rTMS for Stimulant Use Disorders

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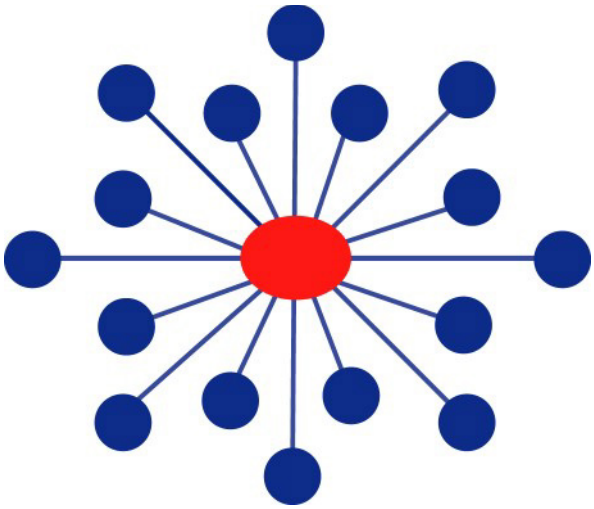
November 10, 2023



NIDA CTN Protocol 0108

rTMS for Stimulant Use Disorders (STIMULUS)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CHRT-CR	Concise Health Risk Tracking – Clinician Rated
CHRT-SR	Concise Health Risk Tracking – Self Report Suicidal Behavior Evaluation
CLIA	Clinical Laboratory Improvement Act
CoC	Certificate of Confidentiality
CI	Confidence Interval
CRF	Case Report Form
CTN	Clinical Trials Network
CUD	Cocaine Use Disorder
DCC	Data Coordinating Center
DLPFC	Dorsolateral Prefrontal Cortex
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
ERC	Ethics Review Committee
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imagining
FTND	Fagerström Test for Nicotine Dependence
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability & Accountability Act
HIV	Human Immunodeficiency Virus
HSP	Human Subjects Protection

Abbreviation	Definition
ICF	Informed Consent Form
IRB	Institutional Review Board
iTBS	Intermittent Theta Burst Stimulation
ITI	Inter-train Interval
ITT	Intention To Treat
LI	Lead Investigator
MC	Medical Clinician
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDMA	Methylenedioxymethamphetamine
MINI	Mini International Neuropsychiatric Interview
MOP	Manual of Procedures
MT	Motor Threshold
NIDA	National Institute on Drug Abuse
MUD	Methamphetamine Use Disorder
OHRP	Office for Human Research Protection
PEST	Parameter Estimation by Sequential Testing
PhenX	Phenotypes and Exposures
PCP	Phencyclidine
PSQI	Pittsburgh Sleep Quality Index
RA	Research Assistant
QA	Quality Assurance
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SD	Standard Deviation
SUD	Substance Use Disorder
TAU	Treatment As Usual
TLFB	Timeline Follow-Back
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Effects
UDS	Urine Drug Screen
VAS	Visual Analogue Craving Scale

2.0 STUDY SYNOPSIS

2.1 Study Objectives

The primary objective of this study is to determine the feasibility of repetitive transcranial magnetic stimulation (rTMS) for individuals with moderate to severe cocaine or methamphetamine use disorder (CUD/MUD). The secondary objective is to gather preliminary data on the efficacy of rTMS for individuals with moderate to severe CUD or MUD. The exploratory objectives include examining the impact of rTMS on self-reported substance use, craving, mood and anxiety, sleep monitored via actigraphy, retention in treatment, changes in health, lifestyle, and function, and resting connectome biomarkers measured by EEG.

2.2 Study Design and Outcomes

The study will be a randomized, double-blind, sham-controlled trial comparing up to 30 sessions of rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) versus up to 30 sessions of sham rTMS delivered over an 8-week treatment period with follow-up visits occurring at end of treatment and at 12- and 16-weeks following randomization. Relapse prevention-targeted Cognitive Behavioral Therapy (CBT) modules also will be available for use to all participants, via a mobile app. The primary outcome is focused on feasibility: the percentage of participants who receive at least 20 rTMS sessions over the 8-week treatment period. The secondary outcome is focused on efficacy: the last UDS of each treatment week (7 day period) will be used for the efficacy analysis and the percentage of negative UDS (out of 8 total) for methamphetamine or cocaine will be the primary efficacy measure. Participants also will be asked to report daily on drug use, craving, ability to resist use, and mood using a digital survey delivered on their mobile phones. Drug use will also be monitored with weekly Timeline Follow-Back and UDS collected at each treatment visit. Actigraphy will be used to monitor sleep during the treatment period. If available at the study site, electroencephalography (EEG) will be used to assess resting connectome biomarkers. Self-report survey measures will be used to assess additional exploratory outcomes.

2.3 Sample Size and Study Population

Approximately 160 adults (aged 18-65) with moderate to severe cocaine use disorder (CUD; n=80) or methamphetamine use disorder (MUD; n=80) interested in cutting down or stopping use will be recruited. Participants who meet DSM-5 criteria for both CUD and MUD will be asked to choose which is the primary substance of choice to determine their diagnostic category. The study will be conducted across 4 sites (with 2 sites – Wake Forest, UT Health San Antonio – discontinuing study participation early), and it is estimated that up to 80 participants will be enrolled at each site. Sites may vary on total enrolled per site, but no more than 160 total participants will be enrolled across all sites. This sample size provides adequate confidence interval length and provides greater than 80% power to detect medium-sized effect sizes, measured as odds ratios, of greater than 4 with a two-sided hypothesis test and significance level of 0.05 within each of CUD and MUD separately. Randomization will be stratified based on current major depressive episode (MDE), study site and CUD or MUD.

2.4 Intervention and Duration

Participants will be randomized to receive up to 30 sessions of rTMS or up to 30 sessions of sham rTMS administered over an 8-week period (3-5 treatments per week). Prior to each rTMS/sham session, a cocaine or methamphetamine-related cue will be presented to the participant. Immediately after the cue presentation (while memory is reactivated) active or sham rTMS stimulation will be administered. Each rTMS/sham session will consist of 75 rTMS trains of 10 Hz for 4 seconds (40 pulses per train) with inter-train interval (ITI) of 11 seconds (a total of 3000 stimuli per session) over the left dorsolateral prefrontal cortex (DLPFC). The rTMS coil (active or sham coil) will be placed over the left DLPFC using the Beam F3 method. The interval between rTMS sessions will vary over the course of the study and for each participant depending on individual scheduling needs, with the primary objective being that each participant receives an adequate dose of treatment (at least 20 sessions) with flexibility in the timing of rTMS delivery to minimize study drop-out. Follow-up visits will be scheduled at the end of treatment (within 1 week after the last rTMS session), and at weeks 12 and 16. Completion of the study, including follow-ups, will take approximately 4 months (112 days) after randomization for individual participants.

Recruitment is expected to take approximately 12-15 months, with follow-ups continuing for approximately 6 months post completion of the recruitment phase. Two months will be allowed for data lock after the end of the follow-up period. Therefore, data lock is projected to occur at approximately 25-27 months after CCTN approval of the final protocol.

2.5 Assessments

The primary outcome measure is the percentage of participants who enter the trial that obtain at least 20 treatment sessions over the 8-week treatment period. Additional feasibility measures will also include the following (as exploratory outcomes):

- Percent of participants that complete at least 75% of daily monitoring
- Percent of participants that complete all follow-up visits

These outcomes will inform future decisions to conduct a larger randomized clinical trial designed to assess efficacy. Targets for the above feasibility measures are 75%.

The secondary (efficacy) outcome measure will be cocaine and methamphetamine use. This efficacy outcome will be measured using the last urine drug screens (UDS) collected for each treatment week and the percent of negative UDS results for cocaine or methamphetamine will be calculated.

Exploratory measures include, but are not limited to: self-reported use (Timeline Follow-Back (TLFB)), cocaine and/or methamphetamine craving (Craving Assessment), depression/anxiety symptoms (Hospital Anxiety and Depression Scale), sleep quality (Actigraphy; Pittsburgh Sleep Quality Index), the Health Related Quality of Life (HRQOL-4) assessment used by NIDA CTN, and resting connectome biomarkers measured by EEG.

2.6 Safety Reporting

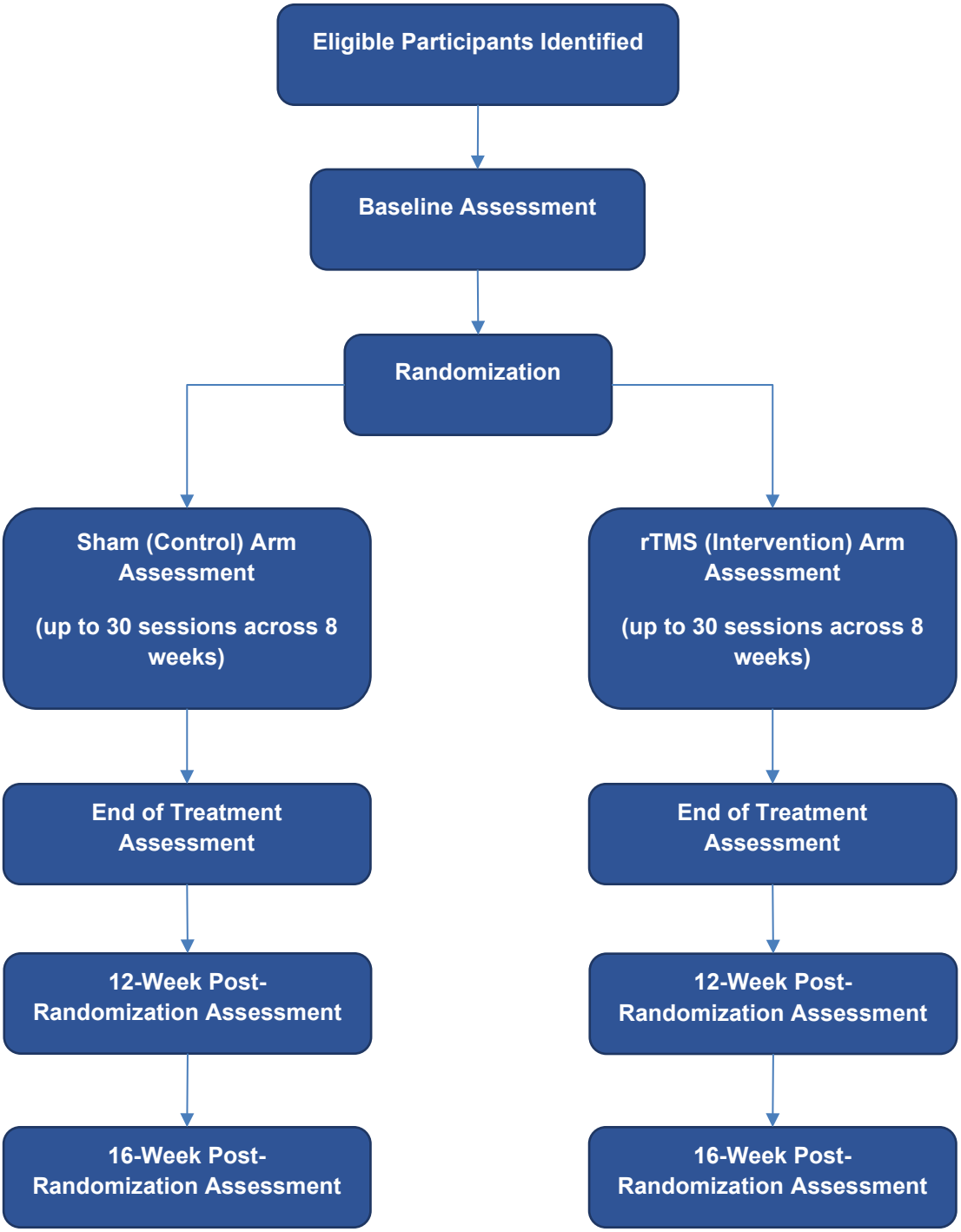
All adverse events (AE) will be solicited and collected from participants during treatment visits and follow-up visits (or in-between visits if reported spontaneously). Reporting timeframes for AEs, serious AEs (SAEs), and unanticipated adverse device effects (UADEs) will follow FDA regulations for abbreviated IDE reporting (21 CFR 812), as well as Institutional Review Board (IRB) and sponsor requirements.

2.7 Analyses

The primary outcome (feasibility — i.e., percent of participants who obtained at least 20 treatment sessions) will be assessed along with a 95% confidence interval (CI) using the Wilson method. The secondary outcome (efficacy — i.e., the percent of negative weekly UDS results over the treatment period) will be assessed using a generalized linear mixed model incorporating treatment, site, week, stratum (MDE), and participant. Exploratory outcomes (e.g., daily self-reports on drug use, craving, ability to resist use, depression/anxiety, sleep quality and mood) will be analyzed using Fisher exact tests, or other non-parametric two-sample tests, and generalized linear regression models, as appropriate.

3.0 STUDY SCHEMA

Figure 1: Basic Study Schema



3.1 Key Research Site Roles

Study sites will include the following key roles:

- Site Principal Investigator (MD; DO; PhD)
- Medical Clinician (MD; DO; NP; PA)
- rTMS Advanced Operator
- rTMS Operator (Optional)
- Research Coordinator
- Research Assistant

4.0 INTRODUCTION

4.1 Background And Significance To The Field

The morbidity and mortality associated with methamphetamine use disorder (MUD) and cocaine use disorder (CUD) are high and are associated with serious psychiatric and physical consequences. Cocaine is one of the most commonly abused stimulants, with 2% of adults in the U.S. endorsing use within the last year (Palamar et al., 2020), and use leads to negative consequences, including cognitive deficits, legal issues, and serious medical conditions, such as cardiovascular disease, kidney disease, and sexually transmitted diseases (Degenhardt and Hall, 2012; Cadet et al., 2015; Akinson et al., 2009; Frazer et al., 2018). Methamphetamine is a widely abused stimulant, and stimulants as a group are second to cannabis as the most widely abused illicit drug in the world (Degenhardt et al., 2016), and use in the U.S. has been increasing (SAMSHA, 2019). MUD leads to similar negative consequences as CUD. Unfortunately, effective management for CUD and MUD remains elusive. Psychological interventions have demonstrated modest benefits, but relapse rates are high (Paulus et al., 2018). There are currently no FDA-approved pharmacotherapies or biological therapies for treating either CUD or MUD (Morley et al., 2017).

TMS is a non-invasive brain stimulation technique which is approved for the treatment of major depressive disorder (MDD) and most recently (August 2020), the BrainsWay Deep TMS platform received FDA clearance as an aid for smoking cessation. rTMS refers to repetitive episodes of TMS stimulation, which is generally the protocol for therapeutic use. There is ample basic science literature suggestive of specific circuit dysfunction that could be engaged by rTMS for therapeutic benefit in individuals with addictions (Ekhtiari et al., 2019). While rTMS targets superficial brain regions, typically the prefrontal cortex, rTMS can also impact deeper brain circuits critical for addiction, such as dopamine release in the caudate nucleus (Strafella et al., 2001). A number of pilot studies have investigated the use of TMS for CUD using a variety of stimulation approaches, study designs, and outcomes (Rao et al., 2019). In one study, 10 individuals with CUD (5 per sham and active arms) underwent 12 sessions over 4 weeks. Cocaine use was assessed with hair analysis at 1, 3 and 6 months. While the data did not support decreased cocaine use over time, an exploratory analysis of only the later time points suggest a delayed effect on cocaine use with active treatment (Bolloni et al., 2016). In a small pilot utilizing accelerated intermittent theta burst stimulation (iTBS; a form of TMS) over the left DLPFC with 3 treatments per day over 10 days (30 total treatments), 9 of the 14 participants who returned for 4-week follow-up showed reduction in total use and money spent on cocaine (Steele et al, 2019). Additionally, deep TMS (H-coil) at 20hz, over the bilateral medial and lateral prefrontal cortex, over 12 sessions within one month, has shown evidence for reducing cocaine cravings (Rapenisi et al., 2016). In summary, a number of small studies have demonstrated promising findings with the use of rTMS to the DLPFC in CUD, but there is methodological variability across studies, and not all studies measured cocaine use as an outcome (Grall-Bronnec et al., 2014; Hanlon et al., 2018). In addition, there are only two controlled studies exploring rTMS in MUD. Investigating DLPFC rTMS in MUD men (N=48) (Liu et al., 2019) and women (n=90) (Liang et al., 2018), both studies reported significantly reduced craving and withdrawal symptoms in the rTMS group, but methamphetamine use was not measured. In looking across rTMS studies in substance use disorders, high

frequency (10-20 hz) TMS over the left DLPFC has most consistently shown evidence for positive outcomes in CUD and MUD (Enokibara et al., 2016; Ekhtiari et al., 2019), although studies in MUD are limited.

