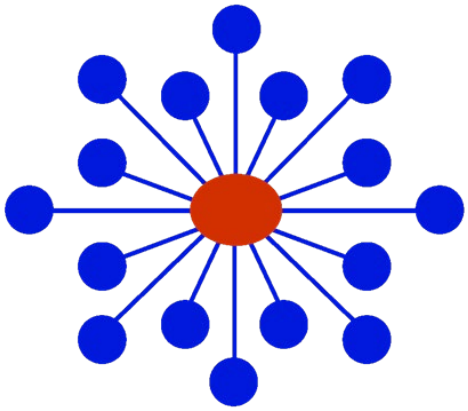
rTMS for Stimulant Use Disorders
NCT04907357
Statistical Analysis Plan
January 17, 2025



Statistical Analysis Plan for NIDA Protocol CTN-0108

rTMS for Stimulant Use Disorders (STIMULUS)

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Device Reaction
BMP	Blinding Management Plan
CBT	Cognitive Behavioral Therapy
CCC	Clinical Coordinating Center
CCTN	Center for Clinical Trials Network
CHRT-CR	Concise Health Risk Tracking – Clinician Rated
CHRT-SR	Concise Health Risk Tracking – Self Report Suicide Behavior Evaluation
CUD	Cocaine Use Disorder
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
EEG	Electroencephalogram
eCRF	Electronic Case Report Form
FSR	Final Study Report
HADS	Hospital Anxiety and Depression Scale
HRQOL-4	Health Related Quality of Life
ITT	Intent-to-Treat
LN	Lead Node
LT	Lead Team
MAR	Missing at Random
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MINI	Mini International Neuropsychiatric Interview
MNAR	Missing Not at Random
MUD	Methamphetamine Use Disorder
NIDA	National Institute on Drug Abuse
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOC	System Organ Class
TLFB	Timeline Followback
UADE	Unanticipated Adverse Device Effects
UDS	Urine Drug Screen
VAS	Visual Analogue Craving Scale

LIST OF eCRFs

A08	Additional Demographics
ACT	Actigraph Device Discontinuation
AD1	Adverse Event
AD2	Serious Adverse Event Summary
AD3	Serious Adverse Event Medical Reviewer
ASU	Alcohol and Substance Use
CCA	Cue Craving Assessment
CHC	Concise Heath Risk Tracking (CHRT) – Clinician Rated Module
CHP	Concise Health Risk Tracking (CHRT-SR) – Participant
CIA	Caffeine Intake Assessment
D08	Demographics
DCA	Daily Caffeine Assessment
DSM	DSM-5 Checklist
EEG	EEG Completion
ERNB	Enrollment 0108B
ENRC	Enrollment 0108C
ENRZ	Enrollment 0108Z
EOT	End of Treatment
FND	Fagerström Test for Nicotine Dependence
HAD	Hospital Anxiety and Depression Scale
HIV	Self-Report of HIV Testing
INV	Inventory – Medication and Supplies
MCQ	Mobile Cocaine Questionnaire
MHA	Mental Health Follow-Up Assessment
MHX	Medical and Psychiatric History
MIN	MINI 7
MJA	Cannabis Use Assessment
MMQ	Mobile Methamphetamine Questionnaire
P08	Pre-Screen Summary
PB2	Penetration of Blind Assessment – Participant Response
PBA	Penetration of Blind Assessment – Staff Response
PBC	Pregnancy and Birth Control Assessment

PCM	Prior and Concomitant Medications
PDR	Protocol Deviation Review
PDV	Protocol Deviation
PEX	Physical Examination
PO1	Pregnancy Outcome 1
PO2	Pregnancy Outcome 2
PO3	Pregnancy Outcome 3
PO4	Pregnancy Outcome 4
PRG	Confirmed Pregnancy and Outcome
PS1	Protocol Satisfaction Survey
PSQ	Pittsburgh Sleep Quality Index
QLP	Quality of Life
STC	Study Completion
T08	Timeline Followback
TAP	TLFB Assessment Period
TMS	rTMS Intervention
TUH	Tobacco Use History
TXS	Treatment Status
UDS	Urine Drug Screen
V08	Visit Documentation
VIT	Vital Signs

1.0 INTRODUCTION

The Statistical Analysis Plan (SAP) for Protocol CTN-0108 STIMULUS expands upon the statistical information presented in the protocol and describes all planned analyses for the primary, secondary, and safety outcome measures including interim analyses, sample size re-estimation, and final analyses occurring after data lock. The Clinical Trial Network (CTN)'s Data and Statistics Center (DSC) will conduct the analyses for the Final Study Report (FSR) as listed in Table 1 below and the Lead Node (LN) will conduct the analyses as noted.

Table 1: Analysis Responsibilities

Content	Section Number	Responsible for Analysis
Participant Enrollment, Disposition, and Follow-up	4.0	DSC
Participant Baseline Characteristics	5.0	DSC
Study Treatment Adherence	6.0	DSC
Analyses of Primary Outcome Measure	7.2	DSC
Supportive Analyses of Primary Outcome	7.3	DSC
Analyses of Secondary Outcome Measures	7.5	DSC
Supportive Analyses of Secondary Outcome	7.6	DSC
Analyses of Exploratory Outcome Measures	7.8	LN
Safety Outcomes	8.0	DSC
Sample Size Re-Estimation	11.1	DSC
Data Quality	12.0	DSC

2.0 SUMMARY OF STUDY DESIGN AND PROCEDURES

2.1 Study Objectives

The primary objective of this study is to determine the feasibility of up to 30 sessions of repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) versus up to 30 sessions of sham rTMS for treatment of individuals with cocaine use disorder (CUD) or methamphetamine use disorder (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. The primary hypothesis is that at least 75% of participants will receive 20 or more rTMS sessions.

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 of urine drug screens (UDS) negative for the primary substance, out of the last UDS per treatment week. This will be used to examine the effect size of rTMS versus sham to inform future clinical trials. The secondary hypothesis states that individuals who receive active rTMS will have a significantly higher percentage of UDS negative results for methamphetamine (if participants are designated in the primary substance of use MUD group) or cocaine (if participants are designated in the primary

substance of use CUD group) over the course of treatment, as compared to those in the sham group.

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 electroencephalogram (EEG), retention in treatment, and changes in health, lifestyle, and function.

2.2 Study Design and Procedures

2.2.1 Study Design

The study is a randomized, double-blind pilot trial comparing rTMS with sham treatment in reducing stimulant use among individuals with CUD or MUD. Eligible and interested participants will be randomized on a 1:1 ratio to one of two groups; groups will receive up to 30 sessions of active rTMS or sham over the course of an 8-week treatment period.

Four study sites will participate in the study. Each study site will aim to enroll approximately 40 (20 for each of CUD and MUD) participants, with the goal of randomizing 160 (80 for each of CUD and MUD) participants total.

2.2.2 Study Assessments

All assessments and corresponding electronic case report forms (eCRF) are described by study period below. A complete schedule of assessments can be found in the protocol.

2.2.2.1 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 on the Pre-Screen Summary (P08) form will determine preliminary eligibility, and formal screening appointments will be scheduled for those who meet these eligibility criteria.

2.2.2.2 Screening and Randomization

After providing written informed consent to participate in the study, participants will be enrolled in Segment B (ENRB) and start the screening assessment phase. Ideally, the screening assessment procedures will be completed in two visits, but they can be completed across more visits if necessary. The screening assessment procedures must be completed within two weeks prior to randomization.

Along with the informed consent and enrollment forms, the screening assessments include the following:

- General Assessments: Demographics (D08), Additional Demographics (A08), Treatment Status (TXS), Quality of Life (QLP), Self-Report of HIV Testing (PhenX Tier 1; HIV), Tobacco Use History (PhenX Tier 1; TUH), and Alcohol and Substance Use (PhenX Tier 1; ASU)
- Medical Assessments: Physical Examination (PEX), Medical and Psychiatric History (MHX), Vital Signs (VIT), Adverse Event (AD1), Serious Adverse Event Summary (AD2), Serious Adverse Event Medical Reviewer (AD3), and Prior and Concomitant Medications (PCM)
- Psychological Assessments: Mini International Neuropsychiatric Interview (MINI; MIN), Hospital Anxiety and Depression Scale (HADS; HAD), Pittsburgh Sleep Quality Index (PSQI; PSQ), Concise Health Risk Tracking – Self Report Suicide Behavior Evaluation

(CHRT-SR; CHP), Concise Health Risk Tracking – Clinician Rated Module (CHRT-CR; CHC), and Mental Health Follow-up Assessment (MHA)

- Substance Use Assessments: Timeline Followback (TLFB; TAP, T08,), Caffeine Intake Assessment (CIA), Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Substance Use Disorder Criteria (DSM-5; DSM), Cannabis Use Assessment (MJA), and Fagerström Test for Nicotine Dependence (FND)
- Lab Testing and Samples: Urine Drug Screen (UDS), urine pregnancy test and Pregnancy and Birth Control Assessment (PBC), Pregnancy Outcome (PO1-4), and Confirmed Pregnancy and Outcome (PRG)
- Administrative: locator form, contact form for mobile surveys, Inventory – Medication and Supplies (INV), Protocol Deviation (PDV), Protocol Deviation Review (PDR), and Protocol Satisfaction Survey (PS1)

Following determination of full study eligibility via screening and completion of baseline assessments, participants will be enrolled into Segment C (ENRC) and randomized. Additional baseline assessments that may be completed after randomization include:

- Cue Craving Assessment (CCA, first question only)
- EEG Completion (EEG)
- Hospital Anxiety and Depression Scale (HAD)
- Daily Mobile Questionnaire (MCQ, MMQ)

If potential participants are deemed ineligible, they will be enrolled into Segment Z as a screen failure (ENRZ).

2.2.2.3 Treatment Period

During the 8-week treatment period, participants may attend up to 30 study visits. Once 30 rTMS or sham sessions have been completed or the visit window for Week 8 has closed, end of treatment (EOT) assessments will be completed.

The following assessments are administered during the treatment period:

- General Assessments: rTMS Treatment Log, rTMS Intervention (TMS), Quality of Life (QLP), EEG completion (EEG; if applicable), and Daily Mobile Questionnaire (MCQ, MMQ)
- Medical Assessments: Vital Signs (VIT), Adverse Event (AD1), Serious Adverse Event Summary (AD2), Serious Adverse Event Medical Reviewer (AD3), Prior and Concomitant Medications (PCM)
- Psychological Assessments: HADS (HAD), PSQI (PSQ), CHRT-SR (CHP), CHRT-CR (CHC), and Mental Health Follow-up Assessment (MHA)
- Substance Use Assessments: TLFB (TAP, T08), Daily Caffeine Assessment (DCA), Fagerström Test for Nicotine Dependence (FND), and Cue Craving Assessment (CCA)
- Lab Testing and Samples: UDS (UDS), urine pregnancy test and Pregnancy and Birth Control Assessment (PBC), Pregnancy Outcome (PO1-4), and Confirmed Pregnancy and Outcome (PRG)
- Administrative: Visit Documentation (V08), locator form and contact form for mobile surveys updates, Penetration of Blind Assessment (PBA, PB2), End of Treatment (EOT), Inventory – Medication and Supplies (INV), Protocol Deviation (PDV), Protocol Deviation Review (PDR), and Actigraph Device Discontinuation (ACT)

2.2.2.4 Follow-up Period

The research team will conduct follow-up assessments through the Week 12 and 16 post-randomization follow-up visits including the following:

- General Assessments: Quality of Life (QLP) and Daily Mobile Questionnaire (MCQ, MMQ)
- Medical Assessments: Vital Signs (VIT), Adverse Event (AD1), Serious Adverse Event Summary (AD2), Serious Adverse Event Medical Reviewer (AD3), and Prior and Concomitant Medications (PCM)
- Psychological Assessments: HADS (HAD), PSQI (PSQ), CHRT-SR (CHP), CHRT-CR (CHC), and Mental Health Follow-up Assessment (MHA)
- Substance Use Assessments: TLFB (TAP, T08) and Fagerström Test for Nicotine Dependence (FND)
- Lab Testing and Samples: UDS (UDS), Pregnancy Outcome (PO1-4), and Confirmed Pregnancy and Outcome (PRG)
- Administrative: Visit Documentation (V08), Penetration of Blind Assessment (PBA, PB2), Inventory – Medication and Supplies (INV), Protocol Deviation (PDV), Protocol Deviation Review (PDR), and Study Completion (STC)

2.2.2.5 External Data Sources

Additional data collected during the following study procedures is stored in external databases:

- Actigraphy: After randomization, participants will be issued an ActiGraph to assess daily sleep quality during the treatment period (Weeks 1-8). Research staff will download data from the device once a week and the participant will return the device at the end of treatment visit, as documented on the ActiGraph Device Discontinuation (ACT) form.
- Cognitive Behavioral Educational Intervention through DynamiCare Health: Participants may participate in cognitive behavioral therapy delivered via a mobile application platform over 20 self-guided modules throughout the treatment period.
- EEG: If available at the study site, EEG will be obtained after randomization and at the Week 4 visit, if obtained at randomization.

