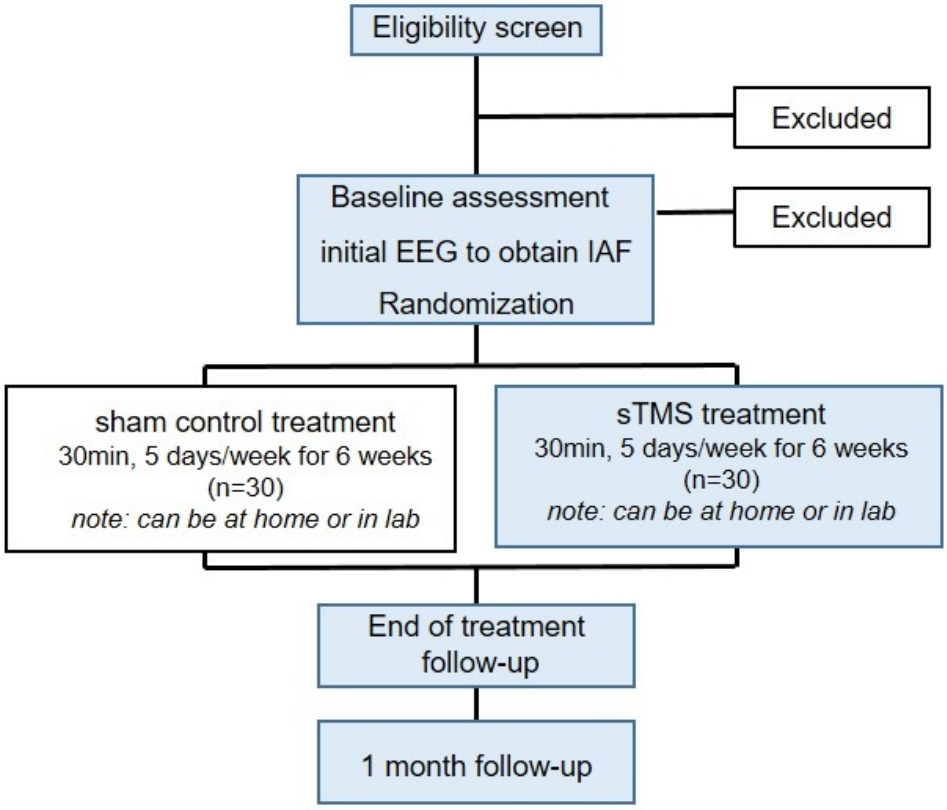

Figure 1. Participant flow diagram (n=60). EEG, electroencephalogram; IAF, individualized alpha frequency; sTMS, synchronized transcranial magnetic stimulation. This includes individuals from all 3 substance groups (alcohol, cocaine and opioids).

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107x115mm (150 x 150 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Present in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1 lines 2-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 line 79
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	No
Funding	4	Sources and types of financial, material, and other support	Page 12 lines 409-414
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 lines 5-42 Page 8 lines 405-407
	5b	Name and contact information for the trial sponsor	Page 1 lines 44-47
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 12 lines 416-419
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3 lines 103-138

	6b	Explanation for choice of comparators	Page 3 Lines 142-145
Objectives	7	Specific objectives or hypotheses	Page 3 lines 140-147
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Pages 7-8, lines 226-233
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4 lines 161-162
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4 lines 161-171 Page 4, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 6-8 Lines 192-281
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 11 Lines 380-387
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 8 Lines 243-255
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 5 lines 186-188
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Pages 9-10 Lines 289-325 Table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 6 Table 2 Page 5 Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Pages 3-4 Lines 151-158
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5 Lines 176-181
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	No
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pages 7-8 lines 227-232.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6 lines 193-222. Table 2. Page 8 Lines 276-281

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 9 Lines 284-287
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 10 lines 329-334
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Pages 10-11 Lines 346-363
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10 Lines 341-343
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10 Lines 337-343
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 11 Lines 377-379
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 11 lines 380-387
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 11 Lines 373-376
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11 Lines 373-374
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	No
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6 Lines 194-195
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 10 Lines 330-334
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12 Line 421
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11 Lines 392-395
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page 11 Lines 382-384
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 11 Lines 390-392
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes, supplementary materials.

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 6 Lines 206-210

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.