4.2 Study Rationale

CUD and MUD are on the rise in the U.S. today. These disorders have severe psychiatric and medical consequences and current treatments have only modest efficacy. Preliminary data suggests that rTMS might be efficacious in the treatment of CUD and MUD. This pilot study will explore the feasibility and, if positive, provide preliminary data about efficacy that could be used to design an adequately powered trial of rTMS in CUD and MUD. The hypothesis is that the delivery of rTMS will be feasible as measured by the percentage of eligible individuals who enter the study and complete at least 20 rTMS treatment sessions. A secondary hypothesis is that rTMS, as compared to a sham rTMS treatment, will be efficacious as measured by the percent of negative UDS results over the treatment period. Study participants will be men and women, aged 18-65, who meet criteria for moderate to severe MUD and/or CUD. We have chosen to enter only those with moderate to severe disease to maximize the potential to see a change in cocaine or methamphetamine use. Because rTMS is an FDA-approved treatment for major depressive disorder (MDD), we will stratify individuals based on current MDE.

4.3 Risk/Benefit Assessment

4.3.1 General Considerations

The Magventure MagPro® stimulators R20, R30, R30 with MagOption, X100, and X100 with MagOption are all FDA 510(k) cleared for stimulation of peripheral nerves for diagnostic purposes (k160280, k061645, k091940) and for treatment of adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode (K172667). The recent K172667 approval was based upon substantial equivalence with a predicate device, previously deemed a non-significant risk device by the FDA. Although the use of the Magventure MagPro® is not considered “significant risk” by the FDA for depression, the precise risks in MUD and CUD are currently unknown. Given the potential morbidity and mortality associated with MUD and CUD and the lack of any FDA-approved treatments for these disorders, rTMS may be able to provide a viable treatment option.

4.3.2 Cocaine and Methamphetamine Use

There is ample basic science literature in the addictions field suggestive of specific circuit dysfunction that could be engaged by rTMS for therapeutic benefit in individuals with addictions (Ekhtiari et al., 2019). Several pilot studies have demonstrated positive results for rTMS in both CUD and MUD using a variety of stimulation approaches, study designs, and outcomes (Rao et al., 2019; Liu et al., 2018; Liang et al., 2018). In looking across rTMS studies in substance use disorders, high frequency (10-20 hz) TMS over the left DLPFC has most consistently shown evidence for positive outcomes in CUD and MUD (Enokibara et al., 2016; Ethairka et al., 2019), but these studies have limitations and further evidence is needed.

In terms of safety, a 2014 review of rTMS studies for any substance use disorder found that the procedure was well tolerated. They note, “Eight studies did not specify rTMS tolerance, which was generally good, as shown in four studies in which no side effects were reported. Only one study reported a case of serious side effects “seizure, probably due to discontinuing benzodiazepine too soon” (Grall-Bronnec & Sauvagnet, 2014). A recent review of the use of neuromodulation in addiction highlights that there is no evidence that standard TMS safety guidelines need to be adjusted for its use in substance use disorders (Ekhtiari et al, 2019). Nonetheless, they do recommend that studies should carefully report their methods, safety monitoring measures, and side effects assessments.

Several small studies using rTMS in both cocaine and methamphetamine use disorders have been performed with similar safety profiles as have been reported in Major Depressive Disorder. The stimulation parameters (site, coil type, frequency, intensity) of these studies are heterogenous. The parameters proposed in this study (10hz over the left DLPFC) have been used extensively in Major Depressive Disorder and they have only been previously reported in methamphetamine use disorder (see Section 4.3.4 below).

As stated above, the FDA recently cleared the BrainsWay Deep rTMS platform for smoking cessation, making it the first substance use disorder to receive FDA clearance with any form of rTMS. In the pivotal study the continuous smoking quit rate was 17.1% in the active arm and 7.9% in the sham arm (Zangen et al., 2020). From a safety perspective, no seizures were reported, and adverse events were comparable to rTMS studies in Major Depressive Disorder.

In the current study, participants will be asked not to participate in any other formal treatment for CUD or MUD, except self-help groups, while they are in this study. As such, there may be some risk of drug use that could be avoided if the individual were engaged in a formal SUD treatment program. However, all participants will receive access to and will be encouraged to participate in a CBT for SUDs which will be provided to all study participants.

4.3.3 Cocaine Use Disorder

In a study of 19 individuals with CUD, three open-label intermittent theta-burst stimulation (iTBS) sessions per day, with approximately a 60-min interval between sessions, for 10 days over a 2-week period (30 total iTBS sessions) was evaluated (Steele et al., 2019). Authors note “iTBS was well-tolerated, despite the expected occasional headaches. A single participant developed a transient neurological event of uncertain etiology on iTBS day 9 and cocaine-induced psychosis 2 weeks after discontinuation.” A case report of this participant’s event was also published, and suggested that psychogenic seizure or tremor was the more likely etiology (Steele et al., 2018).

In a sham controlled study, participants with CUD (N=6) received active treatment with twelve rTMS sessions, administered three times a week for 4 weeks at 100% of motor threshold, over bilateral PFC (Bolloni et al, 2016). The authors noted that other than one participant who experienced a mild headache, no other discomfort was observed during active treatment. Another study of rTMS of the frontal pole in cocaine users (n=25) reported that the procedure was well tolerated and did not report any safety events (Hanlon et al., 2017).

Rapinesi and colleagues (2016) conducted an open label study of seven men with CUD. Participants received alternate day 20 Hz deep transcranial magnetic stimulation (dTMS) in 20 trains targeting the left DLPFC for 12 sessions spread over one month, with no complications or adverse events identified.

4.3.4 Methamphetamine Use Disorder

In a sham-controlled study of 48 male participants with MUD receiving 10 Hz rTMS for 10 minutes per session, targeting the left DLPFC for 10 treatments, no adverse events were reported and all participants in the active group (n=24) completed treatment (Liang et al., 2018). Liu and colleagues (2019) conducted a sham-controlled study of participants with MUD in which 52 subjects were assigned to the active 10 Hz group for 20 rTMS treatments. All completed the treatments, but no specific safety outcomes are reported. They do note however, “the current study suggests that rTMS is a safe, tolerable, and effective for female substance abuse patients.”

4.3.5 Potential Risks of rTMS

Seizure: rTMS can cause seizures, however the rate at which this happens is unknown. In a recent survey (Lerner et al., 2019) of rTMS laboratories and clinics between 2012 and 2016 (inclusive), respondents (N = 174) reported 24 seizures in an estimated 318,560 TMS sessions (.08/1000 sessions). However, TMS delivered within published guidelines to subjects without recognized risk factors only caused 4 seizures (<.02/1000 sessions). Subject risk factors (e.g., brain lesions and epilepsy) increased seizure risk. Seizures appeared more common when safety guidelines were exceeded. Stimulation with the parameters and settings we propose to use appears to cause fewer than 1 seizure per 60,000 sessions. We will carefully adjust the stimulus intensity based on the motor threshold, before beginning treatment.

While the presence of a brain tumor or lesion might be a contraindication for rTMS (although it is not always), this is typically only the case where seizure threshold is significantly lowered due to the lesion or if the lesion is on the rTMS-targeted cortical area. All participants will be asked if they have ever had a seizure or if any member of their family has ever had a seizure. They will be asked if they have any known tumors or lesions. They will be asked if they have ever had an abnormal MRI or CT scan. They will be asked if they have ever suffered a head injury and/or have ever been unconscious for more than a few minutes. A positive response to any of these screening questions will warrant further evaluation by the Medical Clinician (MC) who will determine if the participant is eligible for study participation.

Potential for scalp discomfort, face pain, eye pain, toothache, nausea and headaches: Some people report some mild discomfort when the magnetic pulses are applied over the scalp, which may be mitigated by use of topical anesthetic. Additionally, some people (less than 10%) report face pain, eye pain, or toothache during administration of rTMS (O’Reardon et al., 2007). Further, some people (~25%) report headache following rTMS. However, the headaches are temporary, go away on their own within 60 minutes, and are manageable with common over-the-counter pain remedies (Loo et al., 2008).

Potential worsening of mood with rTMS: Several studies have so far demonstrated the feasibility of rTMS as a treatment for depression without any alarming indicators of exacerbation of symptoms. We evaluate mood at baseline and during the course of the study to evaluate for changing mood symptoms.

Potential induction of mania/hypomania with rTMS: There is limited evidence that rTMS can induce manic or hypomanic episodes. In its use for Major Depressive Disorder, case reports of rTMS emergent manic episodes have been reported (Rachid, 2017). This risk could be elevated in a substance abuse population, given that stimulant use is also associated with mania and hypomania. Mood symptoms will be evaluated throughout the course of study.

Potential effects of rTMS on brain tissue: rTMS is thought to be safe, with no brain damage, despite extensive use in humans and other animals. We have reported a safety study looking at the MRI scans before and after 2 weeks of daily left prefrontal rTMS for depression. No structural changes were found in the left prefrontal lobe of patients who received active rTMS compared to placebo. We have also performed an MRI diffusion imaging study before and after rTMS/Functional Magnetic Resonance Imaging (fMRI) study and found no deleterious effect of rTMS on brain tissue at the site of stimulation.

Potential hearing loss: The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to rTMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Foam earplugs can protect against these changes and will be worn during rTMS sessions (Loo et al., 2008).

Potential changes in cognitive function: There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc.) in rTMS studies (Galletly et al., 2016). Safety studies specifically looking for these changes did not find any effects of rTMS with the exception of one open study in which healthy volunteers were exposed to 150 trains of rTMS at different sites of stimulation in a paradigm that lasted more than 3 hours. There was a significant decrease in scores on a logical memory test. The stimulation parameters exceeded the recommended safety range and there was no control for patient fatigue or other non-specific effects.

Safety in case of pregnancy: This protocol will exclude pregnant women. While the risks of using rTMS with pregnant women are largely unknown and current evidence is limited to case studies, the theoretical risk of rTMS is thought to be low (due to the rapidly dissipating magnetic field and the distance of the fetus from the coil) and case series evidence supports the safety of rTMS in pregnancy (Hizli et al., 2014; Eryilmaz et al., 2015). In fact, current thinking is that rTMS may ultimately be a safer treatment for severe depression during pregnancy (and post-partum) than systemic medications, although more data are needed to confirm safety in pregnancy.

Increased craving is a possible risk due to cue exposure: Since study procedures include exposing participants to cocaine or methamphetamine cues, there is a chance that there may be a transient increase in craving scores. Craving will be rated at the end of rTMS and subjects will be held in a supervised setting until their craving reaches baseline level. If participants continue

to experience high craving, inpatient hospitalization in an SUD unit is an option, but we have conducted cue-induced craving protocols over the last 20 years, we have never had to hospitalize a participant for protracted craving.

Metal implants and non-removable objects: Magnetic stimulation from the rTMS coil may cause metal objects to heat, which could lead to injury. Thus, all participants will be screened for having implanted metal objects, (with the exception of metallic dental fillings), and will be asked to remove any metal jewelry or piercings above the neck.

Unknown Risks: rTMS is an experimental procedure that has not been approved by the FDA as a treatment for CUD or MUD and it may have unknown side effects in this population. The researchers will let participants know if they learn anything that might make them change their mind about participating in the study.

4.3.6 Cautions

In the current study, risks of rTMS will be minimized by the following:

1. Conducting a physical exam and medical history to rule out individuals in whom rTMS may be unsafe
2. Following published safety guidelines for rTMS administration
3. Excluding individuals who may have vulnerabilities to possible side effects, including those with a history of seizure disorder, brain tumor or those with metallic implants above the waist (with the exception of metallic dental fillings)
4. Excluding pregnant women; conducting pregnancy tests periodically during the course of the trial and requiring effective birth control during the treatment phase of the study
5. Use of topical anesthetic cream (if needed) to prevent skin discomfort
6. Conducting motor threshold assessments by trained Advanced rTMS Operators
7. Obtaining UDS prior to each rTMS session and if newly positive for drugs of abuse, re-assessing the motor threshold prior to performing the rTMS
8. Re-assessing the motor threshold following any block of 10 rTMS sessions without recalibration
9. Assessing mood and suicidality at baseline and periodically during the course of the study
10. Frequent evaluation of side effects/adverse events by a Medical Clinician
11. rTMS sessions will be stopped at any point if the participant becomes uncomfortable
12. Providing foam earplugs to minimize risk of transient hearing impairment

Risks of EEG: There are no associated risks of EEG. Skin irritation or discomfort may result from electrodes or cap.

Psychological Stress: Some questionnaires may result in feelings of discomfort, upset, embarrassment, or disappointment.

Risks of Topical Anesthetic (EMLA, Lidocaine or Lidocaine/Prilocaine): Application site reactions (irritation, redness, swelling, stinging, burning), numbness in places where the cream is applied. There is also the risk of having an allergic reaction which could include hives, swelling to the face, throat, lips or tongue, itching, or difficulty breathing.

5.0 PRIMARY AIMS, OBJECTIVES, AND HYPOTHESES

5.1 Primary Aim

The primary objective of this pilot study is to determine the feasibility of up to 30 sessions of rTMS over the left DLPFC versus up to 30 sessions of sham rTMS for treatment of individuals with CUD or MUD. The primary outcome is feasibility — i.e., percent of participants who obtained at least 20 treatment sessions. Additional feasibility outcomes will be assessed as exploratory outcomes.

Primary Hypothesis: At least 75% of participants who enter CTN-0108 will receive 20 or more rTMS sessions.

5.2 Secondary Aims

The secondary objective of this study is to determine the efficacy of up to 30 sessions of rTMS over the left DLPFC versus up to 30 sessions of sham rTMS for treatment of CUD or MUD. The secondary outcome will be determined assessing the percentage negative of the last UDS per treatment week (7-day period). This will be used to examine the effect size of rTMS versus sham to inform future clinical trials.

Secondary Hypothesis: Individuals who receive active rTMS will have a significantly higher % UDS negative results for methamphetamine (if participants are designated in the primary MUD group) or cocaine (if participants are designated in the primary CUD group) over the course of treatment, as compared to those in the sham group.

5.3 Exploratory Aims

The exploratory objectives of this study are to examine other feasibility measures, the impact of rTMS on self-reported substance use, craving, mood and anxiety, sleep monitored via actigraphy, resting connectome profile via EEG, retention in treatment, and changes in health, lifestyle, and function.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The study will be a randomized, double-blind pilot trial comparing rTMS with sham treatment (sham) in reducing stimulant use among individuals with CUD or MUD. Potential participants will be screened for eligibility and undergo an assessment process. Eligible and interested participants will be randomized to one of two groups; groups will receive up to 30 sessions of rTMS (or sham) over the course of an 8-week treatment period. Assessments will be conducted at Screening, weekly during treatment, end of treatment, and at 12- and 16-weeks post-randomization. Participants will be compensated for participating in rTMS/sham sessions and assessments. UDS will be obtained at assessment sessions and prior to each treatment session from all participants.

Given that psychosocial interventions remain the mainstay of treatment for CUD and MUD, we reason that clinical neuromodulation trials should be conducted in the context of concurrent psychosocial treatment. Inclusion of cognitive-behavioral treatment comprised of evidence-based components among all randomized conditions addresses the ethical obligation to provide treatment for participants. All participants will be asked to participate in 20 self-guided CBT sessions developed for individuals with substance use disorders and organized by the DynamiCare company. Participation will be tracked but not incentivized. Participants will also complete brief daily surveys assessing substance use, craving, ability to resist use, mood, and sleep. These surveys will be delivered via ePRO directly to the participants' mobile device. Daily/nightly sleep and activity levels will be monitored in all participants using an ActiGraph device during the treatment period. If available at the study site electroencephalogram (EEG) measurements will be taken to facilitate identification of treatment response biomarkers.

Given the preliminary nature of this study (to better isolate the potential effects of rTMS from the effects of psychosocial substance abuse treatment), participants will not be engaged in formal substance abuse treatment. Participation in self-help groups is allowed. Recruitment will therefore focus on individuals who are willing to try to decrease their cocaine and/or methamphetamine use, but are not engaged or plan to be engaged in formal SUD treatment. If an individual is engaged in formal treatment at the time of recruitment, but chooses to participate in the trial rather than continue treatment, no "wash-out" period will be required. Efforts will be made to advertise and recruit in local communities specifically for individuals interested in decreasing or stopping cocaine and/or methamphetamine use. It is anticipated that enrolled participants will only receive study-related interventions and will not concurrently receive treatment as usual from the sites. However, if an enrolled individual decides to pursue formal treatment and remain in the study, data on time in treatment will be collected. Considering the rigorous time requirements of the rTMS protocol and the fact that we will be providing CBT modules for participant use, we do not anticipate that this will be an issue.