2.2.3 Study Treatments

The study intervention will last 8 weeks and consists of up to 30 study visits including sessions of either rTMS (active) or sham (control) sessions. The first treatment visit may occur on the day of randomization. There is flexibility in scheduling treatment visits; a maximum of 30 sessions can occur over the 8-week treatment period with a maximum of 5 sessions per calendar week (Monday – Sunday), a maximum of 9 treatments in a 7-day period across 2 calendar weeks, and 2 sessions per day (separated by at least one hour). The final treatment visit must occur during Week 8, meaning the 28th visit can occur at the end of Week 6 at the earliest.

2.2.4 Randomization

Following determination of full study eligibility via screening, participants will be randomly assigned to one of the two conditions (active 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 based on study site, presence/absence of current major depressive episode (MDE), and whether the participant enters on primary substance of use CUD or MUD. The sample size within each of CUD and MUD is assumed to be 80. The randomization procedure will be conducted centrally through the DSC, and randomization assignments will not be conveyed to research staff (including rTMS Operators) or participants. The unblinded 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 unblinded 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 (ITT) nature of the study. Further details can be found in the Randomization Plan.

2.2.5 Blinding

This study is double-blinded, with participants, the LN, investigators, site staff, and all DSC and CCC staff other than the select unblinded staff being blinded to the study treatment assignments. 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 remain blind to participants' condition assignments. Further details as well as the blinded and unblinded DSC/CCC and site staff roles are described in the CTN-0108 Blinding Management Plan (BMP).

2.3 Eligibility Criteria for Selection of Study Population

2.3.1 Inclusion Criteria

Individuals must meet all of the inclusion criteria in order to be eligible to participate in the study.

1. Be aged 18-65, inclusive.
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).
3. Have used cocaine or methamphetamine on at least 10 of the last 30 days (based on TLFB).
4. Be interested in decreasing cocaine and/or methamphetamine use.
5. If female, willing to use appropriate birth control method during the treatment phase of the study.
6. Be able to understand the study procedures and provide written informed consent to participate in the study.
7. If prescribed benzodiazepines or anticonvulsants, must be on a stable dose for at least 4 weeks prior to consent.

2.3.2 Exclusion Criteria

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

1. A DSM-5 diagnosis of moderate or severe SUD of any substance other than cocaine or methamphetamine based on DSM-5 Checklist.
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.
3. Is currently engaged in formal SUD treatment.
4. Documented history of unprovoked seizure (lifetime) or any seizure in the past 6 months.
5. Documented history of brain lesion(s) and/or tumor(s).
6. Metal implants or non-removable metal objects above the waist.
7. Currently pregnant.
8. Lifetime history of prior clinical treatment with TMS.
9. Current or lifetime bipolar disorder.

10. Current psychotic disorder or psychotic depression.
11. Serious risk of homicide or suicide.
12. Are a prisoner or in police custody at the time of eligibility screening.
13. Previously randomized as a participant in the study.
14. Planned admission to a residential treatment facility or other formal SUD treatment program.
15. Unwilling or unable to follow study procedures.

3.0 GENERAL ANALYSIS POPULATIONS, DEFINITIONS, AND CONVENTIONS

3.1 Analysis Populations

3.1.1 Pre-screened Population

The pre-screened population consists of all participants who provided verbal consent for and initiated the pre-screen process, defined as submitting the Pre-Screen Summary (P08) eCRF.

3.1.2 Screened Population

The screened population consists of all participants who satisfied preliminary eligibility criteria during pre-screening, provided informed consent, and initiated the screening process. If a participant was previously enrolled in screening, only the final screening is considered for eligibility purposes.

3.1.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all participants who were randomized. Under ITT, all randomized participants will be analyzed by their treatment assignment, regardless of reevaluated eligibility status, treatment received, or subsequent withdrawal from treatment or deviation from the protocol.

3.1.4 Study Completers

The study completers population includes all randomized participants who complete the Week 16 follow-up visit as indicated on the Study Completion (STC) form.

3.1.5 Safety Population

The safety population includes all participants who completed informed consent.

3.2 General Definitions

3.2.1 Study Day

Study Day 1 is defined as the day of randomization.

3.2.2 Study Week

Due to the flexible participant treatment schedule and allowance of visit windows, study week is based on a 7-day target period and allows for visit windows. Because of this, study visit numbers and therefore study week may not align with strict 7-day periods from day of randomization but will never differ by more than 6 days. See Section 4.3 for further information on expected visit attendance and visit numbers. The study week number is defined as the first digit of the visit number (VISNO) captured on each assessment form.

3.2.3 Treatment Period

The 8-week treatment period coincides with Study Days 1-56 and can extend up to the close of the End of Treatment visit window on Day 63 if the participant has not yet reached 30 sessions.

3.2.4 Follow-up Period

The follow-up period consists of two study visits occurring at Week 12 and Week 16, with visit windows which extend to Study Days 77-98 and 105-126, respectively.

3.2.5 Baseline Value

The baseline value for each assessment will be considered the last non-missing value collected during screening prior to randomization, except for:

1) substance use (urine drug screen) which is defined as the first UDS collected during screening, and
2) the following assessments which may be collected after randomization and before the first treatment session:
    - Cue Craving Assessment (CCA, first pre-cue, pre-treatment exposure question only)
    - EEG Completion (EEG)

3.2.6 Hospital Anxiety and Depression Scale (HAD) Safety Window

The safety window for all participants enrolled in the study will begin on the date of participant consent and will continue through the Week 16 follow-up visit.

3.2.7 Adverse Event

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, is considered an AE.

3.2.8 Suspected Adverse Reaction

A 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.

3.2.9 Adverse Device Reaction

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

3.2.10 Unanticipated Adverse Device Effect

An 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)).

3.2.11 Serious Adverse Event

An adverse event, suspected adverse reaction, or adverse reaction is considered “serious” 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 study staff during the protocol-defined follow-up period, whether or not considered to be 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) Involves a congenital abnormality or birth defect.
6) Is an 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.

3.3 Table, Figures and Listings Conventions

Data for the pre-screened and screened populations will be summarized by site. Data for the ITT population will be summarized by treatment group and overall. Additionally, some analyses for the ITT population will also be summarized by site. For all summaries of ITT population, participants will be analyzed according to the treatment arm to which they were randomized, if applicable, regardless of the subsequent sequence of events regarding study intervention exposure. Analyses summarized by study week will be presented as defined in Section 3.2.2. Analyses for the safety population (defined in Section 3.1.5) will be presented by randomized treatment arm. Data quality, including data audits and protocol deviations, will be summarized by site.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, percentiles (median, 25th and 75th percentiles, maximum and minimum). Categorical variables will be summarized in terms of frequencies and/or percentages.

4.0 PARTICIPANT ENROLLMENT, DISPOSITION, AND VISIT ATTENDANCE

4.1 Participant Enrollment

The number of participants pre-screened and screened, and the corresponding reasons for ineligibility, will be summarized by site. The number of participants pre-screened by referral source will be presented by eligibility and site, as well as referral source by reason for ineligibility at pre-screening. Note that participants can be pre-screened and screened multiple times. Participants who are pre-screened more than once are not tracked and all pre-screens are summarized. Participants who were screened multiple times will be re-enrolled and their previous Participant ID will be documented on the ENRB eCRF. They will only be considered for the final screening.

The trajectory of actual randomizations versus the expected number of randomizations (according to the first date of randomization and under the assumption that 2.67 participants are expected to be randomized per month per site) along with the proposed number of randomizations will be graphed by site and overall. Proposed versus actual randomizations will be summarized by site in a tabular fashion.

The distribution of treatment assignments by site and strata will be presented.

4.2 Participant Disposition

Participants are defined as study completers if the Week 16 Follow-up Visit is completed as indicated on the Study Completion (STC) form, and they are considered early study terminations if this visit is not completed. Participant disposition will be summarized by site and treatment arm

for the number and proportion of participants completing the study, the number and proportion of participants terminating early from the study, and the reasons for early study termination.

The CONSORT flow diagram will be generated (Moher et al., 2010).

4.3 Visit Attendance

4.3.1 Treatment Period

The treatment period lasts 8 weeks and consists of up to 30 study visits. Additional information about the visit schedule requirements can be found in Section 2.2.3. Due to there being no prespecified expected visit schedule during the treatment period, the Visit Documentation (V08) eCRF is expected at and documents only one visit per study visit week. Visit attendance during the treatment period will be summarized by the minimum number of expected and attended V08-documented visits in the ITT population by study week, site, treatment arm, and primary substance of use.

4.3.2 Follow-up Period

Two visits are expected per participant in follow-up, one visit at Week 12 and one visit at Week 16. The number of expected visits, number of attended visits, and proportion of expected visits attended will be presented by site, treatment arm, and primary substance of use.

4.3.3 Missed Visits

4.3.3.1 Treatment Period

As described above for Treatment Period attendance (4.3.1), only one Visit Documentation (V08) form is expected per week during the 8-week Treatment Period, whether the visit was attended or missed. In the case where a participant does not attend any visits during a treatment period study week, the V08 form is completed to document the reason for a single missed visit for that week. That is, if the target 7-day period is missed, an V08 form is expected to document a missed visit and the next 7-day target period begins.

While there is no schedule for study visits per protocol, participants are encouraged by site staff to create a schedule on the day of randomization and to confirm the schedule for the next visit after each session. The distinction of scheduled visits for documentation purposes pertains only to missed visits. For example:

- If a participant attends a visit, regardless of if it was scheduled or not, the V08 is marked as visit attended.
- If a participant schedules a visit for the following study week and attends, the V08 is marked as visit attended for that study week, regardless of future visits in that study week being attended or missed.
- If a participant schedules a visit for the following study week and does not attend that scheduled visit but does attend another visit in the study week, the V08 is marked as visit attended.
- If a participant schedules a visit for the following study week and does not attend any visits in that period, the V08 is marked as a missed scheduled visit.
- If a participant does not schedule a visit during a study week and misses the entire study week, the V08 is marked as a missed unscheduled visit.

Information on missed visits for the 8 expected treatment period visits (as defined in the MOP, though additional treatment sessions may be completed) will be presented by site, treatment arm, and primary substance of use, including the number of expected visits, number of scheduled

missed visits, number of unscheduled missed visits, the reasons for scheduled visits missed, and the reason for unscheduled visits missed.

4.3.3.2 Follow-up Period

Information on missed visits during the follow-up period will be presented by site, treatment arm, and primary substance of use, including the number of expected visits, number of missed visits, and the reasons for the missed visits. There are two follow-up visits expected per participant during the follow-up period.

5.0 ANALYSIS OF PARTICIPANT BASELINE CHARACTERISTICS

Baseline demographics and characteristics collected on the Demographics (D08) eCRF including sex at birth, age, ethnicity, race, education completed, marital status, employment status, and baseline substance use collected on the Urine Drug Screen (UDS) eCRF (amphetamine, barbiturate, buprenorphine, benzodiazepines, cocaine, ecstasy, fentanyl, marijuana, methadone, methamphetamine, opiates, oxycodone, and phencyclidine) will be summarized by site, primary substance of use, and treatment arm for all randomized participants. Age will be summarized as both a continuous and categorical variable. This table will be repeated by treatment arm for participants who complete the study. Because randomization is expected to produce balance at baseline between the two treatment arms, comparisons of treatment groups with respect to baseline characteristics will be descriptive only. If meaningful differences between treatment arms are suspected, statistical testing may be performed.

6.0 STUDY TREATMENT ADHERENCE

6.1 Early Treatment Terminations

Participants will be considered early treatment terminations as of the date on the End of Treatment (EOT) form. Participants will be considered early treatment terminations if they permanently halt rTMS/sham treatments or fail to complete 20 of the 30 maximum rTMS/sham sessions and do not complete any sessions in Week 8.

The number and proportion of participants terminating treatment early and the reasons for termination will be presented by site, treatment arm, and primary substance of use.

6.2 Treatment Exposure

Participants will receive up to 30 sessions of either active or sham rTMS across the 8-week treatment period. Treatment exposure is captured on the rTMS Intervention (TMS) form and is defined as a performed rTMS intervention. The number of rTMS sessions performed will be summarized as a continuous variable by study visit week, site, and treatment arm for the ITT population, in participants who met the threshold of 20 rTMS sessions, and in participants who had an rTMS session in Week 8.

A summary of engagement in rTMS sessions will also be presented with the number of sessions attended, initiated and stopped prematurely, and performed summarized by treatment arm and primary substance of use. A plot of the average number of rTMS sessions attended by study week and treatment arm will also be provided.

7.0 FEASIBILITY AND EFFICACY ANALYSES

7.1 Definition of the Primary Outcome Measure

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 hypothesis is that at least

75% of participants will receive 20 or more rTMS (active or sham) sessions. The primary outcome measure does not consider whether a participant was randomized with CUD or MUD or randomized to active or sham rTMS treatment arm.

Note that pausing or early termination of an rTMS session is permitted if requested by the participant or if study staff is concerned for participant safety. If less than 50% of any treatment session is completed, the treatment is not considered performed and does not count towards the total count of treatment sessions. That is, a treatment session counts towards the primary outcome measure if it is marked as performed on the rTMS Intervention (TMS) form (TMS.TMPERFM = '1').

In cases where participants received more than 5 treatment sessions per calendar week, over 30 total sessions throughout the treatment, or sessions past Study Day 56 up to the End of Treatment window (Study Day 63), all sessions will still count towards the primary outcome measure.

7.2 Analysis of the Primary Outcome Measure

The primary feasibility outcome will be summarized in the ITT population (defined in Section 3.1.3) by the number of sessions performed per participant, the number of participants with at least 20 sessions, and a 95% confidence interval by the Wilson method. A forest plot of the estimated percentage and confidence interval will also be provided for the primary outcome analysis and supportive analyses listed in Section 7.3, as applicable. The Wilson method was chosen over others, including an exact or Clopper-Pearson method because this method has been shown to have better performance than exact or Wald methods (Brown et al., 2001.). There is no hypothesis testing.

The corresponding SAS code is provided below:

```
proc freq data = data;
      table y / binomial(level = 2 cl = wilson);
run;
```

where:

- data is a dataset with one row per participant, and
- y is the binary variable indicating whether the participant received at least 20 rTMS treatment sessions (y = 1) or not (y=0).

7.3 Supportive Analyses of the Primary Outcome Measure

7.3.1 Demographic Subgroup Analyses

Per NIH policy (NIH, 2016), subgroup analyses will be implemented to assess whether sex at birth (Male, Female), race (Black, White, Other), ethnicity (Hispanic/Latinx, Not Hispanic/Latinx), age (18-44 years, 45 years or greater), and employment status (Employed, Unemployed, Other are feasibility or effect modifiers. Responses missing, "Don't know," and "Refused to answer" will not be analyzed. The primary outcome percentage will be estimated in each demographic subgroup. Results will be summarized similar to the primary outcome, including a forest plot.

The corresponding SAS code is provided below:

```
proc freq data = data;
      where subgroup = x;
      table y / binomial(level = 2 cl = wilson);
run;
```

where:

- data is a dataset with one row per participant,
- subgroup is the demographic variable of interest,
- x is the subgroup level of interest, and
- y is the binary variable indicating whether the participant received at least 20 rTMS treatment sessions (y = 1) or not (y=0).

7.3.2 Additional Feasibility Analyses

Additional analyses may include estimating the feasibility outcome percentage in the ITT population 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. A one-sided hypothesis test 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. Summaries of the primary outcome by treatment arm and site and by primary substance of use (cocaine or methamphetamine) will be presented as well as a forest plot. SAS code similar to the demographic subgroup analyses can be used for the confidence intervals. The Fisher's exact test p-value SAS code is provided below:

```
proc freq data = data;
     tables y * x / chisq;
run;
```

where:

- data is a dataset with one row per participant,
- y is the binary variable indicating whether the participant received at least 20 rTMS treatment sessions, and
- x is the binary variable of interest (e.g., treatment arm or SUD).

7.4 Definition of the Secondary Outcome Measures

The secondary outcomes of this study are to determine the efficacy of up to 30 sessions of rTMS versus up to 30 sessions of sham rTMS for treatment of CUD or MUD, separately. The secondary outcomes will be determined assessing the percentage negative of the last UDS per study week (target 7-day period including visit windows) over the 8-week treatment period in the participant's respective primary use designation at randomization.

Urine drug screens will be collected at each treatment session prior to the rTMS or sham treatment during the treatment period and tested for substances including cocaine and methamphetamine. All UDS must be within temperature range and unadulterated to be a valid outcome measure. Primary substance of use is defined for the substance designated on the enrollment form (ENRC) on the day of randomization. If UDS was 1) collected at multiple screening visits, 2) collected at the final screening visit on the day of randomization (i.e., an earlier UDS is being used as baseline) and 3) not collected again after randomization before the same-day treatment session, the UDS may be used as a Week 1 result. If two UDS are collected on the last day of the study week, the last UDS collected will be used, as designated by the visit number. UDS collected at the EOT visit may be the last UDS collected during the treatment period and contribute to the secondary outcome if it is within the treatment period window (up to and including Day 63). If a participant ends treatment early, the EOT UDS will contribute to the study week based on 7-day periods from day of randomization.

The hypotheses are that individuals who receive active rTMS will have a significantly higher percent 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.

7.5 Analyses of the Secondary Outcome Measures

The secondary (efficacy) outcome will be analyzed in the ITT population (defined in Section 3.1.3) 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, major depressive episode (MDE), week, and site and a random effect for participant. It is important to note that a repeated measure, binary response of negative UDS, for each UDS provided by each participant, will be used as the outcome, as opposed to the total percentage of negative UDS. The model used still allows inference on the overall probability 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. Section 7.9 describes missing data handling procedures for the secondary outcome sensitivity analyses.

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 SAS code is provided below:

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

where:

- data is a dataset with one row per weekly UDS per participant for the specified primary substance of use,
- y is the binary variable with a value of 1 indicating the UDS for that participant was negative and 0 indicating positive UDS result,
- trt is a binary variable with a value of 1 indicating active 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 (1 – 8, categorical), 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 (i.e., the ICC for UDS) 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 random effect.

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.

Secondary outcome availability and UDS results negative for cocaine and methamphetamine separately as defined by primary substance of use will be summarized by study week, by site, and by treatment arm. A summary of the secondary outcome analysis will be provided by treatment arm separately for each primary substance of use and will include the odds ratio and 95% confidence interval. A forest plot will also be provided.

7.6 Supportive Analyses of the Secondary Outcome Measures

7.6.1 Demographic Subgroup Analyses

The secondary (efficacy) outcome results will be presented and tested within each demographic subgroup described in Section 7.3.1 by including interactions with treatment assignment in the model. Summaries will include the odds ratio, confidence interval, and p-value similar to the secondary outcome, including a forest plot. The corresponding SAS code is provided below:

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

where:

- data is a dataset with one row per weekly UDS per participant for the specified primary substance of use,
- y is the binary variable with a value of 1 indicating the UDS for that participant was negative and 0 indicating positive UDS result,
- trt is a binary variable with a value of 1 indicating active rTMS and 0 indicating sham rTMS,
- subgroup is the demographic variable of interest,
- mde is a binary variable with a value of 1 indicating the presence of MDE,
- week is the study week (1 – 8, categorical),
- site is a categorical variable containing which of the sites each participant was enrolled in, and
- participant is the participant ID.

7.6.2 Additional Efficacy Analyses

In preparation to assist in designing future larger trials of efficacy, estimates of the MDE, site and participant effects from the secondary outcome analysis 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. Summaries will be provided similar to the secondary outcome, including a forest plot.

Additional supportive analyses of the secondary (efficacy) outcome will include the following:

1. Examine if treatment effect varies depending on study week. This can be accomplished by introducing an interaction between week and treatment in the proposed model as given in the subgroup analysis SAS code 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. Summaries will be provided similar to the secondary outcome.
2. Repeat the secondary outcome analysis considering all randomized participants (regardless of primary substance of use designation) for UDS results for the following:
    a) Negative for all substances (amphetamine, barbiturate, buprenorphine, benzodiazepines, cocaine, ecstasy, fentanyl, marijuana, methadone, methamphetamine, opiates, oxycodone, and phencyclidine)
    b) Negative for stimulants (amphetamine, cocaine, and methamphetamine)
    c) Negative for primary substance of use (cocaine or methamphetamine as assessed at randomization)
3. Repeat the secondary outcome analysis in the population of participants who met the threshold of 20 rTMS sessions. Three tests will be performed in the participants' primary substance of use: by primary substance of use cocaine, by primary substance of use methamphetamine, and overall.

7.6.3 Sensitivity Analysis

The following sensitivity analyses of the secondary outcome measure will be performed. The analysis method and summaries will be as defined for the secondary outcome.

1. Defining study week as a strict 7-day period from the day of randomization and excluding UDS that were collected outside the respective 7-day period, despite having been collected within study visit windows. Any UDS collected after Study Day 56 will be excluded. The analysis method and summaries will be as defined for the secondary outcome.
2. Defining time as a continuous measure using Study Day.

7.7 Definition of the Exploratory Outcome Measures

Exploratory outcomes may include, and are not limited to:

- Other feasibility measures:
    - Percent of participants that complete all available questions for at least 75% of daily monitoring surveys (mobile questionnaires: MCQ, MMQ)
        - Expected once per day from Study Day 1 (randomization) to Study Day 112 (Week 16 follow-up visit target date)
        - If multiple surveys are completed, the first is retained for analysis
    - Percent of participants that complete all follow-up visits
- Self-reported cocaine and methamphetamine use (Timeline Follow-Back)
- Cocaine and/or methamphetamine craving (Visual Analogue Craving Scale, VAS, found on both CCA and MCQ/MMQ CRFs)
- Depression/anxiety symptoms (Hospital Anxiety and Depression Scale, HADS)
- Sleep quality (Actigraphy; Pittsburgh Sleep Quality Index, PSQI)
- Quality of life (Health Related Quality of Life, HRQOL-4)

- Impact of personal characteristics (age, handedness) on treatment outcomes
- Cognitive Behavioral Therapy (CBT) participation (Dynamicare dataset)
- Motor threshold changes over the treatment course (TMS; Machine output)

7.8 Analyses of the Exploratory Outcome Measures

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 longitudinal or cross-sectional regression models for ordinal or continuous outcomes.

7.9 Missing Data Analysis

As defined, the primary (feasibility) outcome will have no missing data. Participants that drop out of treatment 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.

The first and second methods for missing data analysis will include: 1) imputing all missing secondary outcome measure UDS as negative, and 2) imputing as positive. If there is at least one UDS per study week for a participant, regardless of the timing within the study week or later visits in the study week with missing UDS collection, the outcome is not considered missing. On the other hand, if there is not a single UDS collected within the study week, then the secondary outcome is considered missing.