6.2 Duration of Study and Visit Schedule

Participants are expected to be engaged in the study for approximately 4 months (with 8 weeks of rTMS/sham plus 2 months of follow-ups). This study is expected to last approximately 2 years, including site initiation and close-out activities.

7.0 STUDY POPULATION

A total of approximately 160 individuals who have been identified as having Cocaine or Methamphetamine Use Disorder and are interested in cutting down or stopping use, approximately 80 in each, will be enrolled.

7.1 Participant Inclusion Criteria

Individuals must meet all of the inclusion criteria in order to be eligible to participate in the study. To be included in this study, participants must:

Table 1: Participant Inclusion Criteria

Criterion	Rationale
1. Be aged 18-65, inclusive.	Defines study population.
2. Have a diagnosis of moderate or severe Cocaine or Methamphetamine Use Disorder (CUD/MUD) over the past 12 months (as determined by DSM-5 diagnostic criteria).	Recruiting participants with moderate or severe CUD or MUD will allow detection of rTMS versus sham effects, that may not be apparent with mild CUD or MUD.
3. Have used cocaine or methamphetamine on at least 10 of the last 30 days (based on TLFB).	Participants must have a current CUD or MUD.
4. Be interested in decreasing cocaine and/or methamphetamine use	Defines study population.
5. If female, willing to use appropriate birth control method during the treatment phase of the study (see list below).	Safety
6. Be able to understand the study procedures and provide written informed consent to participate in the study.	To comply with ethical standards, and to ensure adherence to study procedures, participants must be able to understand the study procedures, risks, and benefits.
7. If prescribed benzodiazepines or anticonvulsants, must be on a stable dose for at least 4 weeks prior to consent.	These medications can raise the seizure threshold, which could affect the motor threshold

Appropriate birth control methods include:

a. Oral contraceptives, contraceptive patch, hormonal vaginal contraceptive ring;
b. Barrier (diaphragm or condom);
c. Contraceptive implant;
d. Medroxyprogesterone acetate injection;
e. Intra-uterine device
f. Complete abstinence from sexual intercourse;
g. Surgical sterilization

7.2 Participant Exclusion Criteria

All individuals meeting any of the exclusion criteria will be excluded from study participation.

Exclusion criteria will include the following:

Table 2: Participant Exclusion Criteria

Criterion	Rationale
1. A DSM-5 diagnosis of moderate or severe SUD of any substance other than cocaine or methamphetamine based on DSM-5 Checklist.	The present study has been specifically designed to target, and assess effects of rTMS versus sham on, CUD or MUD. Defines study population.
2. History of a serious medical disorder that, in the opinion of the Medical Clinician, would make it unsafe to participate in the study or may prevent collection of study data.	Treatment for a serious medical disorder should take precedence over this experimental treatment for SUD. A serious medical disorder could interfere substantially with engagement in the treatment, negatively influencing feasibility and efficacy outcomes.
3. Is currently engaged in formal SUD treatment.	This pilot study is designed to examine the effects of rTMS (versus sham) in the context of a self-guided CBT program.
4. Documented history of unprovoked seizure (lifetime) or any seizure in the past 6 months.	Seizure is a risk associated with rTMS.
5. Documented history of brain lesion(s) and/or tumor(s).	The presence of a brain tumor or lesion might be a contraindication for rTMS (i.e., where seizure threshold is significantly lowered due to the lesion or if the lesion is on the rTMS-targeted cortical area).
6. Metal implants or non-removable metal objects above the waist[1].	Participant safety.
7. Currently pregnant.	While there is no available evidence to date suggesting that rTMS is harmful during pregnancy, the risks of using rTMS with pregnant women are unknown.
8. Lifetime history of prior clinical treatment with TMS	Prior TMS exposure will unblind active and sham groups.

Criterion	Rationale
9. Current or lifetime bipolar disorder.	Mania and hypomanic episodes may be worsened by rTMS. Individuals with comorbid posttraumatic stress disorder, anxiety disorders, and/or depressive disorders will be allowed to participate. Individuals will be screened for current MDE, as randomization will be stratified by presence of current depressive disorder (among other factors).
10. Current psychotic disorder or psychotic depression.	In order to keep the population for this pilot project homogeneous, individuals with psychotic disorders will be excluded.
11. Serious risk of homicide or suicide.	Participant safety.
12. Are a prisoner or in police custody at the time of eligibility screening.	Prisoner or police custody status would preclude engagement in the study, which involves multiple in-person treatment and follow-up visits.
13. Previously randomized as a participant in the study.	Participants may only enroll in the study once
14. Planned admission to a residential treatment facility or other formal SUD treatment program.	This pilot study is designed to examine the effects of rTMS (versus sham) in the context of a self-guided CBT program. Formal treatment for SUD would interfere with assessment of study outcomes.
15. Unwilling or unable to follow study procedures.	Study procedures must be followed, both for participants' safety and to allow assessment of study outcomes.

[1]with the exception of metallic dental fillings

7.3 Participant Recruitment and Retention

Participants will be recruited from multiple sources at each of the 4 study sites. Individuals will be pre-screened by research staff, and those who are likely to meet DSM-5 criteria for CUD and/or MUD will be invited for study assessments. Individuals who meet all inclusion criteria and who do not meet any exclusion criteria will be randomized to a study condition and participate in the study intervention and associated assessments. rTMS/sham will occur in the context of self-guided CBT modules. However, participants will not receive other treatment for SUD at the site while they are participating in the study. Thus, participants must be willing to have the study intervention serve as their sole SUD treatment during study participation, other than self-help groups.

The study will be advertised via media and community outlets, and by clinician and researcher referral, using methods approved by the single Institutional Review Board (sIRB). Screening and enrollment logs will be maintained at each study site; for each potential participant, information will be documented regarding source of initial information about the study — including referral source, if applicable; reasons for ineligibility at the screening assessment levels; and reasons for non-participation of eligible participants.

7.4 Inclusion of Women and Minorities

A variety of study sites will be selected to promote the attraction of a diverse study population. Study sites should aim at recruiting participants comparable to national demographic characteristics of past month cocaine and methamphetamine users. See Table 3 below. The demographic characteristics may vary slightly from site to site based on underlying regional demographic differences. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

Table 3: Demographic Characteristic Percentages in Past Month Cocaine and Methamphetamine Users Aged 18 or older: Results from NSDUH 2018

Characteristic	Cocaine	Methamphetamine
GENDER		
Male	68	64
Female	32	36
HISPANIC ORIGIN AND RACE		
Not Hispanic or Latino	84	82
White	58	73
Black or African American	17	2.5
AIAN[a]	0.4	2.3
NHOPI[b]	0.3	*
Asian	0.4	0.8
Two or More Races	4	4
Hispanic or Latino	16	18

[a] American Indian and Alaskan Native
[b] Native Hawaiian and Other Pacific Islander

* = low precision

Ref: SAMSHA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2017 and 2018.

7.5 Retention Plan

Participant retention for follow-up will focus on continued engagement throughout the follow-up period. Specifically, incentivized daily assessments will continue throughout the follow-up period. Research staff will schedule end of treatment appointments with participants on their last day of treatment, and will schedule follow-up appointments with participants on the day of their end of treatment appointment. Research staff will contact participants using their preferred contact methods (e.g., phone call, text, email) with appointment reminders approximately 1 week, and again 1 day prior to the incentivized follow-up assessments.

8.0 SITE SELECTION

8.1 Sites

As this is a pilot feasibility project, we will recruit over approximately a 22-month period with a 2-month follow-up period (occurring on a rolling basis). Each site is expected to recruit approximately 3-4 participants per month.

The study sites should be experienced in the administration of rTMS as part of a research study recruitment and the management of the needs of individuals with SUDs. Specifically, participating sites should:

1. Be able to rely on the MUSC IRB as the single IRB (sIRB) of record
2. Have an rTMS operator (or other individual certified in rTMS administration procedures) and Medical Clinician experienced in administering active and sham rTMS
3. Have access to the MagVenture MagPro® X100 system properly equipped for double blinding for use during this study
4. Be able to recruit enough individuals with CUD and/or MUD to meet study recruitment goals
5. Have previous experience enrolling individuals with CUD and MUD in clinical trials
6. Be willing to randomize participants to active rTMS versus sham conditions
7. Have ability to conduct rTMS and sham sessions on weekends
8. Be able to provide after hours clinical backup for study-related emergencies
9. Be willing/able to provide payment to participants for attendance and assessment completion

8.2 Rationale for Site Selection

We will choose sites with experience administering rTMS to facilitate timely study start-up and reduction of initial costs and time associated with site training. In order to evaluate the feasibility of treating stimulant use disorders with rTMS, we must start with teams that have successfully administered this therapy in the past. Furthermore, meeting the targeted sample size requires the ability to recruit individuals with CUD or MUD who are seeking treatment. Therefore, we will choose sites with experience in conducting research with and treating this population.

9.0 OUTCOME MEASURES

9.1 Primary Outcome Measure – Feasibility

The primary objective of this pilot study is to determine the feasibility of up to 30 sessions of active rTMS over the left DLPFC versus up to 30 sessions of sham rTMS in individuals with CUD or MUD. The primary feasibility outcome will be the percentage of participants who receive at least 20 sessions over the 8-week treatment period. Treatment session attendance and completion will be tracked over the course of the study, and this record will constitute the primary feasibility outcome.

9.2 Secondary Outcome Measure – Efficacy

The secondary objective of the study is to examine the effect size of up to 30 sessions of rTMS over the left DLPFC versus 30 sessions of sham rTMS on cocaine or methamphetamine use in individuals with CUD or MUD (respectively). The efficacy outcome will be determined using the last UDS in each treatment week. The percent of negative UDS from these 8 samples will be presented as a continuous measure. A negative drug screen for participants in the CUD group would be a UDS absent of cocaine; a negative drug screen for participants in the MUD group would be a UDS absent of methamphetamine.

9.3 Exploratory Outcome Measure(s)

Exploratory objectives of this study include examining the impact of rTMS on self-reported substance use, craving, mood and anxiety, sleep monitored via actigraphy, resting connectome profile via EEG, retention in treatment, and changes in health, lifestyle, and function. Additional feasibility outcomes will be explored, including the following:

- Percent of participants that complete at least 75% of daily monitoring
- Percent of participants that complete all follow-up visits

9.4 Study Timeline

After receiving CCTN approval of the final protocol, approximately 6-9 months of trial preparation activities will elapse prior to commencing enrollment/randomization. Trial preparation will include obtaining IRB approval, developing the data collection systems, developing the manual of procedures (MOP), conducting all research staff training, and sites' securing CLIA Certificates of Waiver (as needed), collecting required regulatory documents and endorsing sites. If feasible, the study may be implemented in a single wave; however, sites may launch on a rolling basis of 1-2 sites per month. Recruitment is expected to take approximately 12-15 months, with follow-up continuing for approximately 6 months post completion of the recruitment phase. Two months will be allowed for data lock after the end of the follow-up period. Therefore, data lock is projected to occur at approximately 27-30 months after CCTN approval of the final protocol.

10.0 STUDY PROCEDURES

10.1 Pre-Screening

Participants will be recruited at each study site. Potential participants responding to recruitment materials or otherwise referred to the study will be pre-screened on the phone or in person to ascertain preliminary eligibility status. A series of questions will determine preliminary eligibility, and formal screening appointments will be scheduled for those who meet these eligibility criteria. A waiver of signed/documented consent and a waiver of HIPAA authorization will be obtained from the sIRB for pre-screening.

10.1.1 Informed Consent Procedures

Prior to the initiation of any study procedures, written informed consent and HIPAA authorizations will be obtained from participants by the designated site research staff. Potential participants will be given a copy of the IRB-approved consent form and asked to read it either on site or at home in accordance with the consent process approved by the sIRB. Those who remain interested after receiving an explanation of the study will be given a short quiz prior to signing the consent form to test their understanding of the project, the purpose and procedures involved, and the voluntary nature of their participation. Those who cannot successfully answer quiz items will have the study re-explained by research staff with a focus on aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study by answering all items on the true/false quiz correctly will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments. As part of the informed consent procedures, participants will be asked to provide or decline consent to be contacted for future studies. After passing the quiz and signing the consent form, participants will be given a copy of the signed form to keep for their records.

10.1.2 HIPAA Authorization and Medical Record Release Forms

Each site will utilize a HIPAA Authorization, either combined into the consent or as a separate document, allowing study access to protected health information obtained by participant report, and in the participant's medical record, as required by their institutions. Sites will be responsible for communicating with their local IRBs or Privacy Boards and obtaining appropriate approvals or waivers as dictated by the sites' reliance agreement with the sIRB to be in regulatory compliance.

10.2 Screening Assessment

After consenting to participate in the study, participants will start the screening assessment phase. Ideally, the screening assessment procedures will be completed in two visits, but they can be completed in more visits if necessary. The screening assessment procedures must be completed within two weeks prior to randomization.

To determine study eligibility, the site's Medical Clinician will review all source documentation related to inclusion and exclusion criteria. Women of childbearing potential must have a negative

pregnancy test the day of randomization (before randomization can proceed). Please see Section 12, Table 6 for details of screening and randomization assessments.

10.3 Randomization

Following determination of full study eligibility via screening, and completion of baseline assessments, participants will be randomly assigned to one of the two conditions (rTMS or sham) for 8 weeks. Random assignment will be on a 1:1 ratio to one of the two conditions. Randomization will be stratified by study site, presence/absence of current major depressive episode, and primary CUD or MUD designation. The randomization procedure will be conducted centrally through the CTN DSC, and randomization assignments will not be conveyed to local research staff or participants. The randomization schedule will be programmed into the rTMS machine so that neither the participant nor the rTMS Operator or research staff knows what condition was assigned. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignments across treatment groups. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated, due to the intent-to-treat nature of the study.

10.4 Treatment/Intervention

Prior to receiving the first active/sham rTMS intervention, the participant will meet with the Advanced TMS Operator to determine the participant's motor threshold (MT). See Section 11.2 for description. Once the participant motor threshold has been determined, participants will receive either active rTMS or sham rTMS treatment as determined at Randomization

10.4.1 rTMS and Sham

Either repetitive transcranial magnetic stimulation (rTMS) or sham (control) will be delivered to study participants during treatment sessions after exposure to approximately 5 minutes of imaginal (script-based) and visual methamphetamine (for MUD participants) or cocaine-related cues (for CUD participants). The delivery of active versus sham intervention will be controlled by a dual active/sham coil. Administration of active versus sham rTMS will be determined by the computer controlling the coil; randomization status will have been entered into files used by the computer during DSC randomization. With this procedure, rTMS Operators and other research staff will be kept blind to participants' condition assignments. The coil will be placed to stimulate the left DLPFC. Section 11 provides specific rTMS parameters and considerations.

Prior to each rTMS/sham session, cues designed to activate craving will be presented. At the first session, participants will complete a triggers worksheet. At each subsequent session, participants will be presented with their completed worksheet and asked to imagine that they are re-experiencing a time when they were tempted to use and to imagine the pleasure they would experience following use. This will continue for approximately one minute, then a set of slides with photographs of cue situations and objects will be presented for approximately two minutes. The post-cue craving assessment will be completed and the rTMS/sham session will begin afterwards. Craving and ability to resist use will also be assessed upon completion of the rTMS/sham treatment session.

Research staff will maintain study visit logs throughout the study period to monitor intervention adherence. Research staff will manage assessment and intervention appointment scheduling. Treatment sessions will be offered daily during the work week, with flexibility to allow occasional evening and weekend appointments, as well as multiple treatment sessions in one day (maximum 2 per day, 5 per study week).

10.4.2 Other Study Procedures:

Actigraphy: After randomization, participants will be issued an ActiGraph to assess daily sleep quality during weeks 1-8. The ActiGraph GT9X Link wristband device is an FDA cleared device. Information obtained from the device includes, but is not limited to, sleep latency, sleep duration, and intervals of waking during the sleep period. Participants will be provided with the device and necessary accessories for wear and battery charging. Research staff will download data from the device once a week. The participant will return the device at the end of treatment visit.

Electroencephalography (EEG): If available at the study site, EEG will be obtained after randomization and again at week 4, to explore the potential for EEG to be used as a biomarker of treatment response. The week 4 EEG will only be obtained for those participants for whom the EEG was conducted at randomization. Participants will wear a cap that will fit snugly on their head for this procedure. It is a quick and well-tolerated procedure to measure the summed electric potential of the brain measured at the scalp. Resting-state EEG will be recorded (5 minutes resting eyes open, 5 minutes resting eyes closed). The post-hoc analyses of the EEG provide a whole-brain connectomic profile (Toll, et al., 2020) before and after the course of treatment, revealing changes in functional brain connectivity. For this study, EEG will be performed at randomization and again at week 4 at study sites equipped to perform EEG. These analyses are considered exploratory. The fronto-parietal control network is known to function atypically in CUD and MUD as pursuit of the addictive substance sabotages executive functioning (Stewart et al, 2016). Additionally, longitudinal EEG recorded in adults at onset of abstinence from cocaine produced activation topographies consistent with the salience network which is integral to cue-related processing (Parvaz et al., 2016). Having established that specific functional networks are known to be atypically connected in addiction disorders and that resting-state EEG can resolve these networks' connectivity, an excellent opportunity presents to explore the diagnostic potential of EEG in CUD/MUD and its ability to predict therapeutic response to rTMS.