The third method for handling missing secondary outcome data involves imputation based on self-report collected via Timeline Followback (TLFB). If the secondary outcome measure is missing, then any self-report use of the primary substance of use (cocaine or methamphetamine as defined at baseline) three days prior to the end of the study week window will result in a positive outcome measure of use. The three days prior to the end of the window represent use prior to attending the last visit of the study week because the secondary outcome measure is the last UDS collected per study week. Use of any type (oral, nasal, smoking, non-IV injection, IV injection, or other, as applicable) will count towards a positive result. Only if a participant is missing all UDS within a given study week, will self-report be used to impute the outcome measure. Study week will be calculated as described in Section 3.2.2. If TLFB is also missing, then the secondary outcome measure will not be imputed. Participants will only be included if there is at least one UDS which contributes to the secondary outcome (whether observed or imputed). For example, a participant who attends their first Study Week 1 visit on the first of the month, does not attend any visits during Study Week 2 and therefore has no UDS collected, and attends during Study Week 3 and completes UDS and TLFB. Then the window for Study Week 2 begins on the 8th and ends on the 14th. TLFB collected for the 11th – 13th will be used to impute Study Week 2 results.

For the fourth method of multiple imputation, separate procedures will be used for intermittent missingness and dropout. The following assumptions are made:

1. For the participants with intermittent missingness, assume missing at random (MAR).

When UDS data reflect intermittent missingness, in which an unobserved outcome was followed by observed outcomes, and the participant remained in the assigned intervention group, the observed outcomes can be used to predict the missing values.

2. For the participants who dropout, assume missing not at random (MNAR).

   Participants who dropped out may have had different patterns of substance use after dropout than those who remained in the study. The values for missing UDS after dropout might not retain the trend of prior observations since the participant was no longer exposed to the study environment. In fact, substance use patterns after dropout for a participant in the active rTMS treatment arm may more closely resemble participants in the sham treatment arm than other active rTMS participants.

Separate analyses will be performed for CUD and MUD as described for the main analysis of the secondary outcome measure in Section 7.4.

In the first step of imputation, a Markov Chain Monte Carlo (MCMC) method will be used to impute the values of missing outcomes from intermittent missingness under the assumption of MAR. The SAS code for imputing missing data from intermittent missingness is given below. Note the categorical variables (e.g., site, strata) must be in the dataset as dummy variables for MCMC imputation.

```
proc mi data = secondout_wide out = imp1
        minimum = 0 maximum = 1 round = 1
        nimpute = 50 seed = 123;
        by trt;
        mcmc impute = monotone chains = multiple;
        var site1 site2 site3 mde week1-week8;
run;
```

where *secondout_wide* is the wide form of the secondary outcome dataset with one observation per participant; *imp1* is the output dataset of monotone missingness; *minimum*, *maximum*, and *round* restrict the imputed values to possible UDS values (negative and positive); *trt* is treatment arm (‘rTMS, ‘Sham); *mde* is the major depressive episode (MDE) stratification value, and *week1-week8* provide the UDS values for Week 1 – Week 8, respectively. The analysis method for imputation will follow that used for the secondary outcome analysis. This step provides 50 imputed datasets with monotone missingness by filling in the missing values from intermittent missingness with the statement “impute = monotone.” The missing values due to intermittent missingness are imputed assuming that the intervention effect is still carried out while the participants remain in the study.

Using the monotone missingness dataset created in the first step, the second step imputes missing values from dropouts under the assumption of MNAR. This process of control-based pattern imputation assumes that after dropout the unobserved values in the active rTMS arm followed the path of the observed values in the sham arm. Based on this assumption, only the observed values in the sham arm are used to derive the posterior distribution of the parameters from which the missing values in both active rTMS and sham arms are imputed. This approach is conservative as it tended to reduce the difference between active rTMS and sham. The SAS code for imputing missing data from dropout is below.

```
proc mi data = imp1 out = imp2
        minimum = . . . 0 0 0 0
        maximum = . . . 1 1 1 1
        round = . . . 1 1 1 1
```

```
        nimpute = 1 seed = 123;
        class trt site mde;
        var site mde week1 week2 week3 week4 week5 week6 week7 week8;
        monotone reg;
        mnar model(week1 week2 week3 week4 week5 week6 week7 week8/
        modelobs=(trt=Sham));
run;
```

where *site* is the participant's site, *mde* is the major depressive episode (MDE) stratification value, and the remaining variables and proc mi options were as described above. The *monotone reg* statement specifies a regression imputation method for monotone missingness and *mnar* imputed missing values under the MNAR assumption for variables week1-week8. The *modelobs* statement specifies that only observations where trt = Sham are used to derive the imputation model following the control-based pattern imputation method.

After the complete datasets are generated, the dataset is transposed into long form by week and analyses of the imputed datasets using the standard procedure for generalized linear mixed effect model are performed separately for each imputed dataset using the *by _imputation_* statement.

```
proc glimmix data = imp_long method = quad;
        by _imputation_;
        class trt (ref = 'Sham' )site week mde patid;
        model y(event = '1') = trt mde week site /
                dist = binary link = logit solution;
        random intercept / subject = patid;
        estimate "rTMS vs Sham" trt 1 -1 / cl e ilink exp;
ods output estimates = est_imp;
run;
```

To draw statistical inference based on the results from the imputations, the combination rules are applied in MIANALYZE procedure (Little and Rubin, 2002; van Buuren, 2007). Proc MIANALYZE is set to estimate the pooled variance from two components: within-imputation variance and between-imputation variance. Within-imputation variance is the average of the mean of the within variance estimate in each imputed dataset. Between-imputation variance reflects the extra variance due to the missing data, which is estimated by taking the variance of parameter of interest estimated over imputed datasets.

```
proc mianalyze data = est_imp;
        modeleffects estimate;
        stderr stderr;
        ods output parameterestimates = est_pooled;
run;
```

The pooled results are then exponentiated to calculate the odds ratio and 95% confidence limits.

7.10 Updates to Secondary Outcome Analytic Methods

Following database lock, it was determined the planned model-based analyses for the secondary outcome measure could not be completed due to limitations in the data, particularly a lack of variability in the UDS data, estimates at the boundary of the parameter space, and small subgroup sample sizes. This led to highly imprecise estimates which were considered unreliable.

7.10.1 Secondary Outcome Analyses

The following changes to the analysis plan for the secondary outcome measure, including the main analysis, demographic subgroup analyses, and supportive analyses, were presented by DSC statisticians to the Lead Node on 02OCT2024. During this presentation, limited summary statistics were presented to the LN to illustrate the issues encountered during analysis. This included three redacted summary tables with masked treatment arm and subgroup names. Note that no results were presented; percentages only (no counts) were used, and no measures of significance were shown. The Lead Investigator and LN statisticians reviewed and made decisions regarding alternative modelling approaches to consider given the lack of variability and parameter space boundary issues. Thus, the additional analytic method decisions were made by parties that had not been privy to any unblinded information regarding the secondary outcome that could possibly impact their determination.

The general approach to dealing with models specified in version 1.0 of the SAP that produced unreliable results is as follows. If the original generalized linear mixed model including fixed effects for treatment, major depressive episode (MDE), week, and site and a random effect for participant converges and produces reliable results, the model will be used and results reported, as pre-specified in the initial version of the SAP. If that model does not converge or produce reliable results (e.g. an OR confidence interval limit over 50), a simplified model will be attempted. The simplified model will include a fixed effect for treatment arm and a random effect for participant. If the simplified model does not converge or produce reliable results, only the summary statistics for percentage negative UDS by primary substance of use, treatment arm, and subgroup (as applicable) will be presented.

If the model does not converge or produce reliable results due only to no variability in a subgroup, results will be presented within the other levels of the subgroup. This may occur if there are no participants in one treatment arm of a subgroup or all participants in that subgroup have no positive UDS results. No p-value will be reported as there is no planned test for significance between treatment arm and subgroup.

Furthermore, demographic and supportive analyses subgroups with three or more levels will be collapsed down to two levels: race (White, Non-White), employment status (Employed, Unemployed), and site (BSW UT Health San Antonio; SC Wake Forest, BSW University of Texas Southwestern, and SC MUSC Department of Psychiatry).

7.10.2 Missing Data Analysis

The analysis method for imputation will follow that used for the secondary outcome analysis. If the full original model does not produce reliable results, the simplified model with a fixed effect for treatment arm and a random effect for participant will be used. If the simplified model does not converge or produce reliable results, summary statistics will be reported.

Multiple imputation results may not be reported if the planned imputation algorithms fail due to lack of variability in the observed data.

8.0 SAFETY OUTCOMES AND ANALYSIS

The safety outcomes will be presented in the safety population defined in Section 3.1.5. All adverse events, serious adverse events, adverse device reactions, and unanticipated adverse device effects will be coded using MedDRA® dictionary version 26.1 or higher.

8.1 Adverse Events

Adverse events (AEs) are defined in Sections 3.2.7. The number and proportion of the following measures will be provided by treatment arm and overall: participants with at least one AE,

participants with at least one AE by maximum severity, total number of AEs, and severity of AEs. The number and proportion of participants experiencing the AE at least once will also be summarized by System Organ Class (SOC) and Preferred Term (PT).

A listing will include site, participant ID, date of randomization, event onset date, event description, severity, alternate etiology, outcome, resolution date, SAE associated with (if applicable), and the MedDRA® coded PT and SOC.

8.2 Serious Adverse Events

Serious Adverse Events (SAEs) are defined in Section 3.2.11. The number and proportion of the following measures will be provided by treatment arm and overall: participants with at least one SAE, participants with at least one SAE type, total number of SAEs, and type of SAE. The number and proportion of participants experiencing the SAE at least once will also be summarized by SOC and PT. A listing of SAEs similar to the listing of AEs will be presented. Narratives for all serious adverse events will be provided.

8.3 Adverse Device Reactions

Adverse Device Reactions (ADRs) are defined in Sections 3.2.9. An adverse event that is assessed as related to the use of the study device on the Adverse Event (AD1) form is considered an ADR. Summary tables and listing, similar to AEs, will be provided by treatment arm and SOC and PT. The listing will also include if the ADR was unanticipated.

8.4 Unanticipated Adverse Device Effects

Unanticipated Adverse Device Effects (UADEs) are defined in Section 3.2.10. Summary tables and listing, similar to AEs, will be provided by treatment arm and SOC and PT.

8.5 Suicide Risk

8.5.1 Self-Reported

The CHRT-SR (CHP) form is a self-reported assessment of suicidality and related thoughts and behaviors (Trivedi et al., 2011) assessed at screening, weekly during the treatment period, and at follow-up visits. Participants reporting suicide ideation/intent is defined as answering “Agree” or “Strongly Agree” on any of the Concise Health Risk Tracking – Participant Rated (CHRT-SR) questions 14, 15 or 16: “I have been having thoughts of killing myself”, “I have thoughts about how I might kill myself” or “I have a plan to kill myself.” The number and percentage of randomized participants with suicide ideation/intent will be summarized by presence or absence of current MDE assessed at baseline, study period, treatment arm, and overall.

A detailed listing for all visits for randomized participants who report suicide ideation/intent at any visit will be provided by treatment arm. The listing will include site, participant ID, date of randomization, presence or absence of current MDE assessed at baseline, visit, date of assessment, and responses to the suicide risk questions.

8.5.2 Clinician Rated

The Concise Health Risk Tracking – Clinical Rated (CHRT-CR) is a clinician-rated assessment of suicidal thoughts, actions, or related behaviors performed by the Medical Clinician if a participant had suicide ideation/intent on the CHRT-SR and is collected on the CHC eCRF. The number and percentage of randomized participants with passive suicide ideation; active/non-specific suicidal ideation; active suicidal ideation with method; active suicidal ideation with method and intent; active suicidal ideation with method, intent, and plan; and suicide attempt reported, will be summarized by presence or absence of current MDE assessed at baseline, study period, treatment arm, and overall.

A detailed listing of all visits for each randomized participant who endorses suicidality at any visit will be provided by treatment arm. The listing will include site, participant ID, date of randomization, presence or absence of current MDE assessed at baseline, visit, date of assessment, the responses to the questions summarized in the table, and if a suicide attempt was reported.