10.4.3 Safety Monitoring of Intervention

Intervention tolerability and effects will be systematically assessed before and after each treatment. This includes assessing for factors that impact seizure threshold (e.g., increased stimulant use). Retesting of MT may occur as outlined in the rTMS intervention section below. Participants will be encouraged to contact research staff between visits to address any immediate concerns regarding adverse events and medication changes; however, information on adverse events and medication changes also will be collected during assessment and intervention appointments. The Study Medical Clinician will meet with the participant before, during, or after any study intervention if the rTMS Operator or participant is concerned for the potential of a serious adverse event, including seizure. If suspected seizure occurs during study intervention, the Study Medical Clinician will arrange for the participant to be transferred to local emergency

room for further management. In the event of a seizure during the study, the participant will be discontinued from further study intervention.

10.4.4 Cognitive-Behavioral Educational Intervention

Participants in both conditions (rTMS and sham) will also participate in a CBT for SUD educational intervention that will be delivered via a mobile application platform developed and managed by DynamiCare Health. Twenty (20) self-guided modules will deliver evidence-based CBT and motivational strategies and educational therapeutic content to participants. Participants will be asked to complete 2-3 modules per week during the treatment phase (rTMS or sham). Modules are brief (less than 30 minutes to complete), contain both didactic and interactive content (i.e., activities to reinforce didactic content), are available anytime, and may be completed in single or multiple "sessions." Modules may be completed in any order. Participation will be tracked but will not be incentivized. Session topics and a brief summary of content are provided in Table 4 below.

Table 4: Cognitive Behavioral Educational Session Topics

Module Title	Content Summary
Hijacking the Brain: Disease of Addiction	Signs of addiction: loss of control and Overview of disease of addiction
Triggers (learning about triggers): Part 1	Identifying personal triggers and reaction (positive and negative) to them
Triggers (practice scenarios): Part 2	Practice 3 scenarios identifying triggers, and subsequent reaction/behavior
Healthy Coping Skills: Part 1	Planning for encountering triggers and introduction to healthy coping options
Healthy Coping Skills: Part 2	Avoiding triggers and managing/coping with unavoidable triggers
Justification	Identification of own justifications for substance use
Relapse Prevention Plan: Part 1	Planning for triggers, implementing healthy coping plan, attaining sober support
Relapse Prevention Plan: Part 2	Implementing a healthy coping plan for triggers
Relapse Prevention Plan: Part 3	Identifying sober support and putting relapse prevention plan into practice
Relapse Prevention Tips: Part 1	Avoiding relapse: Skills training for HALT, urge surfing, and setting healthy boundaries
Relapse Prevention Tips: Part 2	Reviewing HALT, urge surfing, and boundary setting
Building Discrepancy – Decision Making Skills	Focus on evaluating & responding vs. reacting; Differentiating between healthy vs. unhealthy coping
Cognitive Behavioral Model: Part 1	Introducing tripartite model and evaluating thoughts for cognitive distortions
Cognitive Behavioral Model: Part 2	Reviewing CBT model and introducing reframing

Module Title	Content Summary
Rational vs. Irrational Thoughts	Identifying irrational thoughts based in fear rather than fact
Self-Care Assessment	Building a healthy lifestyle via activities that promote physical, mental & emotional heath
Dealing with Stressors	Defining stress and identifying warning signs of chronic stress (e.g., fatigue)
Mindfulness	Introducing core mindfulness components of awareness and acceptance; Mindfulness practice exercise
Grounding Techniques	Teaching techniques including: (1) Refocusing on present moment during uncomfortable feelings, distressing memories, triggers, and (2) 5-4-3-2-1 exercise and practice
Using Your Strengths	Identifying personal strengths and their role in achieving personal goals

10.4.5 Clinical Deterioration “Rescue” Plan

A clinical deterioration “rescue” plan will be in place for participants who experience psychiatric or SUD deterioration during the study. Symptoms will be monitored closely throughout the trial to assess for deterioration (e.g., using the suicidality items on the Concise Health Risk Tracking questionnaire). Those who endorse suicidal thoughts or intent on the CHRT-SR will be further assessed on the CHRT-Clinician Rated assessment. Appropriate intervention will be arranged for any participant demonstrating gross clinical deterioration or suicide risk. The rescue measures will include referral for appropriate clinical intervention, including removal from the study and referral to SUD treatment should the participant demonstrate increasing substance use.

10.4.6 Follow-up

The study intervention will last 8 weeks (approximately 30 rTMS sessions). The research team will conduct follow-up assessments at the end of treatment and at weeks 12 and 16 post-randomization. There will be flexibility in exact timing of the follow-up assessments in order to accommodate participants’ schedules and to allow for either in-person or electronic communication (e.g., phone or other HIPAA compliant mechanism). In the event that follow-up visits are conducted remotely, the UDS will not be performed.

10.4.7 Referral for Participants Needing Continued Treatment

At the end of study participation (the last follow-up visit), if a participant requires or requests continuing treatment for CUD and/or MUD (as well as other SUDs), an appropriate treatment referral will be made.

10.5 End of Treatment Assessment and 12- And 16-Week Post-Randomization Follow-Up Assessments

Follow-up assessments are expected to be conducted at the end of treatment, and at 12- and 16-weeks post randomization and will be conducted by research staff. Printed reminders for the follow-up assessments will be given to the study participant during the end of treatment

assessment appointment. In addition, research staff will send a reminder in the mail/text/email/or social media (based on study participant preference) about 7 days prior to the scheduled follow-up with an additional reminder notification via mail/text/email/or social media (based on study participant preference) the day before the scheduled follow-up. The end of treatment visit may occur on the day of the last treatment in week 8, or up to 1 week later. Week 12 and 16 follow-up visits may occur no more than 1 week prior to the visit or 2 weeks after the scheduled visit. See Section 12 for assessments to be completed.

10.6 Collection of Biospecimens

Urine samples will be collected from all participants for urine drug screen (UDS), the main efficacy outcome measure of the study. This will occur at screening, randomization, during each treatment session prior to beginning the intervention, during the end of treatment visit and follow-up assessments (UDS will be omitted if follow-up visits are performed remotely). A newly positive UDS will result in recalibration of the motor threshold before rTMS delivery. For females of child-bearing potential, a urine pregnancy test will be administered. Results of the urine pregnancy test will be obtained prior to performing the UDS, at screening, randomization, at weeks 4 and 8 of treatment and at any other time a woman reports she might be pregnant. A positive pregnancy test post-randomization will result in the cessation of rTMS/sham treatment. The research staff will follow the participant until an outcome of the pregnancy is known and reported.

10.7 Premature Withdrawal of Participants

All participants will be followed for the duration of their participation in the study unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, the participant acquiring an exclusionary condition, lack of funding, or Data and Safety Monitoring Board (DSMB) early termination of the study for safety reasons.

Should participants be lost to follow-up, efforts to pursue participant locator information such as multiple contact options (e.g., phone, address, email, social media) and collateral contact information will be maintained. At any time, participants may decide that they no longer wish to continue to participate in the study.

10.8 Discontinuing of Study Intervention

Efforts will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up.

10.9 Study Pause Rules

The safety and preliminary efficacy of using rTMS to assist those with SUD has been evaluated in several studies (see Rao et al., 2019). Nevertheless, the study DSMB will have access to all adverse events and other reportable events. Should the DSMB (or sponsor) determine that the study should be temporarily suspended or terminated, the Lead Investigators will work with the sIRB of record and each of the participating sites to promptly inform them of the reasons for study termination or temporary suspension and to identify the circumstances in which the study may resume.

The following study stopping rules will automatically pause or halt further enrollment and will trigger a review by the DSMB:

- Two or more participants experience severe (Grade 3) neurological reactions
- One serious, unexpected and related adverse reaction

10.10 Blinding

10.10.1 Type of Blinding

This is a double-blind, sham-controlled study.

10.10.2 Maintenance of Blind

With the exception of specified individuals at the DSC and the safety staff at the CCC, all other study personnel and participants will remain blind to intervention status until completion of the trial at all study sites. A Data and Safety Monitoring Board (DSMB) will review study data. DSMB reports will be blinded, though the blind may be broken in the closed session upon request.

10.10.3 Breaking the Blind

In rare cases, it may be necessary to break the blind for a particular participant before completion of the trial (e.g., pregnancy or other medical necessity). The request to break the blind for an individual participant will be made by study Lead Investigators and/or site Principal Investigator.

Unblinding the participant should only occur in cases of medical emergency when knowledge of the treatment group investigational method may be necessary for clinical management and decision-making. The decision to break the blind for a participant will be made jointly by the CCC Safety/Medical Monitor and at least one of the Lead or site Principal Investigators.

10.11 Participant Remuneration

Because of the expected difficulty of maintaining high follow-up rates in the study population, adequate compensation for time and inconvenience is critical. Compensation will be in accordance with the IRB of record's policies and procedures, subject to IRB approval, and will occur on the following study activities:

- Consent and baseline data collection
- Treatment session attendance
- Daily assessment
- End of treatment assessment
- Week 12 follow-up assessment
- Week 16 follow-up assessment
- Completion of EEG (if available at the study site)
- Returning smart-phone device or to reimburse for data plan usage for those who used their own device

Compensation will occur following each visit with procedures specified in the SOP. Sites may reimburse participants directly for mileage expenses based on procedures specified in site operating procedures (SOPs).

11.0 rTMS INTERVENTION

11.1 Overview

Study participants will be randomized to receive up to 30 sessions of either active rTMS or sham across 8 weeks. Flexible treatment appointments will be offered, with every effort made to schedule participants for 3-5 sessions/week. Stimulation will follow FDA-approved protocol for Major Depressive Disorder: 10 Hz stimulation at 120% of the motor threshold intensity and a total of 3000 pulses per session using a figure-8 coil. We will not restrict sites to using a specific device model, as long as the device is capable of delivering this stimulation protocol with sham treatment above.

11.2 Structure And Content Of Treatment Sessions

Resting MT will be determined prior to initial treatment using the Parameter Estimation by Sequential Testing (PEST) algorithm. A revised MT will be determined in the following clinical scenarios:

1. If UDS becomes positive for methamphetamine or cocaine after previously being negative.
2. If participant reports increased methamphetamine or cocaine use since last treatment.
3. If participant has had 10 treatments without repeat motor threshold determination.
4. Study Medical Clinician determines, based on their clinical judgement, seizure threshold has decreased for any other reason.

Whenever MT is retested, treatment intensity for the following rTMS sessions will be based on the revised MT.

Topical anesthetic (e.g., EMLA, Lidocaine or Lidocaine/Prilocaine) may be applied prior to rTMS/sham to help reduce scalp discomfort.

Prior to each treatment stimulation onset, a set of cocaine or methamphetamine-related cues will be presented to the participant. Immediately after the offset of the cue presentation (while memory is reactivated) active or sham rTMS stimulation will be administered.

Each treatment session will consist of 75 rTMS trains of 10 Hz for 4 seconds with inter-train interval (ITI) of 11 seconds (a total of 3000 stimuli per session) over the left DLPFC (19 minutes). These parameters are consistent with those recommended in a recent consensus statement for rTMS treatment for Major Depressive Disorder (McClintock et al., 2018).

The rTMS coil will be placed over the DLFPC using the Beam F3 method. Participants in the control group will receive sham treatment in a similar manner. Administration of active versus sham rTMS will be determined by the computer controlling the coil; randomization status will have been entered into files used by the device computer during DSC randomization. Treatment assignment will not be revealed to the participants or study personnel (double-blind). To improve treatment tolerability, a ramp-up will be used where the stimulation intensity is gradually increased

during the treatment session. Participants will be expected to ramp to full intensity by the tenth rTMS/placebo session; however, participants will not be excluded if they are unable to tolerate the full treatment dose. Rather, ramp up will be attempted every 5 sessions and dose will be documented.

11.3 Sham rTMS

Adequate sham stimulation protocols are a critical factor in clinical trials to ensure that effects can be ascribed specifically to rTMS. Since rTMS generates sensory perceptions, such as clicking sounds, and muscle contractions (Conde et al., 2019), sham strategies aim to mimic the sight, sound, and feel of real stimulation, while attempting to avoid any direct neuronal effects on the central nervous system. The delivery of active versus sham intervention will be controlled by a dual active/sham coil. Administration of active versus sham rTMS will be determined by the computer controlling the coil; randomization status will have been entered into files used by the computer during DSC randomization. With this procedure, rTMS Operators and other research staff will be kept blind to participants' condition assignments. In the sham condition, participants and staff will hear identical sound as active treatment, but the magnetic field will be delivered in the opposite direction (away from the brain). Additionally all participants will be equipped with small electrodes on the scalp adjacent to the magnetic coil. In the sham condition, the device will discharge a very mild electrical stimulation through those electrodes to mimic the tactile sensation of the magnetic field. This stimulation can cause muscle twitching and tactile sensation, but unlike magnetic stimulation does not penetrate the brain. For participants with prior rTMS exposure, the lack of tactile sensation from the magnetic field in the sham condition could lead to unblinding and hence prior exposure is exclusionary for study participation. Sham rTMS approaches require further development but are sufficient in clinical settings in which patients are generally naïve to rTMS as will be the case in this study (Duecker & Sack, 2015; Y. Levkovitz et al., 2015; C.E. Sheffer et al., 2013).

11.4 Scheduling

Every effort will be made to be flexible in scheduling rTMS visits, including Saturday and after-hours sessions (site resources permitting) and scheduling 2 rTMS sessions on 1 day (site resources permitting). Participants will receive study intervention over 8 weeks in order to complete up to 30 rTMS sessions. End of treatment assessment will be scheduled within 1 week after the last treatment session. Follow-up assessments will be scheduled at weeks 12 and 16 post-randomization.

The interval between rTMS sessions will vary over the course of the study and for each participant depending on individual scheduling needs, with the primary objective being that each participant receives an adequate dose of treatment (at least 20 sessions) with flexibility in the timing of rTMS delivery to minimize study drop-out. The target minimum number of treatments is 20 treatments over 8 weeks, with an ideal number of 30 treatments. No more than 5 treatments are permitted in a study week. Initially, participants are encouraged to complete 5 treatments per week and hence complete 20 treatments within 4 weeks. Weeks 5-8 are planned as a taper, but can be used to make up missed visits. Participants who miss a treatment, may also receive up to 2 treatments on a given day. Multiple treatments on a given day should be spaced at least 1 hour apart, from

the time the first treatment session ended. Therefore, some participants may be able to receive 5 treatments a week in 3 calendar days.

12.0 STUDY ASSESSMENTS

12.1 Overview

Study assessments were chosen to help understand the feasibility and effects of rTMS on individuals with stimulant use disorders. The assessments for this study balance the value of comprehensive data against feasibility and participant burden. Screening will evaluate full eligibility, including diagnosis of CUD and/or MUD and other psychiatric diagnoses. The study clinician must review and approve all safety and eligibility assessments to confirm participant eligibility prior to randomization. Excluding collection of study participant characteristics and locator information, the participant baseline data will include past alcohol and drug use including cocaine and methamphetamine using the Timeline Follow-Back (TLFB) method, use of other substances, quality of life, and other data chosen to evaluate the efficacy of rTMS in stimulant users (e.g., sleep). Table 5 provides a listing of administrative/data collection forms, and Table 6 includes the schedule for study specific assessments and procedures.

Table 5: Administrative Forms/Data Collection

	SC	RND	Double-Blind Treatment Phase								Post	FU	FU
Study Week	0	0	1	2	3	4	5	6	7	8	EOT	12	16
Pre-Screen Summary	X												
Randomization Enrollment Form	X												
Daily rTMS Treatment Log			X	X	X	X	X	X	X	X			
Visit Documentation			X	X	X	X	X	X	X	X	X	X	X
Protocol Deviation Form	-	-	-	-	-	-	-	-	-	-	-	-	-
End of Treatment Form											X		
Study Completion													X
Mental Health Assessment Follow-up	-	-	-	-	-	-	-	-	-	-	-	-	-
Serious Adverse Event Summary	-	-	-	-	-	-	-	-	-	-	-	-	-
Inventory Medication and Supplies	-	-	-	-	-	-	-	-	-	-	-	-	-
Actigraph Device Discontinuation			-	-	-	-	-	-	-	-	X		
EEG Completion (if available)		X				X							

- Completed as necessary

12.2 Administrative Forms

12.2.1 Pre-Screen Summary

This form provides the lead team with basic information for each potential participant pre-screened from each site.

12.2.2 Randomization Enrollment

The Randomization Enrollment form collects information regarding eligibility during the screening phase. Eligibility will be re-assessed prior to randomization. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process and randomization.

12.2.3 Daily rTMS Treatment Log

This form is reported by study coordinator and captures treatment parameters for each rTMS treatment. This includes information such as current motor threshold, date of treatment, date of last motor threshold determination, duration of treatment, treatment location, coil-type, number of trains in treatment, and number of pulses in treatment.

12.2.4 Visit Documentation Form

This form documents visit attendance or non-visit attendance. This assessment has been recently developed to document visits that could occur out of window, offsite, or missed due to COVID-19. This is a visit-based form expected at most visits. If a visit is missed for any reason, this form will capture the reason a study visit was missed. Completing this form and indicating that the visit was not attended, will remove the requirement for all assessments scheduled for that visit. Active tracking and follow-up should be performed for all missed visits. The form also captures specific data collection settings if applicable (such as in clinic, offsite, or remote).

12.2.5 Protocol Deviation Form

This form should be entered into the electronic data capture system whenever a protocol deviation occurs. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations. This form will also capture protocol deviations that were a result of COVID-19 specific restrictions.

12.2.6 End of Treatment Form

This form tracks the participant's status with regard to the study intervention. It will be completed at the end of treatment visit or at the end of the treatment visit window.

12.2.7 Study Completion Form

This form tracks the participant's status in the study. It is completed at the week 16 follow-up visit, or once the week 16 follow-up visit window lapses for participants who do not complete this final follow-up. If the participant withdraws consent, dies or is removed from the study per judgement of research staff, this form will be completed at the time of termination from the study. This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the site PI attestation of review of all study data.

12.2.8 Mental Health Follow-Up Assessment

This assessment must be completed if the participant endorses suicidal thoughts in the Concise Health Risk Tracking – Self Report (CHRT-SR) Suicidal Behavior Evaluation. The completion of the Mental Health Assessment form documents that a clinician has been notified. The site is required to have the participant evaluated by a qualified clinician in accordance with the site's specific SOP.

12.2.9 Serious Adverse Event Summary

This form will be completed for a given participant if they have a reportable serious adverse event and is intended to capture vital safety data for those events

12.2.10 Actigraph Device Discontinuation

This form will collect information on when the participant stopped using/wearing the actigraph device, as well as the reason for discontinuation of use.

12.2.11 EEG Completion

For sites equipped to conduct EEG assessments, this form documents whether the EEG was completed, and if not, why the EEG was not performed. The form is completed after randomization and again at week 4.

Table 6: Schedule of Assessments and Procedures

	SC	RND	Double-Blind Treatment Phase								Post	FU	FU
Study Week	0	0	1	2	3	4*	5	6	7	8*	EOT^	12	16
Informed Consent	X												
Locator Form and Updates	X	-	-	-	-	-	-	-	-	-	-	-	
EMA Contact Form		X	-	-	-	-	-	-	-	-	-	-	
PhenX Toolkit Core Tier 1[♯]													
Demographics	X												
Treatment Status Form	X												
Quality of Life	X										X	X	X
Self-Report of HIV testing	X												
Tobacco Use History	X												
Alcohol and Other Substance Use	X												
Medical Assessments													
Physical Exam	X												
Medical and Psychiatric History	X												
Vital Signs	X		X			X				X	X		
Adverse Events	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concomitant Medications[¥]	X	-	-	-	-	-	-	-	-	-	-	-	-
Penetration of Blind Assessment						X					X		X
Electroencephalogram (EEG) (if available)		X				X							
Psychological Assessments													
MINI 7.0.2	X												
Hospital Anxiety and Depression Scale (HADS)	X	X	X	X	X	X				X	X	X	X
Pittsburgh Sleep Quality Index	X					X				X		X	X
CHRT-SR Suicidal Behavior Evaluation[¥]	X		X	X	X	X	X	X	X	X	X	X	X
CHRT-CR Suicidal Behavior Evaluation	-		-	-	-	-	-	-	-	-	-	-	-
Substance Use Self-Report													
TLFB[¥]	X		X	X	X	X	X	X	X	X	X	X	X

	SC	RND	Double-Blind Treatment Phase								Post	FU	FU
Study Week	0	0	1	2	3	4*	5	6	7	8*	EOT^	12	16
Caffeine Intake Assessment	X		X	X	X	X	X	X	X	X			
DSM-5 Checklist	X												
Cannabis Use Assessment	X												
Fagerström Test for Nicotine Dependence ♮	X					X					X	X	X
Cue Craving Assessment€			X	X	X	X	X	X	X	X			
Other Assessments													
Protocol Satisfaction Form											X		
Daily Mobile Survey∞		X	X	X	X	X	X	X	X	X	X	X	X
Actigraphy		X	X	X	X	X	X	X	X	X			
Lab Testing													
Urine Drug Screen	X		X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test‡	X	X				X				X			

SC=Screening/Assessment, RND=Randomization, EOT=End of Treatment, FU=Follow-Up, ♮tobacco smokers only, ‡females only, ♯required by NIDA/CCTN. Timepoints 1-8 represent weeks of treatment; ¥assessment will occur weekly during the 8-week treatment/sham phase, €assessment will occur after cue presentation and end of rTMS session at each visit during the treatment/sham phase; ∞assessment will occur daily during the treatment/sham phase, and throughout the follow-up period. (-) indicates administration as appropriate. ^EOT will also be completed for participants who withdraw early from the study.*If either weekly visits 4 or 8 are missed, assessments that are only completed at those visits should be performed at the next attended visit.

12.3 General Assessments

12.3.1 Locator Form

A locator form is used to obtain information to assist in finding participants during study participation. This form collects the participant's current address, email address, and phone numbers. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected. Social security number, driver's license number and other information will be collected to aid both in searches of public records (for locating participants in the above scenario) and issuing appropriate tax documents based on participant compensation. This information will be collected on paper at screening and will be updated at each visit or whenever the participant reports a change in locator information. No information from this form is used in data analyses.

12.3.2 EMA Contact Sheet

A system-based form will be used to collect participant's email address and mobile number. This information will be used to distribute daily mobile surveys assessing cocaine or methamphetamine related outcomes to participants, and will be updated by site staff if participants change service providers, mobile numbers and/or email addresses throughout the course of the study. In addition, participants will be able to unsubscribe or re-enroll to the mobile surveys during the course of the study, and site staff will also have the ability to unsubscribe or re-enroll participants to receive mobile surveys within the system.

12.3.3 Phen-X Toolkit Core Tier 1

The Substance Abuse and Addiction Collection of the Phen-X Toolkit (http://www.phenxtoolkit.org/) includes measures that are being adopted across NIDA-funded research. The Core Tier 1 collection includes measures for demographics (age, ethnicity, gender, race, educational attainment, employment status, marital status), BMI, and self-report of HIV test; substance use measures include age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances. Core Tier 1 assessments are completed at screening only.

12.3.4 Additional Demographics

A study-specific demographics form will collect information regarding gender identity and sexual orientation.

12.3.5 Protocol Satisfaction Survey

Participants will complete a Protocol Satisfaction Survey at the end of treatment visit. If the participant does not attend that visit, it should be completed at the next attended visit (either the week 12 or 16 post-randomization follow-up visit. This form will assess the acceptability of study procedures, time, compensation, treatment intervention and other aspects of their experience, including a free-response (qualitative) item regarding how the treatment/intervention made them feel.

12.3.6 Quality of Life

Participants will complete a standardized quality of life assessment used by the NIDA CTN from the CDC Behavioral Risk Factor Surveillance System (BRFSS), the Health Related Quality of Life (HRQOL-4) measure. This form assesses health-related quality of life in the past 30 days, and includes an overall self-reported rating of general health (from ‘Poor’ to ‘Excellent’). This form is collected at screening, EOT, week 12, and week 16.

12.4 Medical Assessments

12.4.1 Physical Examination

A brief physical exam will be performed by the study Medical Clinician at the screening visit to assess whether individuals are medically stable for study inclusion. For staff/participant convenience, this may be done at Randomization as long as it is completed prior to randomization.

12.4.2 Medical and Psychiatric History

The study clinician obtains a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information. This is collected during screening. For staff/participant convenience, this may be done at Randomization as long as it is completed prior to randomization.

12.4.3 Vital Signs

Valid measures of height (at screening only) weight, blood pressure, and pulse will be collected at screening, initial treatment visit in week 1, initial treatment visit in week 4, initial treatment visit in week 8 and end of treatment.

12.5 Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Adverse Device Effects (UADE)

12.5.1 AEs, SAEs and UADEs

At each visit the study staff assesses for AEs and SAEs by asking the study participant, “How have you been feeling since your last visit?” AEs and SAEs may also be spontaneously reported to study staff at any visit following consent. The Medical Clinician will review all AEs at least weekly. Any AE suggesting medical or psychiatric deterioration will be brought to the attention of a Medical Clinician immediately for further evaluation and management. Similarly, any SAE will be brought to the attention of the Medical Clinician immediately for further evaluation and reporting as required. Visits will emphasize overdose risk and risk-management; any reported overdose is recorded as an AE or SAE. AE and SAE reporting are according to the reporting definitions and procedures outlined in the protocol and in accordance with applicable regulatory requirements.

Device safety data will include the incidence of SAEs (e.g., worsening depression, suicidal ideation, suicide attempt, suicide, switching to hypomania/mania, seizure, death, and device malfunction resulting in patient or operator injury). In accordance with FDA recommendations, this protocol includes a suicide severity rating scale (CHRT) to assess both suicide intent and behavior. Incidence of common adverse events such as headache, application site pain will be collected, as well as discontinuation rate due to adverse events. Severity and duration of each AE will be determined. Data on each AE will include information about the intervention that was performed and whether the event was resolved. In addition, study staff will assess participants for signs of UADE, and will bring potential UADEs to the Medical Clinician for evaluation. Any UADE identified will be reported in accordance with applicable regulatory requirements (i.e., reported to the IRB for an abbreviated IDE as regulated under 21 CFR 812).

Any events that meet the definition of an AE and/or SAE are reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant are captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires; and withdrawal symptoms not listed in the specific structured questionnaires reported at any visit.

12.5.2 Prior and Concomitant Medications

For safety purposes, all medications taken by the participant for the 30 days prior to screening, during screening, and during the active study will be documented on a Prior/Concomitant Medications assessment. All medications taken by the participant while in the study should ideally be pre-approved by the Medical Clinician.

12.5.3 Penetration of Blind Assessment

Participants and primary study personnel will be asked whether they think the participant is receiving rTMS or sham. This will be collected at the initial visit of treatment week 4, end of treatment, and final Follow-Up visit (week 16).

12.5.4 EEG Biomarker of Treatment Response

Electroencephalography (EEG) is a quick and well-tolerated procedure to measure the summed electric potential of the brain measured at the scalp. Resting-state EEG will be recorded (5 minutes resting eyes open, 5 minutes resting eyes closed) using a saline-based, high-density (≥64 channels) montage. At sites where EEG is available this procedure will be done prior to rTMS/sham treatment and again at approximately week 4. The week 4 EEG will only be obtained for those participants for whom the EEG was conducted at randomization.

12.6 Psychological Assessments

12.6.1 Mini International Neuropsychiatric Interview Plus

The MINI (Sheehan et al., 1998) is a semi-structured interview designed to ascertain a current, past, or lifetime history of the major Axis I psychiatric disorders in DSM-IV and ICD-10. Based on the original MINI, an expanded version (MINI 7.0.2) has been developed and validated for DSM-5. The MINI 7.0.2 will be administered (excluding the substance use section) by trained staff and used to evaluate for psychiatric disorders during the screening appointment. Equivocal diagnoses will be confirmed by the Medical Clinician.

12.6.2 Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond & Snaith, 1983) is a brief, validated instrument that screens for both depression and anxiety (Bjelland et al., 2002). It will be administered at screening, once during weeks 4 and 8 of treatment, at the end of treatment assessment, and at each follow-up assessment.

12.6.3 The Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) will be used to complement standard AE assessment of sleep changes. The PSQI is a relatively brief, validated instrument that measures sleep quality. The PSQI is designed to be administered every 30 days and will be completed following the schedule outlined in the study timetable.

12.6.4 Concise Health Risk Tracking – Participant Rated Module (CHRT-SR) Suicidal Behavior Evaluation

The CHRT-SR (Trivedi et al., 2011) is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner et al., 2007). The CHRT-SR will be assessed at screening, every week during the treatment phase, at the end-of-treatment assessment, and at the 12- and 16-week follow-up assessments. Responses on the measure will always be reviewed by research staff prior to visit

conclusion. Individuals who report a significant suicidal/homicidal risk, as indicated by a response of 2 or greater (Agree or Strongly Agree) on Items 14, 15 or 16 (the final 3 suicidal thoughts items) will be assessed by a qualified clinician before leaving the clinic (see the Concise Health Risk Tracking – Clinician Rated measure below).

12.6.5 Concise Health Risk Tracking – Clinician Rated Module (CHRT-CR)

The CHRT-CR will be performed by the Medical Clinician only if a participant answers any of questions 14-16 on the CHRT-SR as Agree or Strongly agree as described above. This assessment will also include, as needed, more comprehensive risk assessment/safety planning provisions, as well as potentially hospitalization, following site-specific hospitalization protocols.

12.7 Substance Use Assessments

12.7.1 Timeline Follow-Back (TLFB)

The Timeline Follow-Back (Sobel & Sobel, 1992) procedure will be used to elicit the participant's self-reported use, quantity, and route of administration of substances at baseline, throughout the treatment period, and at end of treatment and follow-up assessments. At screening, this form will be used to assess substance use for the 30-day period prior to screening. The TLFB will be administered throughout the active treatment phase and through the end of the follow-up period to document the participant's self-reported use of substances for each day since the previous TLFB assessment. We plan to use the TLFB to track self-reported use of all substances. At the 12- and 16-week post-randomization follow-up, substance use is reported since the last visit.

12.7.2 Caffeine Intake Assessment

At screening, the Caffeine Intake Assessment will be modeled after the Supplemental Beverage Questions in use for the ABCD Study (Lisdahl et al., 2018). If a participant endorses use of any caffeinated beverages, they are then asked the typical number of caffeinated drinks they had per week in the past 30-days (covering categories of coffee, espresso, tea with caffeine, soda with caffeine, and energy drinks). A briefer version of the Caffeine Intake Assessment (Daily Caffeine Assessment) will be conducted prior to each rTMS/sham session (covering the past 24-hours) in a manner consistent with the FORM-90 approach.

12.7.3 DSM-5 Checklist

The DSM-5 (American Psychiatric Association, 2013) Checklist is a semi-structured, interviewer-administered instrument that provides current diagnoses for substance use disorders based on DSM-5 diagnostic criteria. The DSM-5 Checklist will be administered for each substance the participant reports using in the last 12 months (including cocaine and methamphetamine).

12.7.4 NIDA Cannabis Use Assessment

This survey assesses participants' recreational and medical cannabis/marijuana use frequency over the past 12 months, including reasons for use (e.g., to address medical/psychological

concerns, to replace other substances or medications), method of administration, and perceived harm or benefit associated with use. This form will be completed at screening.

12.7.5 Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is used for assessing cigarette use and nicotine dependence (Heatherton et al., 1991) and will be administered to each participant at screening, at treatment week 4, end of treatment, and at each follow-up.

12.7.6 Cue Craving Assessment

The craving scale will assess current craving immediately following cue exposure, as well as after each rTMS/sham session. An additional item assessing ability to resist using is presented after each rTMS/sham session. This assessment will be performed immediately following cue presentation and at the end of each rTMS/sham session to make sure the participant is not experiencing significant craving before leaving the study site.

12.8 Daily Assessments

12.8.1 Daily Monitoring

To augment data collection in this trial, we will administer remote assessments/surveys to participants on their mobile devices through ePRO. Brief, electronic remote surveys will be administered to participants on day 1 of treatment and will occur daily until the week 16 follow-up time point (regardless of when the follow-up visit actually occurs). Data collection in-between study visits is critical for study outcomes and capturing an accurate picture of the recovery process. Remote surveys may also aid in retention of study participants and allow research members to more intensively follow-up with participants should they miss a survey (allowing for more potential contact with participants).

Remote surveys will be delivered to the participant's mobile phone as a survey invite link through an SMS text message (and via email). If participants do not have smartphones, one will be provided for use during the course of the study. Participants will also have the option to receive remote surveys via email. The survey invite includes an individualized link that contains embedded data. Participants will have 24 hours to complete the survey, up until the time the next survey is delivered. Responses will be date and time-stamped. In the case that two surveys are completed in the same day, the first survey of the day will be retained.