8.6 Pregnancy

A listing of pregnancies by treatment arm including site, participant ID, date of randomization, date staff aware of pregnancy, date pregnancy confirmed, date of pregnancy outcome, pregnancy outcome, and indicator of normal infant will be generated. Narratives will also be provided.

8.7 Death

A listing of deaths by treatment arm will be presented by treatment arm and contain site, participant ID, date of death, description, SOC, and PT. Narratives of deaths will also be provided.

9.0 SIGNIFICANCE TESTING AND MULTIPLICITY

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 is planned for the primary or secondary outcomes.

10.0 SAMPLE SIZE AND 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.

10.1 Precision Analysis

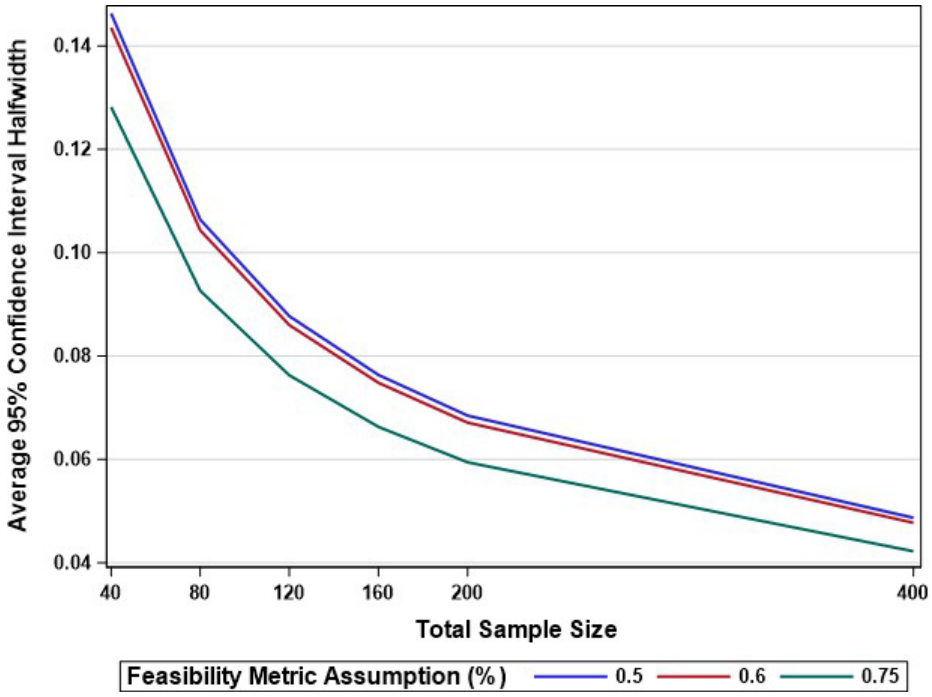
A simulation study was conducted where a dataset with a sample size of 160 was generated where each participant had a binary feasibility outcome generated from a Bernoulli distribution with $pp = 0.75$ because the goal rate for the outcome is 75%. The 95% confidence interval halfwidth was then calculated 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 $p\hat{p} - 0.066$ to $p\hat{p} + 0.066$ where $p\hat{p}$ is the estimate percentage. 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 2: 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 1: Plot of Confidence Interval Halfwidth by Sample Size for Primary (Feasibility) Outcome



10.2 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 is 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).

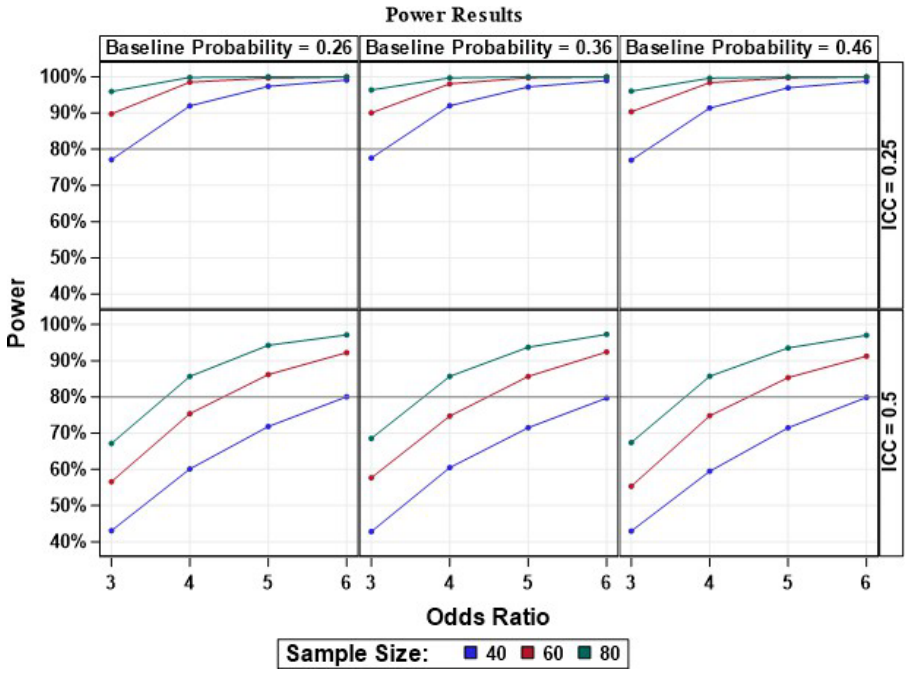
Once the dataset was simulated, a mixed effect logistic regression model was fit with only binary treatment (1 for real rTMS), binary stratum, week, and site as fixed effects and a random effect to account for correlation between UDS from the same participant. Each weekly UDS enters the model as a binary 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 (2016) 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 3: 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 2: Plot of Power by Sample Size and Treatment Effect for Secondary (Efficacy) Outcome



11.0 INTERIM ANALYSES AND DATA MONITORING

11.1 Sample Size Re-Estimation

There was no planned sample size re-estimation. In October 2022, the NIDA CCTN requested a sample size re-estimation due to slower than expected recruitment. The precision analysis related to the primary (feasibility) outcome was repeated for additional sample sizes of N = 60, 100, 110, 130, 140, and 150 under the previously assumed feasibility metrics of 50%, 60% and 75% of participants randomized will receive 20 or more sessions.

The power analysis for the secondary (efficacy) outcome was repeated with the following parameters updated utilizing data from the observed sham treatment arm:

1. The average standard deviation of UDS results was estimated to update the parameter for the correlation between UDS from the same participant. Both treatment arms were used to estimate the ratio as this does not explore the treatment effect and therefore would not impact Type I error.
2. The probability of success was estimated based on observed sham treatment arm data across primary use subgroups due to small observed sample size at the time of data freeze and to preserve the blind. Note that only data from the sham treatment arm was used to protect the double blind. Additionally, no knowledge of the treatment effect was gained and no adjustments for Type I error would need to be made.
3. A smaller treatment effect (odds ratio = 1.5) was included. As noted in the protocol, an odds ratio of 2.0 is considered clinically meaningful.

An additional sample size re-estimation was requested by NIDA CCTN and conducted in December 2023 following the same methods. All analyses during both rounds were performed by blinded DSC statisticians.

11.1.1 Results of the Sample Size Re-Estimation

The NIDA CCTN reviewed the sample size re-estimation report issued December 8, 2022 based on database freeze November 9, 2022. The report included the following summaries:

1. Precision Analysis: If the sample size is reduced from N = 160 to N = 120 under the hypothesized feasibility of 75%, the average halfwidth of the confidence interval would increase by 0.01 or 1% (from .066 to .076). Under the more conservative case of 50% feasibility, the halfwidth would increase by 0.012. From a statistical perspective, the impact of reducing the sample size on precision for the primary outcome is not substantial, though whether this level of precision is acceptable for N=120 is largely a scientific question.
2. For a total sample size of 120 and assuming the current observed ratio of methamphetamine use disorder (MUD) to cocaine use disorder (CUD) enrollments continues (i.e., n=50 for CUD and n=70 for MUD), 80% power is achieved at the observed probability of negative UDS for an effect size of an odds ratio (OR) = 3.0. There is less power to detect smaller treatment effects, though for many of the scenarios considered in the original power calculations this was also the case. While an odds ratio of 2.0 is considered clinically meaningful, this pilot study is not powered for efficacy, so it is not required to detect such an OR of that magnitude.

Following review and feedback from the LN, NIDA CCTN determined the study should continue under the existing protocol as the primary outcome feasibility analysis would not be impacted by any considered change to the sample size. While the study was not powered for the secondary efficacy outcome, it was determined that the investigators should continue recruiting as many participants as possible in the time remaining, given that targeting the clinically meaningful effect size of 2.0 would require a larger sample size to ensure adequate power.

Table 4: Confidence Interval Halfwidth for Primary (Feasibility) Outcome

Feasibility Metric Assumption (%)	Total Sample Size	Average 95% Confidence Interval Halfwidth
50%	40	0.146
	60	0.122
	80	0.106
	100	0.096
	110	0.091
	120	0.088
	130	0.084
	140	0.081
	150	0.079
	160	0.076
	200	0.068
	400	0.049

Table 4: Confidence Interval Halfwidth for Primary (Feasibility) Outcome		
Feasibility Metric Assumption (%)	**Feasibility Metric Assumption (%)**	**Feasibility Metric Assumption (%)**
60%	40	0.144
	60	0.119
	80	0.104
	100	0.094
	110	0.090
	120	0.086
	130	0.083
	140	0.080
	150	0.077
	160	0.075
	200	0.067
	400	0.048
75%	40	0.128
	60	0.106
	80	0.093
	100	0.083
	110	0.080
	120	0.076
	130	0.073
	140	0.071
	150	0.068
	160	0.066
	200	0.059
	400	0.042

Table 5: Re-estimation Power Analysis Results for Secondary (Efficacy) Outcome			
		Power n per Use Disorder Subgroup	
Probability of Negative UDS in Sham Arm	**Odds Ratio**	**n = 50**	**n = 70**
-0.025	1.5	14%	13%
	2.0	25%	36%
	3.0	67%	82%
Observed Probability	1.5	15%	20%
	2.0	42%	56%
	3.0	86%	96%
+0.025	1.5	19%	27%
	2.0	54%	70%
	3.0	95%	99%

The second sample size re-estimation conducted in December 2023 followed the same methods with current data used to estimate the UDS standard deviation and probability of success. The report provided to NIDA CCTN February 13, 2024 contained the following results:

1. The target sample size in each use disorder group required in order to detect clinically meaningful effect size of 2.0 with at least 80% power is 92.
2. With 52 participants, the number of participants recruited in the cocaine use disorder group as of database freeze December 15, 2023, there is at least 80% power to detect an odds ratio of 3.0.

It was determined that the with the number of participants recruited in each use disorder group, assuming the recruitment rate in that group as of late December 2023, it would take approximately 14 months to achieve the sample size in the cocaine use disorder group to be able to detect the clinically meaningful effect size. The protocol was not amended, and NIDA CCTN recommended the study recruitment not be extended.

Table 6: Power to detect OR=2.0 for various sample sizes	
N per Group	**Power**
52	53.1%
80	73.2%
90	79.4%
91	79.7%
92	81.6%

Table 7: Power for n=52 and various odds ratios and probabilities of a negative UDS		
Probability of Negative UDS	**Odds Ratio**	**Power**
-0.025	2	40%
	3	85%
Observed	2	53%
	3	94%
0.025	2	63%
	3	97%

11.2 Safety Interim Analyses

No classical interim analyses relating to futility will be implemented in this pilot study.

11.2.1 DSMB Reports and Meetings

Safety interim looks will be performed for the regular DSMB meetings or at unscheduled times per the DSMB's request. These will include analysis of adverse events, device effects, death, suicide risk, pregnancy, and narrative reports on serious adverse events.

11.2.2 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 and sponsor will have access to all adverse events and other reportable events. Should the 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

12.0 DATA QUALITY

12.1 Data Audits

A summary of data audit results from site interim monitoring visits conducted by CCC monitors will be presented by site, including date of audit, total fields audited, total data discrepancies, and error rate.