Two versions of the daily survey will be utilized, based on participant report of their primary stimulant substance(s) of abuse during screening: (1) primary cocaine; or (2) primary methamphetamines. The survey will ask participants to answer whether or not they used their primary reported substance of abuse (Yes/No); to rate their craving using a Visual Analog Scale; to rate their ability to resist use of primary substance on a Visual Analog Scale; to rate their overall mood on Visual Analog Scale; and to rate overall sleep quality on a Visual Analog Scale. Participants will receive the survey link at the same time each day, and be asked to report on the last 24 hours.

12.8.2 Actigraphy

The ActiGraph GT9X Link wristband device will be used to collect participants' daily sleep data. Information obtained from the device includes, but is not limited to, sleep latency, sleep duration, and intervals of waking during the sleep period. Participants will be provided with the device and necessary accessories for wear and battery charging. Data will be extracted from the device by research staff during study visits.

12.9 Lab Testing And Samples

12.9.1 Urine Drug Screen for Other Substances

To assess the efficacy outcome, Urine Drug Screens (UDS) will be collected at screening, randomization, at each treatment session prior to beginning the rTMS/sham treatment, at the end of treatment visit and follow-up visits (UDS will be omitted if follow-up visits are performed remotely). All urine specimens will be collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. Urine drug screen (UDS) testing will be performed using a FDA cleared for use one-step urine drug dip card following the manufacturer's recommended procedures. Single dipsticks will be used for fentanyl testing. Fentanyl dipsticks are not FDA cleared, therefore, results cannot be used for clinical care. Results can only be used to add to the study database to characterize a study population. The UDS will test for the presence of the following drugs: opioids, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, buprenorphine, phencyclidine (PCP), fentanyl and ecstasy (MDMA). In the event urine specimen tampering is suspected, either based on the observation or the adulterant tests, research staff should request a second urine sample and may observe the urine collection process according to clinic standard operating procedures. A further validity check is performed using a commercially available adulterant test strip.

12.9.2 Urine Pregnancy Test

A urine pregnancy test will be conducted at screening to determine eligibility for study procedures. If the test is positive, no further procedures will be conducted, and the participant will be excluded from study procedures. If screening and randomization do not occur on the same day, urine pregnancy test will be repeated before randomization procedure. Additional urine pregnancy tests will be administered prior to the first visit of treatment week 4 and treatment week 8. If positive, women will no longer receive the rTMS intervention. Pregnancy will be followed through resolution. Women will need to agree to use an appropriate form of birth control throughout the treatment phase of the study.

13.0 TRAINING REQUIREMENTS

13.1 Overall

A comprehensive Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training, with the team comprised of the Lead and Co-Lead Nodes, CCC, DSC, as well as other participating nodes and subject matter experts, as applicable. Remote training will be conducted as possible, including training in rTMS and EEG monitoring (where applicable).

The CTN-0108 research staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, study interventions, safety and safety event reporting, study visits and procedures, data management, quality assurance, laboratory procedures, etc. The Lead Node is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The CCC is responsible for the development and delivery of non-intervention training, including regulatory and laboratory procedures, safety and safety event reporting, quality assurance and monitoring, etc. The DSC is responsible for training related to data management (DM), the electronic data capture system, and good clinical DM practices. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

In addition to general and study-specific training, the Training Plan will include a description of the delivery methods to be used for each training module (e.g., via self-study, online, webcast, or teleconference). Research staff are required to complete institutionally required training per their research site, Institutional Review Board(s), and authorities with regulatory oversight. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site Principal Investigator and the Lead Node, and audited by the CCC. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

13.2 rTMS Training and Supervision

All sites must have experience in the delivery of rTMS. Site Operating Procedures (SOPs) for the use of the MagVenture MagPro X100 system and the Provider Manual will be provided to research staff. Training will be provided for study-specific rTMS procedures by the certified rTMS Investigative Team member and reviewed quarterly. Additionally, rTMS Operators, rTMS Advanced Operators, and Site PIs will be trained by MagVenture in the administration of rTMS using their equipment and receive a MagVenture Certification of Completion. At each site, the Medical Clinician will supervise (as defined in the MOP) the rTMS delivery.

14.0 CONCOMITANT THERAPY/INTERVENTION

14.1 General

Individuals are not allowed to engage in any other treatments specifically targeting their substance use disorder, other than the study provided CBT app, because this could interfere with the ability to detect the effect of rTMS. Study participants may engage only in self-help group activities (e.g., Alcoholics Anonymous, Narcotics Anonymous, SMART Recovery) focused on their substance use disorder. However, participants may engage in treatments targeting other psychiatric disorders.

14.2 Medications Prohibited/Allowed During Trial

Anticonvulsants and/or benzodiazepines can raise the seizure threshold and interfere with the efficacy of rTMS. Participants who are prescribed anticonvulsants or benzodiazepines must be on a stable dose for at least 4 weeks prior to consent. Medications will be assessed as part of the standard medical assessments (see Table 5 in Section 12) at screening, each treatment session, end of treatment visit (if applicable), as well as 12- and 16-week follow-up visits.

15.0 STATISTICAL DESIGN AND ANALYSES

15.1 General Design

15.1.1 Study Hypotheses

The primary hypothesis for this trial relates to feasibility:

Primary (Feasibility) Hypothesis: More than 75% of all participants randomized in CTN-0108 will receive 20 or more rTMS sessions.

The secondary hypothesis for this trial relates to efficacy. It is stated separately for MUD and CUD for clarity.

Secondary (Efficacy, CUD) Hypothesis: Individuals who enroll with primary CUD and receive active rTMS will have a significantly higher percentage of weekly negative UDS results over the course of treatment, as compared to those in the sham group.

Secondary (Efficacy, MUD) Hypothesis: Individuals who enroll with primary MUD and receive active rTMS will have a significantly higher percentage of weekly negative UDS results over the course of treatment, as compared to those in the sham group.

15.1.2 Primary and Secondary Outcomes (Endpoints)

The primary (feasibility) outcome measure is the percentage of participants who obtain at least 20 rTMS treatment sessions over the 8-week treatment period. The primary outcome measure does not consider whether a participant was randomized with CUD or MUD.

The secondary (efficacy) outcome measure for each participant is the number and percent of weekly negative UDS results over the treatment period. The last UDS collected in a study week is used for that week. A UDS will be considered as negative for participants with primary CUD if it indicates no cocaine use. A UDS will be considered as negative for participants with primary MUD if it indicates no methamphetamine use.

Exploratory outcomes may include, and are not limited to:

- Other feasibility measures:
  - Percent of participants that complete at least 75% of daily monitoring
  - Percent of participants that complete all follow-up visits
- Self-reported cocaine and methamphetamine use (Timeline Follow-Back)
- Cocaine and/or methamphetamine craving (VAS)
- Depression/anxiety symptoms (Hospital Anxiety and Depression Scale)
- Sleep quality (Actigraphy, Pittsburgh Sleep Quality Index)
- Quality of life (HRQOL-4 quality of life assessment)
- Impact of personal characteristics (age, handedness) on treatment outcomes
- CBT participation
- Motor threshold changes over the treatment course

15.1.3 Recruitment

A total of approximately 160 individuals with moderate to severe cocaine (approximately N=80) and methamphetamine (approximately N=80) use disorder who have an interest in cutting down or stopping their use will be recruited (up to 80 participants per site; no more than 160 participants total). This sample size provides adequately sized 95% confidence intervals for the primary outcome and greater than 80% power to detect medium-sized effect sizes, measured as odds ratios, of greater than 4 with a two-sided hypothesis test and significance level of 0.05 for the secondary (efficacy) outcome for both CUD and MUD.

15.1.4 Randomization and Factors for Stratification

Randomization will be stratified based on study site, MDE, and whether the participant enters on primary CUD or MUD. The sample size within each of CUD and MUD is assumed to be 80. Following determination of full study eligibility via screening, and completion of baseline assessments, participants will be randomly assigned to one of the two conditions (rTMS or sham) for 8 weeks of treatment. Random assignment will be on a 1:1 ratio to one of the two conditions. Randomization will be stratified by study site, MDE, and CUD or MUD primary group designation. The randomization procedure will be conducted centrally through the CTN DSC, and randomization assignments will not be conveyed to research staff (including rTMS Operators) or participants. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignments across treatment groups. The DSC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization slot, once used, will not be re-allocated due to the intent-to-treat nature of the study.

15.2 Rationale For Sample Size and Statistical Power

The rationale for the sample size is broken into two parts: precision analysis for the primary (feasibility) outcome and typical power analysis for the secondary (efficacy) outcome.

15.2.1 Precision Analysis

A simulation study was conducted where a dataset with a sample size of 160 was generated where each participant had a binary feasibility outcome generated from a Bernoulli distribution with $p = 0.75$ because the goal rate for the outcome is 75%. The 95% confidence interval halfwidth was then calculated using the Wilson method. This process was repeated 100,000 times. The average 95% confidence interval halfwidth was calculated across the 100,000 simulated datasets.

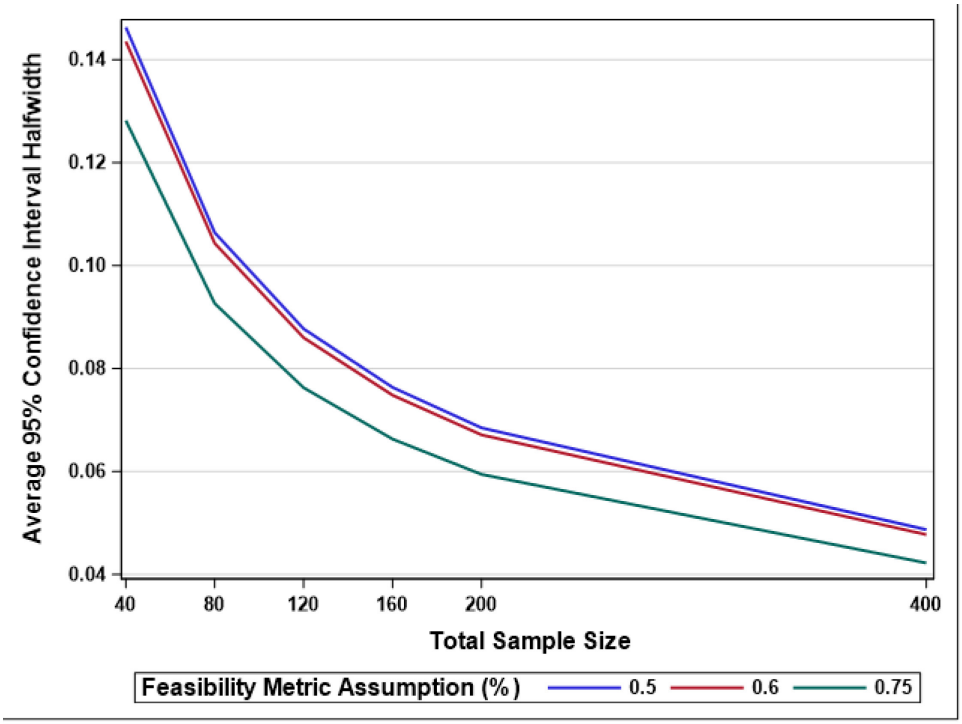
Also considered in the simulation study were different sample sizes and proportion used for generating the binary outcome. Different sample sizes (40, 80, 120, 160, 200, 400) were included to gauge the effect of decreased and increased sample sizes on 95% confidence interval halfwidths as an increase in sample size does not have a constant effect on halfwidth. Different proportions (0.5, 0.6, 0.75) were considered for generating the binary outcome because, generally, as a proportion approaches 0.5 or 50% the variability increases. An increase in variability directly increases confidence interval halfwidth.

Results are presented in the table and graph below. At a sample size of 160 and a proportion of 0.75 (75%), the average 95% confidence interval halfwidth is approximately 0.066. That is, the 95% confidence interval would have about 6.6% on each site. For example, a confidence interval in this setting would look something like $\hat{p} - 0.066$ to $\hat{p} + 0.066$ where $\hat{p}$ is whatever the estimate percentage is. The halfwidth increased up to only 7.6% for the sample size of 160 when a proportion of 0.5 was used. Only relatively marginal decreases in halfwidth occurred up to a sample size of 400. A total sample size of 160 is considered appropriate for this study.

Table 7: Confidence Interval Halfwidth for Primary (Feasibility) Outcome

Feasibility Metric Assumption (%)	Total Sample Size	Average 95% Confidence Interval Halfwidth
50%	40	0.146
	80	0.106
	120	0.088
	160	0.076
	200	0.068
	400	0.049
60%	40	0.144
	80	0.104
	120	0.086
	160	0.075
	200	0.067
	400	0.048
75%	40	0.128
	80	0.093
	120	0.076
	160	0.066
	200	0.059
	400	0.042

Figure 2: Plot of Confidence Interval Halfwidth by Sample Size for Primary (Feasibility) Outcome



15.2.2 Power Analysis

Similarly, power analysis via simulation studies was conducted for the secondary (efficacy) outcome. Since participants enrolled with cocaine use disorder and participants enrolled with methamphetamine use disorder are analyzed separately, a sample size of 80 is used. Participants randomly assigned to receive the sham rTMS had their number of negative UDS generated from a binomial distribution with n = 8 and p = 0.36. The probability of 0.36 for a negative UDS was based on the results found in Terraneo et al. (2016) when comparing rTMS to control on cocaine use. They found, at baseline, an average of about 4.5 use days per week. This would mean then that there's roughly 4.5/7 = 0.64 probability of use on any given day and thus about 0.36 probability of no use on any given day. Although the UDS look-back period may be roughly 3 days, so that to be truly negative a participant would have to be not using for past 3 days, which may mean that true probability of negative UDS may be less than 0.36, a proportion further from 0.5 (holding all else constant) would generally result in higher power. Therefore, the use 0.36 is conservative in this sense. Regardless, different values were considered as well to gauge the sensitivity of the results to this assumption of 0.36. This same base probability, p, in the sham group is used for methamphetamine as well because no results on methamphetamine use when studying rTMS have been found. Participants randomly assigned to real rTMS had their number of negative UDS generated from a binomial distribution with n = 8 as well, but with p varying based on the effect sized used. In the same paper by Terraneo et al. (2016), they found roughly a 6.5 odds ratio (OR) for any use. The power analyses performed here considers a few lower, more conservative, odds ratio levels of 2, 3, 4, and 5. This includes the clinically meaningful odds ratio of 2. In order to match the model to be fit and to allow correlation between UDS from the same participant, a

random effect from a normal distribution was added to the logit of the probability value used to generate the number of negative UDS for each participant, with fixed standard deviation. The standard deviation used was determined based on a small set of possible within-participant correlation, or intraclass correlation (ICC), values. Specifically, ICCs of 0.25 and 0.5 were considered, relating to standard deviations of about 1.05 and 1.81 respectively based on the latent variable method of Goldstein, Browne, and Rasbash 2002.

Once the dataset was simulated, a mixed effect logistic regression model was fit with only binary treatment (1 for real rTMS), binary stratum, week, and site as fixed effects and a random effect to account for correlation between UDS from the same participant. Each weekly UDS enters the model as a binary response. If the model estimation procedure had issues with not being positive definite, the model was refit with the random effect removed. Once the model was fit, it was determined whether the treatment covariate was significant or not at the 0.05 confidence level (i.e., if the p-value was less than 0.05). If the covariate was significant, the treatment effect was considered significant. This process, along with data generation, was repeated 10,000 times. The proportion of times the treatment effect was considered to be significant was the power. A power of at least 80% was desired.