12.2 Protocol Deviations

Protocol deviations will be summarized by site and will include the number of deviations reported, the number of participants each deviation affects, frequencies for the types of protocol deviations, and information on whether the protocol deviation was deemed minor or major. A detailed listing of protocol deviations by deviation category will be provided. The listing will include site, participant ID, date of protocol deviation, date protocol deviation entered in EDC (Electronic Data Capture), deviation type, reason for protocol deviation, relatedness to COVID-19, deviation

description, corrective action to be taken, plan to prevent recurrence, IRB reporting required, IRB notification at continuing review, and planned or actual IRB report date.

13.0 SOFTWARE TO BE USED FOR ANALYSES

All analyses performed by the DSC and the Lead Node will use SAS Version 9.4 software. The LN may also use R Version 4.3.2.

14.0 UPDATES TO THE STATISTIAL ANALYSIS PLAN

SAP Version	Date of Approval	Summary of Changes
1.0	06JUN2024	Initial Version
2.0	17JAN2025	• Details added to Section 7.9 Missing Data Analyses in order to clarify statistical approaches • Section 7.10 Updates to Secondary Outcome Analytic Methods added

15.0 REFERENCES

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16.0 LIST OF PROPOSED TABLES, LISTINGS, AND FIGURES

The below listing contains the tables, listings, and figures which will be provided by the DSC.

Table 8: Proposed Tables, Listings, and Figures

Section	Title	Population
Enrollment, Participant Disposition, and Visit Attendance	Summary of Pre-screening by Site	Pre-screened
	Summary of Eligible Pre-screens by Referral Source and Site	Pre-screened
	Summary of Reason for Pre-screen Ineligibility by Referral Source	Pre-screened
	Summary of Screening by Site	Screened
	Summary of Pre-screening, Screening, and Randomization by Site	Pre-screened
	Randomizations by Site, Strata, and Treatment Arm	ITT
	Figure of Expected and Actual Randomizations Overall	ITT
	Figure of Expected and Actual Randomizations by Site	ITT
	Proposed and Actual Randomizations by Site	ITT
	Summary of Participant Disposition by Site	ITT
	Summary of Participant Disposition by Treatment Arm	ITT
	CONSORT Flow Diagram	ITT
	Summary of Attendance at Treatment Period Visits by Site	ITT
	Summary of Attendance at Treatment Period Visits by Treatment Arm	ITT
	Summary of Attendance at Treatment Period Visits by Primary Substance of Use	ITT
	Summary of Attendance at Follow-up Visits by Site	ITT
	Summary of Attendance at Follow-up Visits by Treatment Arm	ITT
	Summary of Attendance at Follow-up Visits by Primary Substance of Use	ITT
	Summary of Missed Visits in Treatment Period by Site	ITT
	Summary of Missed Visits in Treatment Period by Treatment Arm	ITT
	Summary of Missed Visits in Treatment Period by Primary Substance of Use	ITT
	Summary of Missed Visits in Follow-up Period by Site	ITT
	Summary of Missed Visits in Follow-up Period by Treatment Arm	ITT

Table 8: Proposed Tables, Listings, and Figures		
Section	**Title**	**Population**
	Summary of Missed Visits in Treatment Period by Primary Substance of Use	ITT
Participant Characteristics at Baseline	Summary of Baseline Characteristics by Site	ITT
	Summary of Baseline Characteristics by Treatment Arm	ITT
	Summary of Baseline Characteristics by Primary Substance of Use	ITT
	Summary of Baseline Characteristics in Study Completers by Treatment Arm	Study Completers
Treatment Exposure	Summary of Early Treatment Terminations by Site	ITT
	Summary of Early Treatment Terminations by Treatment Arm	ITT
	Summary of Early Treatment Terminations by Primary Substance of Use	ITT
	Summary of Treatment Exposure by Site	ITT
	Summary of Treatment Exposure by Treatment Arm	ITT
	Summary of Treatment Exposure in Participants with rTMS Session Threshold Met by Treatment Arm	ITT
	Summary of Treatment Exposure in Participants with rTMS Session Performed during Week 8 by Treatment Arm	ITT
	Summary of Engagement in rTMS Sessions by Treatment Arm	ITT
	Summary of Engagement in rTMS Sessions by Primary Substance of Use	ITT
	Average Number of rTMS Sessions Attended by Treatment Arm and Week	ITT
Primary Outcome	Summary of Primary Outcome Analysis	ITT
Supportive Analyses of the Primary Outcome	Summary of Primary Outcome by Sex	ITT
	Summary of Primary Outcome by Race	ITT
	Summary of Primary Outcome by Ethnicity	ITT
	Summary of Primary Outcome by Age	ITT
	Summary of Primary Outcome by Employment Status	ITT
	Summary of Primary Outcome Analysis by Primary Substance of Use	ITT
	Summary of Primary Outcome Analysis by Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Primary Substance of Use and Treatment Arm	ITT

Table 8: Proposed Tables, Listings, and Figures		
Section	**Title**	**Population**
	Summary of Primary Outcome by Primary Substance of Use and Treatment Arm: Conditional Results	ITT
	Summary of Primary Outcome Analysis by Site	ITT
	Forest Plot of Primary Outcome Results	ITT
Secondary Outcome	Summary of Secondary Outcome Availability by Site	ITT
	Summary of Secondary Outcome Availability by Treatment Arm	ITT
	Summary of Secondary Outcome Analysis by Treatment Arm	ITT
	Summary of Negative UDS Results by Treatment Arm	ITT
Supportive Analyses of the Secondary Outcome	Summary of Secondary Outcome by Sex and Treatment Arm	ITT
	Summary of Secondary Outcome by Race and Treatment Arm	ITT
	Summary of Secondary Outcome by Ethnicity and Treatment Arm	ITT
	Summary of Secondary Outcome by Age and Treatment Arm	ITT
	Summary of Secondary Outcome by Employment Status and Treatment Arm	ITT
	Summary of Secondary Outcome Analysis by Major Depressive Episode	ITT
	Summary of Secondary Outcome Analysis by Site	ITT
	Forest Plot of Secondary Outcome Results	ITT
	Summary of Secondary Outcome Analysis: Participant Effect	ITT
	Summary of Secondary Outcome Analysis: Week by Treatment Arm	ITT
	Summary of Secondary Outcome Supportive Analysis by Treatment Arm	ITT
	Summary of Negative UDS in Participants with rTMS Session Threshold Met by Treatment Arm	ITT
	Summary of Secondary Outcome Sensitivity Analysis by Treatment Arm	ITT
Safety Outcomes	Summary of Adverse Events by Treatment Arm	Safety
	Summary of MedDRA Coded Adverse Events by Treatment Arm	Safety
	Listing of Adverse Events by Treatment Arm	Safety

Table 8: Proposed Tables, Listings, and Figures		
Section	**Title**	**Population**
	Summary of Serious Adverse Events by Treatment Arm	Safety
	Summary of MedDRA Coded Serious Adverse Events by Treatment Arm	Safety
	Listing of Serious Adverse Events by Treatment Arm	Safety
	Summary of Adverse Device Reactions by Treatment Arm	Safety
	Summary of MedDRA Coded Adverse Device Reactions by Treatment Arm	Safety
	Listing of Adverse Device Reactions by Treatment Arm	Safety
	Summary of Unanticipated Adverse Device Effects by Treatment Arm	Safety
	Summary of MedDRA Coded Unanticipated Adverse Device Effects by Treatment Arm	Safety
	Listing of Unanticipated Adverse Device Effects by Treatment Arm	Safety
	Summary of CHRT – Participant Rated by Treatment Arm	Safety
	Listing of CHRT – Participant Rated by Treatment Arm	Safety
	Summary of CHRT – Clinician Rated by Treatment Arm	Safety
	Listing of CHRT – Clinician Rated by Treatment Arm	Safety
	Listing of Pregnancies by Treatment Arm	Safety
	Listing of Deaths by Treatment Arm	Safety
Data Quality	Summary of Data Audits	N/A
Protocol Deviations	Summary of Protocol Deviations	N/A
	Listing of Protocol Deviations	N/A
Safety Narratives	SAE Narratives	Safety
	Pregnancy Narratives	Safety
	Death Narratives	Safety

17.0 APPENDICES

17.1 Shells for Proposed Tables, Listings, and Figures

17.1.1 Enrollment, Participant Disposition, and Visit Attendance

Table 1: Summary of Pre-screening by Site					
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Number pre-screened[1]	N				
Number of ineligible pre-screens	N (X.X%)				
Criterion resulting in ineligibility[2]					
Less than 18 years of age or greater than 65 years of age	N (X.X%)				
Has not used cocaine or methamphetamine on at least 10 of the last 30 days					
Did not express interest in decreasing stimulant use					
Currently engaged in formal treatment for stimulant use disorder					
Currently pregnant					
Unwilling to use effective birth control during study					
Has previously received TMS in a clinical setting					
Has serious medical problem that would preclude safe or consistent participation in the study					
History of unprovoked seizure (lifetime) or any seizure in last 6 months					
History of brain lesion(s) and/or tumor(s)					
Current moderate or severe SUD, other than CUD or MUD					
Currently prescribed anticonvulsants or benzodiazepines, but not on stable dose for at least 4 weeks					
Suicidal or homicidal ideation					
Is a prisoner or in police custody					
Expected to be prisoner/in custody soon					
Metal implants or non-removable metal objects above the waist					
Current/lifetime history of mania or hypomania					
Previously randomized as a participant in the study					
Planned admission to a residential treatment or other formal SUD treatment program					
No longer interested					
Lives too far away/transportation issues					
Other					

[1] Participants who were pre-screened more than once were not tracked and all pre-screens are summarized.

[2] Percentages are calculated based on the denominator of the number of ineligible pre-screens and may sum to greater than 100% if multiple eligibility criteria were not met for potential participants.

Table 2: Summary of Eligible Pre-screens by Referral Source and Site					
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Number pre-screened[1]	N				
Number of eligible pre-screens[2]	N (X.X%)				
Referral source[3]					
Flyer	N (X.X%)				
Word of mouth					
Newspaper ad					
Public transit ad					
Radio ad					
TV ad					
Social media					
Craigslist					
Clinical referral					
Clinicaltrials.gov					
Other					
Number of ineligible pre-screens[2]					
Referral source[4]					
Flyer					
Word of mouth					
Newspaper ad					
Public transit ad					
Radio ad					
TV ad					
Social media					
Craigslist					
Clinical referral					
Clinicaltrials.gov					
Other					

[1] Participants who were pre-screened more than once were not tracked and all pre-screens are summarized.

[2] Percentages are calculated based on the denominator of the number of pre-screens.

[3] Percentages are calculated based on the denominator of the number of eligible pre-screens.

[4] Percentages are calculated based on the denominator of the number of ineligible pre-screens.

Table 3: Summary of Reason for Pre-screen Ineligibility by Referral Source					
	Criterion Resulting in Ineligibility[4]				
	Current Moderate or Severe SUD, Other Than CUD or MUD	**Current/ Lifetime History of Mania or Hypomania**	**Has Not Used Cocaine or Methamphetamine on at Least 10 of the Last 30 Days**	**Metal Implants or Non-removable Metal Objects Above the Waist**	**Other**
Number pre-screened[1]	N				
Number of ineligible pre-screens[2]	N (X.X%)				
Referral source[3]					
Flyer	N (X.X%)				
Word of mouth					
Newspaper ad					
Public transit ad					
Radio ad					
TV ad					
Social media					
Craigslist					
Clinical referral					
Clinicaltrials.gov					
Other					

[1] Participants who were pre-screened more than once were not tracked and all pre-screens are summarized.

[2] Percentages are calculated based on the denominator of the number of pre-screens.

[3] Percentages are calculated based on the denominator of the number of ineligible pre-screens.

[4] Percentages are calculated based on the denominator of the number of ineligible pre-screens and may sum to greater than 100% if multiple eligibility criteria were not met for potential participants.