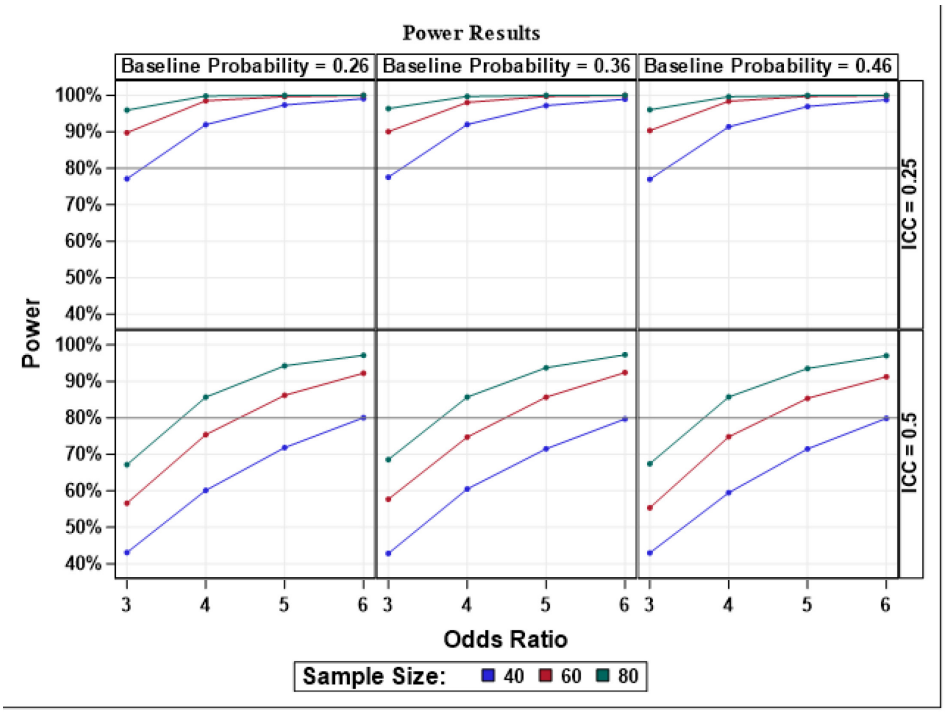
The power to detect a significant treatment effect decreases as treatment effect size and sample size decrease. To this end, the simulation study also considered other sample sizes (40, 60, and 100) and different treatment effect sizes, with the highest odds ratio being 5 and the lowest being 2, a clinically meaningful level. Note that this range of odds ratios is below the estimate found in Terraneo et al. (2016), (of 6.5) for a similar outcome. As previously mentioned, differing proportions in the sham rTMS arm are also considered to gauge the sensitivity of the results to the assumption of 0.36, specifically 0.26 and 0.46 were also considered.

The results are presented in the table and plot below. In both, the treatment effect is classified based on Cohen's h (Cohen 1988) as medium. With the assumption of a 0.36 baseline probability in the sham rTMS group, regardless of the ICC used, a sample size of 80 shows power of 80% or greater for an odds ratio of at least 4. That is, it achieves greater than 80% power at an odds ratio of 4, well below the effect size Terreneo et al found for a similar outcome. A clinically meaningful odds ratio of 2 does not reach 80% power at any considered sample size, including 100, under any scenario. The results do not appear to be overly sensitive to the assumption of a 0.36 baseline probability in the sham rTMS group, as the results for 0.26 and 0.46 are very similar. The results however were dependent on assumed ICC. Because of this, a sample size of 60 requires an odds ratio of at least 5 when the ICC is 0.5. While this study isn't directly powered for efficacy, the results presented here show that a sample size of 80 allows greater than 80% power to detect a significant treatment difference at reasonable, medium-sized, treatment effects (lower than found in a similar study with a similar outcome), is relatively robust to assumptions made in the power analysis, and the use of a sample size of 80 for both MUD and CUD is, therefore, reasonable.

Table 8: Power Analysis Results for Secondary (Efficacy) Outcome

				Power			
ICC	**Baseline Probability**	**Odds Ratio**	**Treatment Effect Size**	**N = 40**	**N = 60**	**N = 80**	**N = 100**
0.25	0.26	2.0	Medium treatment effect	41%	53%	66%	75%
		3.0		77%	90%	96%	99%
		4.0		92%	99%	100%	100%
		5.0		97%	100%	100%	100%
	0.36	2.0	Medium treatment effect	43%	56%	67%	75%
		3.0		78%	90%	96%	99%
		4.0		92%	98%	100%	100%
		5.0		97%	100%	100%	100%
	0.46	2.0	Medium treatment effect	43%	55%	67%	76%
		3.0		77%	90%	96%	99%
		4.0		91%	98%	100%	100%
		5.0		97%	100%	100%	100%
0.5	0.26	2.0	Medium treatment effect	22%	27%	33%	40%
		3.0		43%	57%	67%	77%
		4.0		60%	75%	86%	92%
		5.0		72%	86%	94%	97%
	0.36	2.0	Medium treatment effect	23%	29%	35%	42%
		3.0		43%	58%	69%	77%
		4.0		60%	75%	86%	92%
		5.0		72%	86%	94%	97%
	0.46	2.0	Medium treatment effect	22%	28%	33%	41%
		3.0		43%	55%	67%	76%
		4.0		59%	75%	86%	92%
		5.0		71%	85%	94%	97%

Figure 3: Plot of Power by Sample Size and Treatment Effect for Secondary (Efficacy) Outcome



15.2.3 Projected Number of Sites

Four study sites will participate in the study.

15.2.4 Projected Number of Participants per Site

Each study site will enroll approximately 40 (20 for each of CUD and MUD) participants, with the goal of randomizing approximately 160 (80 for each of CUD and MUD) participants across the 4 study sites.

15.3 Statistical Methods for Primary and Secondary Outcomes

15.3.1 Primary (Feasibility) Outcome

The primary feasibility outcome of the percentage of participants who receive 20 or more rTMS sessions will be summarized by the estimated percentage and a 95% confidence interval by the Wilson method. This method was chosen over others, including an exact or Clopper-Pearson method because the Wilson method has shown to have better performance than exact or Wald methods (Brown et al., 2001.). There is no hypothesis testing. The corresponding shell SAS code is provided below.

```
proc freq data = dat;
     table y / binomial(cl = wilson);
run;
```

y is the binary variable indicating whether the participant received at least 20 rTMS treatment sessions.

15.3.2 Secondary (Efficacy) Outcome

The secondary (efficacy) outcome will be analyzed with a generalized linear mixed model approach to adjust for correlation between UDS from the same participants and to provide conditional interpretation of the treatment effect. The model will include fixed effects for treatment, MDE, week, and site and a random effect for participant. It is important to note that a binary response of negative UDS, for each UDS provided by each participant, will be used as the outcome as opposed to just their percentage of negative UDS. The model used still allows inference on the overall probably of a negative weekly UDS during the treatment period. Additionally, week will enter the model as a categorical variable to allow greater flexibility on the effect of week.

The assessment of the significance of the treatment will be done by testing the significance of the treatment parameter at the 0.05 significance level. The treatment effect will be measured by an odds ratio with an associated 95% confidence interval. The corresponding shell SAS code is provided below.

```
proc glimmix data = dat method = quad;
     class site week participant;
     model y(event = '1') = trt mde week site / dist = binary link
= logit;
     random intercept / subject = participant;
run;
```

dat is a dataset with one row per weekly UDS per participant. y is the a binary variable with a value of 1 indicating the UDS for that participant was negative, trt is a binary variable with a value of 1 indicating real rTMS and 0 indicating sham rTMS, mde is a binary variable with a value of 1 indicating the presence of MDE, week is the study week, and site is a categorical variable containing which of the sites each participant was enrolled in.

In the event that the estimate of the variance component related to the within participant correlation is so close to 0 that it causes the overall covariance matrix to not be positive definite, the model will be refit without the random effect for the correlation within participant. This is accomplished simply by removing the line starting with random in the shell SAS code shown above.

An odds ratio (as the exponential of the trt coefficient), along with 95% confidence interval, will be provided to assess the effect of treatment. An odds ratio of greater than 1 would indicate an increased odds of a negative weekly UDS for active rTMS versus sham rTMS during the treatment period. That is, a positive effect of rTMS versus sham. Similarly, a value of less than 1 indicates a decreased odds of a negative weekly UDS for active rTMS versus sham rTMS during the treatment period. That is, a negative effect of rTMS versus sham. A p-value will also be provided to test the significance of the effect.

The model and results will be conducted and presented separately for those participants randomized with CUD or MUD.

15.4 Significance Testing

The secondary (efficacy) outcome will be evaluated using a two-sided test on the significance of the treatment parameter in the proposed model with a type I error rate of 5%. No attempt will be made to control family-wise type I error rate when testing for CUD and MUD participants. No other hypothesis testing will be performed on the primary or secondary outcomes.

15.5 Types of Analyses

15.5.1 Additional Feasibility Analysis

The primary analysis method used for the primary (feasibility) outcome will be completed over all 160 participants. Additional analysis may include estimating the feasibility outcome percentage separately for both CUD and MUD participants, separately for real and sham rTMS, as well as separately for the four combinations of the two factors. Testing may be performed using fisher's exact test at an 0.05 significance level to determine if there are differences in the percentages across or within the factors, though emphasis is placed on estimation and 95% confidence intervals.

15.5.2 Additional Efficacy Analysis

In preparation to assist in designing future larger trials of efficacy, estimates of the MDE, site and participant effects may be explicitly given. For the participant effect, this will likely be an estimate of the variance in the outcome attributed to the within participant correlation.

Additional supportive analysis of the secondary (efficacy) outcome will be examining if treatment effect varies depending on study week. This can be accomplished by introducing an interaction between week and treatment in the proposed model and examining the significance of the joint or type III test on that interaction. If significant, estimates of treatment effect based on study week can be presented.

15.5.3 Interim Analysis

A DSMB will monitor the progress of the trial. No classical interim analyses relating to futility or sample size re-estimation will be implemented in this pilot study. Safety halting rules are presented in the Study Halting Rules section elsewhere in the protocol.

15.5.4 Exploratory Analysis

Recall the exploratory outcomes may include, and are not limited to

- Other feasibility measures:
  - Percent of participants that complete at least 75% of daily monitoring
  - Percent of participants that complete all follow-up visits
- Self-reported cocaine and methamphetamine use (Timeline Follow-Back)
- Cocaine and/or methamphetamine craving (VAS)
- Depression/anxiety symptoms (Hospital Anxiety and Depression Scale)

- Sleep quality (Actigraphy, Pittsburgh Sleep Quality Index)
- Quality of life (HRQOL-4 quality of life assessment)
- Resting connectome biomarkers measured by EEG
- Differences in outcomes based on number of CBT sessions completed
- Impact of handedness on treatment outcome
- Impact of changes in motor threshold over treatment course on treatment outcome

The other feasibility measures may be analyzed analogously to the primary (feasibility) outcome. The other exploratory outcomes may be summarized and analyzed as appropriate for the type of outcome, such as fisher exact tests and/or logistic regression models for binary outcomes and non-parametric tests of mean/median differences and other types of regression models for ordinal or continuous outcomes.

15.6 Missing Data and Dropouts

As defined, the primary (feasibility) outcome will have no missing data. Participants that drop out early will still be evaluated as to whether they attended at least 20 rTMS sessions.

The secondary (efficacy) outcome is expected to have missing data, specifically UDS results. The proposed analysis model takes into account all available data and missing data are assumed to be missing at random (a weaker assumption than missing completely at random). That is, missingness is allowed to depend on observed covariates. As such, the prespecified analysis method does not need missing data to be imputed or handled in some special way. That being said, alternative methods of handling missing data may be considered as sensitivity analyses. Some specific examples may involve imputing a negative UDS in place of missing if that UDS is immediately surrounded by negative UDS, imputing missing UDS results based on self-reported use, or imputing all missing UDS as positive. More technical methods incorporating a missing not at random assumption may also be considered.

15.7 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants enrolled in the active medication phase of the trial. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of ‘frequencies and percentages.

15.7.1 Subgroup Analyses

Per NIH policy, subgroup analyses will be implemented to assess whether sex, race, and/or ethnicity are feasibility or effect modifiers. The primary outcome percentage will be estimated in each demographic subgroup. The secondary (efficacy) outcome results will be presented and tested (as applicable) within each demographic subgroup by including interactions with treatment assignment in the model.

15.8 Safety Analysis

AEs, SAEs and UADEs, will be summarized by body system and preferred term using MedDRA codes (per The Medical Dictionary for Regulatory Activities). AEs will be presented as: (1) the number and proportion of participants experiencing at least one incidence of each event overall; and (2) the total number of each event overall in tabular form. Listings of SAEs /UADEs will be sorted by system organ class (SOC), and preferred term (PT). Detail in these listings will include severity, relationship to study medication(s), and action taken, as available.

16.0 REGULATORY COMPLIANCE AND SAFETY

16.1 Investigational Device Exemption Applicability

This study represents an investigation of a device other than a significant risk device, and as such will be considered an approved IDE application subject to the abbreviated IDE regulations as stated in 21 CFR 812.2(b). The Sponsor will obtain and maintain IRB approval accordingly, and will be subject to all applicable reporting requirements.

16.2 Statement of Compliance

This trial will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation Good Clinical Practice (GCP) Guidelines, applicable United States (US) Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

16.3 Institutional Review Board Approval

This study will utilize a single IRB (sIRB). Prior to initiating the study, site investigators will obtain permission to rely on the MUSC IRB from their local IRBs. Local IRBs will enter into a reliance agreement with MUSC. Each participating site must have sIRB approval prior to conducting the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the lead investigators for sIRB approval prior to implementation. In addition, the sIRB will approve all consent forms, and recruitment materials, and any study-specific materials given to the participant. Annual progress reports will be submitted to the sIRB annually or at a frequency requested so that continuous study approval is maintained without lapse. The lead investigator is responsible for maintaining in his research files copies of all performance site(s) current IRB/IEC approval notice(s), IRB-approved consent document(s), including approval for all protocol modifications. The lead site will submit regulatory documents to the sIRB on behalf of the participating sites. Participating sites will receive electronic notifications of approval or changes required directly from the sIRB. The lead team will also have access to all of these documents.

Prior to initiating the study, participating site investigators will obtain written approval from the single Institutional Review Board (sIRB) of record to conduct the study at their respective site, which will include approval of the study protocol. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for

maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site, and must be available at any time for audit. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the sIRB of record, according to its usual procedures.

MUSC Institutional Review Board will be the single IRB of record for the protocol, and will provide study oversight in accordance with 45 CFR 46 and applicable FDA regulations. Participating institutions have agreed to rely on MUSC Institutional Review Board, and will enter into reliance/authorization agreements for Protocol CTN-0108. MUSC Institutional Review Board will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Some sites may meet Exception Criteria to the NIH sIRB Policy and may not utilize the IRB of Record.

16.4 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation. The informed consent form(s) will include all of the required elements of informed consent, and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study site must have the study informed consent(s) approved by the sIRB. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the Clinical Coordinating Center (CCC) to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(b), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c) and any applicable CCTN requirements. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with the sIRB and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

During the informed consent process, research staff will explain the study to the potential participant and provide the potential participant with a copy of the consent form to read and keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a qualified staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant will consent by signing and dating the consent document. The person obtaining consent will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is

properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and Human Subjects Protection training, as mandated by NIDA standard operating procedures.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary, and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

16.5 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study sponsor and study IRB of record, (as applicable), for further review.

16.6 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency and the participant. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure

computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 16.12, Records Retention and Requirements.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

16.6.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive information (e.g., drug use). It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

16.6.2 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with the IRB(s) or Privacy Board(s) of record and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

16.7 Investigator Assurances

Each site must have on file an active Federalwide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page and investigator agreement, providing assurances that the study will be performed according to the standards stipulated therein.

16.7.1 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

16.8 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately, and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the Lead Investigator and NIDA CCTN.

Qualified node personnel (Node QA monitors) will provide site management for each site during the trial. Node QA staff will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

16.9 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and/or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

16.10 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment

procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. This study will not enroll or interact with prisoners and as such the study will not obtain a prisoner certification.

If a participant in the study becomes incarcerated or otherwise meets the 45 CFR 46 Part C definition of a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under Subpart C of 45 CFR 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the participant must be suspended immediately. The lone exception to this regulation is if the investigator asserts that it is in the best interests of the prisoner-participant to remain in the study. The investigator must promptly notify the IRB of this occurrence.

16.11 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

16.12 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The Sponsor and Lead Investigator must be notified in writing and acknowledgment from these parties must be received by the site prior to the destruction or relocation of research records.

16.13 Reporting to Sponsor

The site Principal Investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. AE, SAE, and UADE reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

16.14 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the Southern Consortium Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional

Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

16.15 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

16.16 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the research site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

1. Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
2. Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
3. Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the IRB of record as needed. All protocol deviations will be monitored at each site for

(1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing the sIRB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and sIRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

16.17 Safety Monitoring

Each participating site will have a site Medical Clinician (MD, DO, NP, or PA) for this study, who will review or provide consultation for each Adverse Event (AE), Serious Adverse Event (SAE) and Unanticipated Adverse Device Effects (UADE) as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Site Medical Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Safety Monitor/Medical Monitor to this protocol to independently review the safety data from this study and present it to the DSMB for periodic review. The Safety Monitor/Medical Monitor will determine which safety events require expedited reporting to NIDA, the DSMB and/or regulatory authorities (i.e., reported to the IRB for an abbreviated IDE as regulated under 21 CFR 812). This will include all UADEs, which is defined as any serious adverse effect, any life-threatening problem or death caused by, or associated with a device, if that was not previously identified in the application; or any other unanticipated serious problem associated with a device. The site research staff will be trained to monitor AEs, SAEs and UADEs. The site Medical Clinician and the Safety Monitor/Medical Monitor will collaborate to evaluate the effect and to determine its reportability. All SAEs are reported into Advantage eClinical^{SM} within 24 hours of awareness. If an UADE is identified, the site Medical Clinician/Principal Investigator must notify the IRB of record as soon as possible, but in no event later than 10 working days after the Medical Clinician/Principal Investigator first learns of the event. The Safety/Medical Monitor will prepare a UADE safety report summarizing the event and this will be distributed to all site Principal Investigators.