Table 4: Summary of Screening by Site					
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Number screened[1]	N				
Number of ineligible screens	N (X.X%)				
Criteria resulting in ineligibility[2]					
Inclusion criteria					
Between ages of 18 and 65	N (X.X%)				
Able to understand the study and provide written informed consent					
Meets current (past 12 months) DSM-5 criteria for moderate to severe CUD or MUD					
Interest in decreasing cocaine and/or methamphetamine use					
Used cocaine or methamphetamine on at least 10 days in the 30 days prior to consent					
If female, willing to use an effective form of birth control during the treatment phase of the study					
If prescribed benzodiazepines and/or anticonvulsant medications, has been on a stable dose for at least 4 weeks prior to consent					
Exclusion criteria					
Has a diagnosis of moderate or severe SUD of any substance other than cocaine or methamphetamine	N (X.X%)				
If female, participant currently pregnant					
Has a serious medical disorder that in the judgement of the medical clinician would preclude safe or complete study participation					
Has received TMS treatment in a clinical setting in their lifetime					
Currently engaged in formal SUD treatment					
Planning to be admitted to a residential treatment facility or other formal SUD treatment program					
Has a documented history of unprovoked seizure (lifetime) or any other seizure in the past 6 months					
Has a documented history of brain lesion(s) and/or brain tumor(s)					
Has any metal implants or non-removeable metal objects above the waist					
Participant meets criteria for current or past manic or hypomanic episode (bipolar I or II)					
Participant meets criteria for current psychotic disorder or psychotic depression					
Participant is at serious risk of homicide or suicide					
Participant is a prisoner or in police custody at time of eligibility screening					
Has previously been randomized to participate in this study					
Unwilling or unable to follow study procedures					

Table 4: Summary of Screening by Site					
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Lost to follow-up					
Other reasons for screen failure					
Reason 1					
…					
Number of participants eligible but not randomized[3]	N (X.X%)				
Reason not randomized[4]					
Declined study participation	N (X.X%)				
Death					
Judgement of site/research staff					
Failed to return to clinic prior to randomization					
Other					

[1] Participants may be screened multiple times and were only considered for the final screening (N=X).

[2] Percentages are calculated based on the denominator of the number of ineligible screens and may sum to greater than 100% if multiple eligibility criteria were not met for potential participants.

[3] Percentages are calculated based on the denominator of the number that screened eligible.

[4] Percentages are calculated based on the denominator of the number of participants eligible but not randomized.

Table 5: Summary of Pre-screening, Screening, and Randomization by Site									
Site	**Number of Pre-screens[1]**	**Number of Screens[2]**	**Percent of Eligible Pre-screens Screened**	**Number of Ineligible Screens**	**Percent of Ineligible Screens**	**Number Eligible but Not Randomized**	**Number Randomized**	**Percent of Eligible Pre-screens Randomized**	**Percent of Screens Randomized**
Site 1	N	N	X.X%	N	X.X%	N	N	X.X%	X.X%
Site 2									
Site 3									
Site 4									
Total									

[1] Participants who are pre-screened more than once are not tracked and all pre-screens are summarized.

[2] Participants may be screened multiple times and were only considered for the final screening (N=X).

Table 6: Randomizations by Site, Strata, and Treatment Arm					
	Strata		Treatment Arm[1]		
Site	Primary Substance of Use	Major Depressive Episode[2]	Sham (N=XX)	rTMS (N=XX)	Total[3] (N=XX)
Site 1	Cocaine	Absent	N (X%)	N (X%)	N (X%)
		Present			
	Methamphetamine	Absent			
		Present			
Site 2	Cocaine	Absent			
		Present			
	Methamphetamine	Absent			
		Present			
Site 3	Cocaine	Absent			
		Present			
	Methamphetamine	Absent			
		Present			
Site 4	Cocaine	Absent			
		Present			
	Methamphetamine	Absent			
		Present			
Total	Cocaine	Absent			
		Present			
	Methamphetamine	Absent			
		Present			
	Overall	Cocaine			
		Methamphetamine			
		Overall[4]			

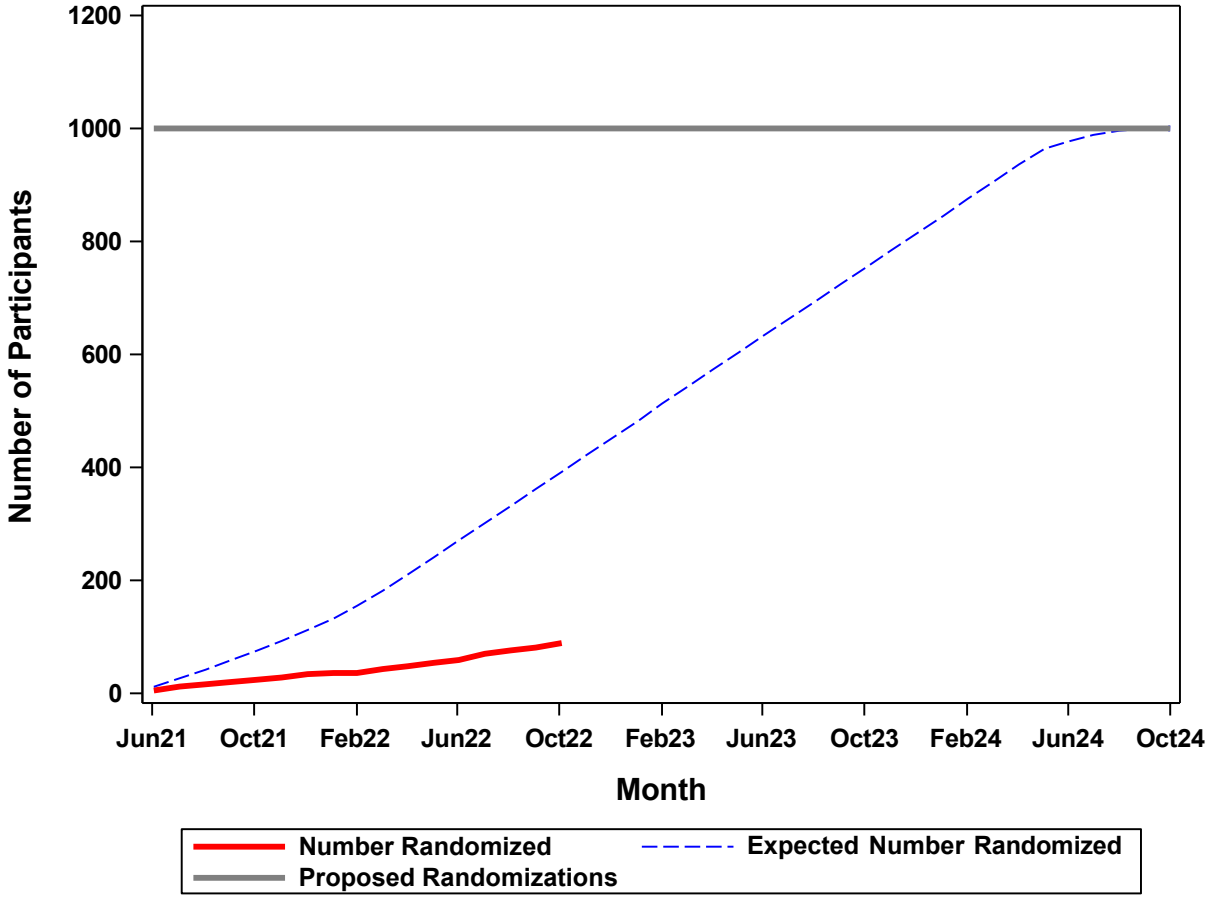
[1] Percentage is calculated based on the denominator of the number randomized in the treatment arm at the site.

[2] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

[3] Percentage is calculated based on the denominator of the number of participants at each site or overall.

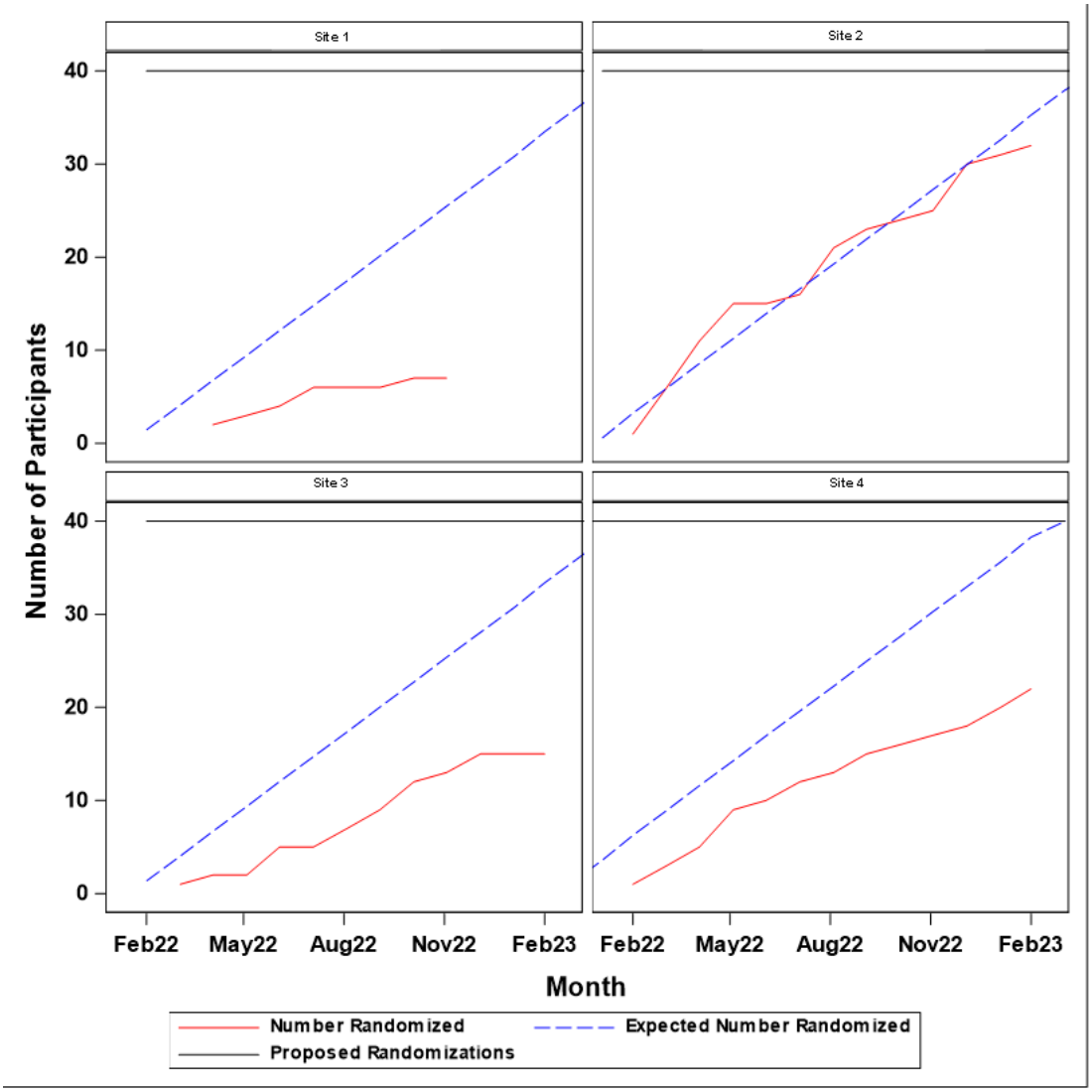
[4] Percentage is calculated based on the denominator of the total number randomized.

Figure 1: Expected and Actual Randomizations Overall



Example figure provided.

Figure 2: Expected and Actual Randomizations by Site



Example figure provided.