Each of the sites has established practices for managing medical and psychiatric emergencies, and the research staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

16.17.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed,

or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

16.17.2 Safety Monitor/Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for reviewing all AEs, SAEs and UADEs reported. All SAEs and UADEs will be reviewed within one business day of being reported in the EDC. The Safety/Medical Monitor will also indicate concurrence or not with the details of the report provided by the site. Where further information is needed the Safety Monitor/Medical Monitor will discuss the event with the site. Reviews of SAEs and UADEs will be conducted in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn summarize each SAE/UADE and report the narrative to the sponsor within pre-defined timelines, and if an event meets the criteria for expedited reporting, this will be provided to the site investigator to report to the IRB. Written SAE and UADE reports will be presented at Data Safety Monitoring Board (DSMB) meetings and to the DSMB at any time per request.

16.17.3 Adverse Events (AEs)

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Appendix A.

Events captured on study specific forms are not recorded separately as an AE, unless they meet the SAE definition. Any of these events that meet the definition of an SAE are reported on the AE/SAE form set. Any spontaneous reporting of withdrawal symptoms by the participant are captured on AE form in the following situations: withdrawal symptoms reported at visits without scheduled specific structured questionnaires; and withdrawal symptoms not listed in the specific structured questionnaires reported at any visit.

16.17.4 Serious Adverse Events (SAEs)

All safety events will be evaluated to determine if they meet the criteria for an SAE/UADE. For the purposes of this study, admission for labor and delivery will be reported on a study specific form and will not be reported as an SAE.

17.0 DATA MANAGEMENT

17.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, a web-based distributed data entry system, along with ePRO for mobile surveys, will be implemented. Systems will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

17.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the Advantage eClinical User's Guide.

17.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

17.4 Data Collection

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the timely completion of the eCRFs for each research participant. In some situations, data collected on source documents will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above. Data from the actigraph devices will be uploaded from each device and sent to the DSC; information about CBT module usage will be sent directly from the vendor to the DSC. Finally, where applicable, EEG data will be sent via secure file transfer from each site to University of Texas Southwest for analysis. EEG data will be sent to the DSC via secure file transfer to be archived and preserved for Data Share.

Mobile survey data will be completed by participants on mobile devices or computers and therefore paper backups will not be employed.

17.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the Advantage eClinical system in accordance with the Advantage eClinical User's Guide. Only authorized individuals shall have access to eCRFs.

17.6 Data Editing

Completed data will be entered into Advantage eClinical. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical. Mobile survey data will be monitored for completeness and data quality to the extent possible as these self-reported assessments will be completed remotely by participants. As noted above, if participants complete more than one mobile survey within a 24 hour period, only the first entered for the day will be retained for analysis.

17.7 Data Transfer/Lock

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

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

17.8 Data Training

The training plan for research staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

17.9 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

18.0 DATA SHARING, PUBLIC ACCESS AND PUBLICATIONS

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm).

Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome(s) publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

19.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 6.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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21.0 APPENDIX A: ADVERSE EVENT REPORTING AND PROCEDURES

Each participating site's Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Adverse Events, Serious Adverse Events and Unanticipated Adverse Device Effects

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study device related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the site Medical Clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study device caused the adverse event. A reasonable possibility implies that there is evidence that the study device caused the event.

Adverse reaction is any adverse event caused by the study device.

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

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the site Medical Clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the research staff during the protocol-defined follow-up period, whether or not considered caused by the study device, must be reported.

2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the Medical Clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.

3) Requires inpatient hospitalization or prolongation of existing hospitalization.

4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5) Is a congenital abnormality or birth defect.

6) Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered “unexpected” if it is not listed in the investigator brochure, package insert or product safety summary or is not listed at the specificity or severity that has been observed. If neither is available, then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy

Any pregnancies that occur while a participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant during the active treatment period will be discontinued from further rTMS procedures, referred for medical care, and the pregnancy followed until an outcome is known.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site’s Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained personnel will elicit participant reporting of AEs, SAEs and UADEs at each study visit designated to collect AEs. Participants will be asked specifically about common adverse events associated with device use including headaches, device application site pain and hearing changes. Adverse event (medical and/or psychiatric) assessment will initiate with participant consent and follow-up of ongoing adverse events will continue through resolution or 30 days post last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult with the Safety Monitor/Medical Monitor as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Sites are responsible for reporting SAEs to the IRB of record, per the IRB of record’s guidelines. For device studies, the Site Principal Investigators are required to submit a safety report of a UADE to the IRB of record as soon as possible, but in no event later than 10 working days after the Site Principal Investigator first learns of the event (§ 812.150(a)(1)).

Sites are required to enter reportable AEs and all SAE/UADEs in the Advantage eClinical[SM] system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate SAEs and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Sites should make every effort to follow each SAE/UADE until a known outcome is determined, even beyond the end of the study as necessary. An unknown outcome of an SAE is strongly discouraged.

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study Medical Clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event:

Grade 1	Mild	Transient or mild discomfort (typically < 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible, but unlikely
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible

Guidelines for Determining Causality

The site Medical Clinician will use the following question when assessing causality of an adverse event to study device where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study device caused the event?

Site's Role in Monitoring Adverse Events

Local quality assurance monitors will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Sponsor's Role in Safety Management Procedures of AEs/SAEs/UADEs

A NIDA-assigned Safety Monitor/Medical Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Safety Monitor/Medical Monitor in Advantage eClinical^{SM} and, if needed, additional information will be requested. The Safety Monitor/Medical Monitor will also report events to the sponsor and the DSMB. The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the CCC Safety Monitor/Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the Safety Monitor/Medical Monitor in writing for review by the sponsor and DSMB. Subsequent review by the Safety Monitor/Medical Monitor DSMB and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable. The device or study sponsor will be responsible for providing initial device safety information and updated safety information during the study for site investigators and all reviewing IRBs.

Regulatory Reporting for an abbreviated IDE study

It is anticipated that this study will fall under an abbreviated IDE in which the IRB of record (MUSC as the sIRB) will assume responsibility for oversight. If an SAE meets the expedited reporting criteria (serious, unexpected and possibly related to the intervention, e.g., UADE), the Safety Monitor/Medical Monitor on behalf of the sponsor will prepare an expedited report (MedWatch Form 3500 or similar) for the IRB as soon as possible and no later than 10 calendar days.

Reporting to the Data and Safety Monitoring Board

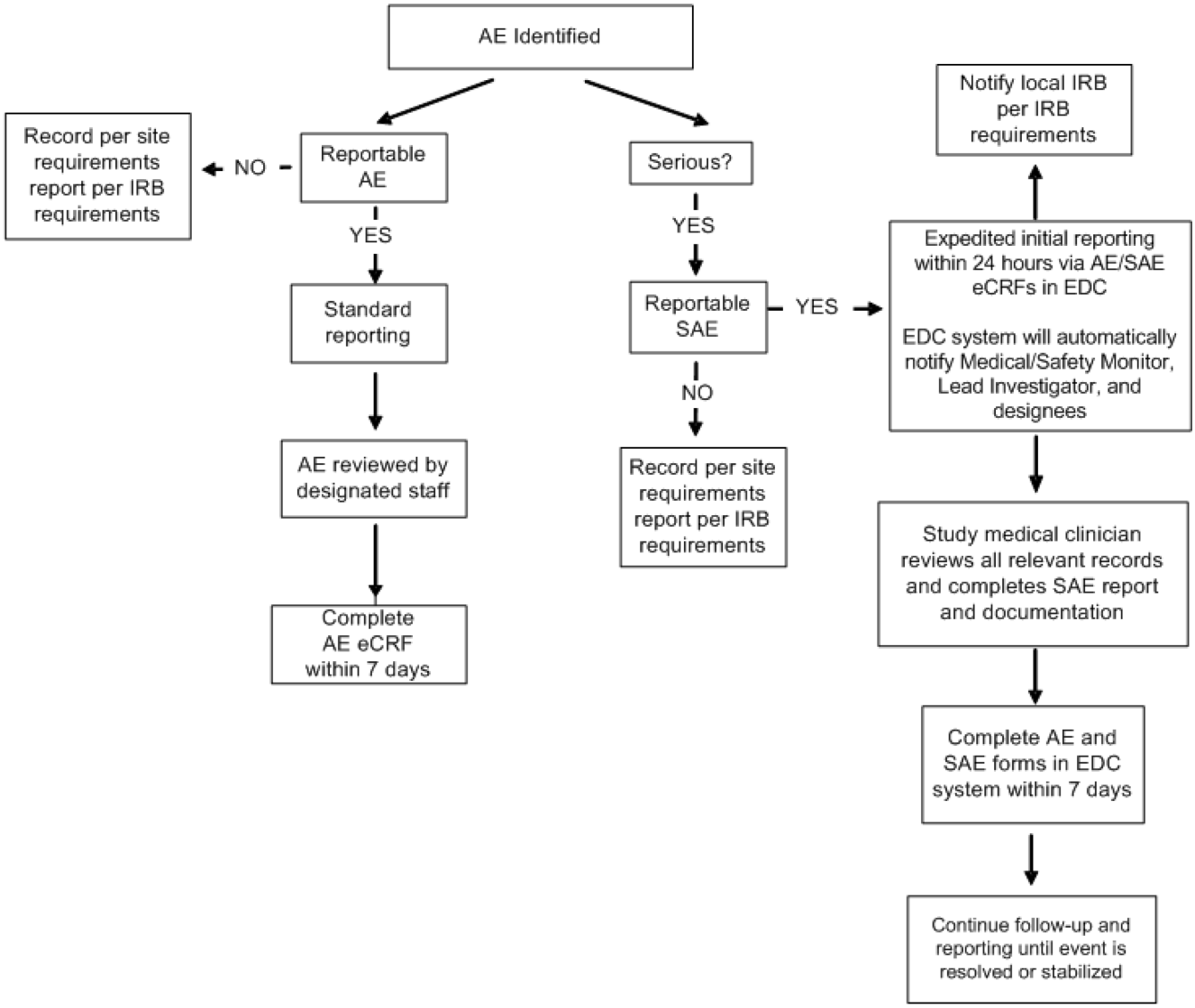
The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs or if halting rules are met.

Participant Withdrawal

The site Medical Clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study intervention. The site Medical Clinician should consult with the site Principal Investigator, the Lead Investigator and/or Safety Monitor/Medical Monitor as needed. If necessary, a site Medical Clinician may suspend any trial treatments and institute the necessary medical therapy

to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end of rTMS/sham visit to assure safety and to document outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

21.1 Adverse Event Reporting (Chart)



22.0 APPENDIX B: DATA AND SAFETY MONITORING PLAN (DSMP)

1.0 Brief Study Overview

Approximately 160 adults will be enrolled in this 8-week, double-blind, sham-controlled trial of rTMS in the treatment of adults with moderate to severe CUD or MUD. Participants will receive up to 30 rTMS/sham sessions over the 8-week period in addition to a self-paced electronic CBT intervention. In addition to substance abuse outcomes, this study will assess sleep via a wearable actigraph, and will have an optional EEG assessment that will occur at randomization and end of treatment. Participants will have follow-up visits at weeks 12 and 16 post randomization. The objectives of this study are to determine the feasibility and gather preliminary data on the efficacy of rTMS for individuals with CUD or MUD.

2.0 Oversight of Clinical Responsibilities

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and Medical Clinicians to assess, report, and monitor adverse events.

All adverse events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol.

The occurrence of AEs, serious adverse events (SAEs) and UADEs will be assessed at each clinic visit during the study. SAEs will be followed until considered resolved or stable.

Reportable AEs are required to be entered into the data system within 7 days of the research staff becoming aware of the event. Reportable SAEs/UADEs (including death and life-threatening events) are required to be entered into the data system within 24 hours of site's knowledge of the event).

B. CCC Safety Monitor/Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Safety Monitor/Medical Monitor or designee is responsible for reviewing all AEs, SAEs and UADEs reported. The CCC Safety Monitor/Medical Monitor is alerted via email each time an SAE/UADE is reported in the EDC. All SAEs will be reviewed at the time they are reported in the EDC. The Safety Monitor/Medical Monitor or designee will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety Monitor/Medical Monitor or designee will discuss the event with the research staff. Reviews of SAEs by the CCC Safety Monitor/Medical Monitor or designee will be documented in the Advantage eClinicalSM data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

Regulatory Reporting for an abbreviated IDE study

It is anticipated that this study will fall under an abbreviated IDE in which the IRB of record (MUSC as the sIRB) will assume responsibility for oversight. If an SAE meets the expedited reporting criteria (serious, unexpected and possibly related to the intervention, e.g., UADE), the Safety Monitor/Medical Monitor on behalf of the sponsor will prepare an expedited report (MedWatch Form 3500 or similar) for the IRB as soon as possible and no later than 10 calendar days.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and narratives of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to the sIRB and disseminated to participating sites.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors and local Node QA monitors. Investigators will host periodic visits for the monitors and local Node QA monitors. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., pharmacy, research office), source data/documentation, and reports for the purpose of monitoring and auditing by the monitors, as well as for inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and site Principal Investigator supervision and involvement in the trial. The monitors will interact with the research staff to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

Local Node site visit reports are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the Clinical Study Manager for the study.

E. Management of Risks to Participants Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on site will be kept locked separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

The site's study clinician will evaluate all pertinent screening and randomization assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. AEs and concomitant medications will be assessed and documented at each study visit. Individuals who experience an AE that compromises safe participation in a study will be discontinued from further rTMS intervention and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of- intervention visit to assure safety and to document end-of-intervention outcomes.

Pregnancy

A positive pregnancy test post-randomization will result in the cessation of rTMS/sham treatment. The research staff will follow the participant until an outcome of the pregnancy is known and reported.

Study Specific Risks

rTMS is a well-tolerated, non-invasive intervention. Although there is a theoretical risk of seizure, seizures have not been reported using current rTMS safety procedures. The most common side effects are headache and mild scalp discomfort where the magnetism is applied. Other possible side effects include temporary hearing loss (which will be mitigated by wearing ear plugs), and changes in mood. Participants will be asked not to participate in any other formal treatment for CUD or MUD, besides self-help groups, while they are in this study. As such, there may be some risk of drug use that might have been avoided if the individual were engaged in a formal SUD treatment program. However, all participants will receive access to and are encouraged to participate in a CBT for SUDs which will be provided to all study participants.

3.0 Data Management Procedures

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. Advantage eClinical^{SM} will be utilized as the electronic data

capture system for the collection of most of the data. It will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. Data collection for mobile surveys may use a separate system and/or may not maintain 21CFR11 compliance due to the lack of an audit trail; while not ideal, data is unlikely to be collected in its entirety, if at all, without relaxing this restriction.

4.0 Data And Statistics Center Responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data collected in Advantage eClinical and mobile survey system (developed in ePRO) required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical[SM] and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, and 6) perform data cleaning activities prior to the final study database lock.

5.0 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical[SM] or will be collected via direct entry into the eCRF. If Advantage eClinical[SM] is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data will be entered into Advantage eClinical[SM] in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. Selected eCRFs may also require the Investigator's signature (wet or electronic). In some situations, data collected on source documents will not be entered into Advantage eClinical[SM], but when it is entered, it will follow the guidelines stated above. Data collected in the mobile survey system will be monitored for data quality to the extent possible as this data will be directly entered by participants into the web-based survey system remotely.

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Principal Investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

6.0 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and missing forms are available to sites at all times in Advantage eClinical[SM] for all data entered in eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical[SM] on a scheduled basis. Sites will resolve data queries by entering all corrections and changes directly into Advantage eClinical[SM] or verifying the data are correct as is.

As described above, the CCC will conduct regular monitoring visits, during which, audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information items such as on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site staff, the local node QA staff, the Lead Investigator, the coordinating centers, and NIDA CCTN, to monitor each sites' progress on the study.

7.0 Data Lock And Transfer

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individual participants and their research data will be identified by a unique study identification number; further, some identifiable data may be collected in eClinical. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final raw datasets will be transferred to the Lead Investigator or designee. De-identified versions of these datasets also will be provided to the NIDA CCTN-designated party for storage and archiving. These datasets will also be posted on the NIDA Data Share website.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html