Table 7: Proposed and Actual Randomizations by Site						
Site	**Proposed Randomization**	**Date Site Opened for Enrollment**	**Date of First Randomization**	**Actual Randomizations**	**Actual/ Proposed (%)**	**Date of Last Randomization**
Site 1	N	mm/dd/yyyy	mm/dd/yyyy	N	X.X%	mm/dd/yyyy
Site 2						
Site 3						
Site 4						
Total						

Table 8: Summary of Participant Disposition by Site					
	Site 1	**Site 2**	**Site 3**	**Site 4**	**Total**
Number of participants randomized	N				
Number of study completers[1]	N (X.X%)				
Number of early study terminations[2]	N (X.X%)				
Reason for early study termination[3]					
Participant failed to return to clinic and unable to contact	N (X.X%)				
Participant stopped participation due to practical problems (no childcare, transportation, other)					
Participant moved from area					
Participant incarcerated					
Participant terminated due to AE/SAE					
Participant terminated for other clinical reasons					
Participant had a significant psychiatric risk (suicidal, homicidal, psychotic)					
Participant withdrew consent					
Participant deceased					
Participant terminated for administrative issues					
Participant terminated due to pressure or advice from outsiders					
Participant feels treatment no longer necessary, cured					
Participant feels treatment no longer necessary, not working					
Participant was ineligible and should not have been enrolled in study					
Participant terminated for other reason					

[1] A participant is a study completer if they had a Study Completion (STC) form indicating completion of the study.

[2] A participant is an early study termination if they had an STC form indicating they did not complete the study.

[3] Percentage is calculated based on the denominator of number of early terminations.

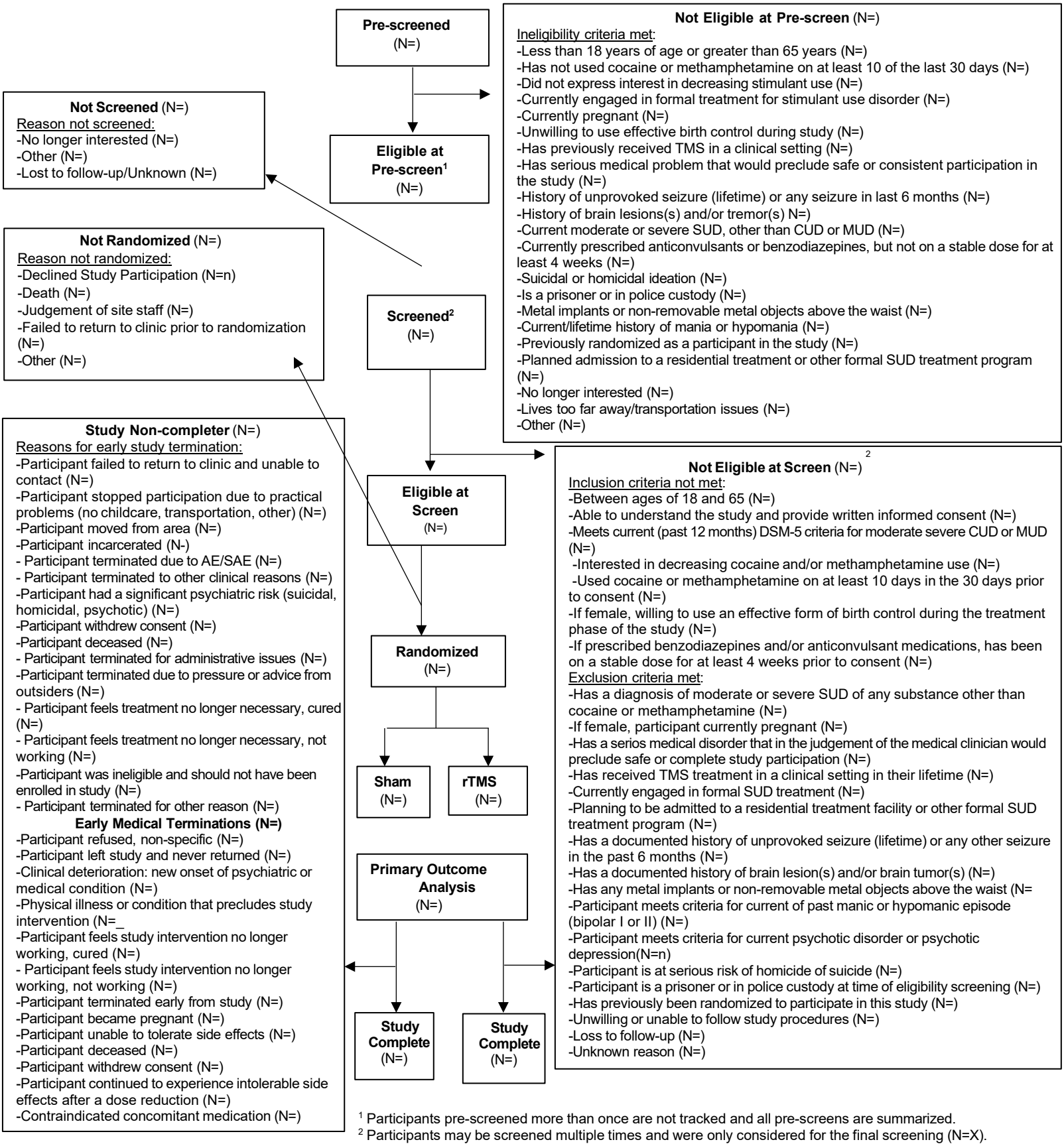
Table 9: Summary of Participant Disposition by Treatment Arm			
	Treatment Arm		
	Sham	rTMS	Total
Number of participants randomized	N		
Number of study completers[1]	N (X.X%)		
Number of early study terminations[2]	N (X.X%)		
Reason for early study termination[3]			
Participant failed to return to clinic and unable to contact	N (X.X%)		
Participant stopped participation due to practical problems (no childcare, transportation, other)			
Participant moved from area			
Participant incarcerated			
Participant terminated due to AE/SAE			
Participant terminated for other clinical reasons			
Participant had a significant psychiatric risk (suicidal, homicidal, psychotic)			
Participant withdrew consent			
Participant deceased			
Participant terminated for administrative issues			
Participant terminated due to pressure or advice from outsiders			
Participant feels treatment no longer necessary, cured			
Participant feels treatment no longer necessary, not working			
Participant was ineligible and should not have been enrolled in study			
Participant terminated for other reason			

[1] A participant is a study completer if they had a Study Completion (STC) form indicating completion of the study.

[2] A participant is an early study termination if they had an STC form indicating they did not complete the study.

[3] Percentage is based on the denominator of number of early terminations.

Figure 3: CONSORT Flow Diagram



[1] Participants pre-screened more than once are not tracked and all pre-screens are summarized.
[2] Participants may be screened multiple times and were only considered for the final screening (N=X).

Table 10: Summary of Attendance at Treatment Period Visits by Site

Study Visit[1]	Site 1 (N=XX)	Site 2 (N=XX)	Site 3 (N=XX)	Site 4 (N=XX)	Total (N=XX)
Week 1	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)
Week 2					
Week 3					
Week 4					
Week 5					
Week 6					
Week 7					
Week 8					
Total					

[1] Visit attendance is calculated as the number of participants who attended the visit as documented on the Visit Documentation (V08) form over the number of expected visits. One visit was expected per participant per study week during the treatment period. Study week is determined by study visit number.

Table 11: Summary of Attendance at Treatment Period Visits by Treatment Arm

Study Visit[1]	Treatment Arm		Total (N=XX)
	Sham (N=XX)	rTMS (N=XX)	
Week 1	N (X.X%)	N (X.X%)	N (X.X%)
Week 2			
Week 3			
Week 4			
Week 5			
Week 6			
Week 7			
Week 8			
Total			

[1] Visit attendance is calculated as the number of participants who attended the visit as documented on the Visit Documentation (V08) form over the number of expected visits. One visit was expected per participant per study week during the treatment period. Study week is determined by study visit number.

Table 12: Summary of Attendance at Treatment Period Visits by Primary Substance of Use			
	Primary Substance of Use		
Study Visit[1]	Cocaine (N=XX)	Methamphetamine (N=XX)	Total (N=XX)
Week 1	N (X.X%)	N (X.X%)	N (X.X%)
Week 2			
Week 3			
Week 4			
Week 5			
Week 6			
Week 7			
Week 8			
Total			

[1] Visit attendance is calculated as the number of participants who attended the visit as documented on the Visit Documentation (V08) form over the number of expected visits. One visit was expected per participant per study week during the treatment period. Study week is determined by study visit number.

Table 13: Summary of Attendance at Follow-up Visits by Site					
Study Visit[1]	Site 1 (N=XX)	Site 2 (N=XX)	Site 3 (N=XX)	Site 4 (N=XX)	Total (N=XX)
Week 12	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)
Week 16					
Total					

[1] Visit is considered attended if the Visit Documentation form (V08) indicates that the visited was attended.

Table 14: Summary of Attendance at Follow-up Visits by Treatment Arm			
	Treatment Arm		
Study Visit[1]	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Week 12	N (X.X%)	N (X.X%)	N (X.X%)
Week 16			
Total			

[1] Visit is considered attended if the Visit Documentation form (V08) indicates that the visited was attended.

Table 15: Summary of Attendance at Follow-up Visits by Primary Substance of Use

Study Visit[1]	Primary Substance of Use		Total (N=XX)
	Cocaine (N=XX)	Methamphetamine (N=XX)	
Week 12	N (X.X%)	N (X.X%)	N (X.X%)
Week 16			
Total			

[1] Visit is considered attended if the Visit Documentation form (V08) indicates that the visited was attended.

Table 16: Summary of Missed Visits in Treatment Period by Site					
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Number of expected visits[1]	N				
Number of missed expected visits[2]	N (X.X%)				
Number of missed scheduled visits[3]	N (X.X%)				
Reason for missed visit[4]					
Participant illness	N (X.X%)				
Participant incarcerated					
Participant family issues					
Participant employment issues					
Participant refused					
Participant death					
Participant concerned about being reported for use of drugs					
COVID-19: Illness					
COVID-19: Public health measures					
COVID-19: Other					
Other					
Unknown					
Number of missed unscheduled visits[3]	N (X.X%)				
Reason for not scheduling visit[5]					
Missing; unable to contact	N (X.X%)				
Participant incarcerated					
Participant refused					
Staff error					
COVID-19: Illness					
COVID-19: Public health measures					
COVID-19: Other					
Other					
Unknown					

[1] One visit per participant per study week is expected. Visit documentation and reasons for missed visits is only collected for expected visits.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Percentage is calculated based on the denominator of number of missed visits.

[4] Percentage is calculated based on the denominator of number of missed scheduled visits.

[5] Percentage is calculated based on the denominator of number of missed unscheduled visits.

Table 17: Summary of Missed Visits in Treatment Period by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Number of expected visits[1]	N		
Number of missed expected visits[2]			
Number of missed scheduled visits[3]	N (X.X%)		
Reason for missed scheduled visit[4]			
Participant illness	N (X.X%)		
Participant incarcerated			
Participant family issues			
Participant employment issues			
Participant refused			
Participant death			
Participant concerned about being reported for use of drugs			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			
Number of missed unscheduled visits[3]	N (X.X%)		
Reason for not scheduling visit[5]			
Missing; unable to contact	N (X.X%)		
Participant incarcerated			
Participant refused			
Staff error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			

[1] One visit per participant per study week is expected. Visit documentation and reasons for missed visits is only collected for expected visits.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Percentage is calculated based on the denominator of number of missed visits.

[4] Percentage is calculated based on the denominator of number of missed scheduled visits.

[5] Percentage is calculated based on the denominator of number of missed unscheduled visits.

Table 18: Summary of Missed Visits in Treatment Period by Primary Substance of Use

	Primary Substance of Use		Total (N=XX)
	Cocaine (N=XX)	Methamphetamine (N=XX)	
Number of expected visits[1]	N		
Number of missed expected visits[2]			
Number of missed scheduled visits[3]	N (X.X%)		
Reason for missed scheduled visit[4]			
Participant illness	N (X.X%)		
Participant incarcerated			
Participant family issues			
Participant employment issues			
Participant refused			
Participant death			
Participant concerned about being reported for use of drugs			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			
Number of missed unscheduled visits[3]	N (X.X%)		
Reason for not scheduling visit[5]			
Missing; unable to contact	N (X.X%)		
Participant incarcerated			
Participant refused			
Staff error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			

[1] One visit per participant per study week is expected. Visit documentation and reasons for missed visits is only collected for expected visits.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Percentage is calculated based on the denominator of number of missed visits.

[4] Percentage is calculated based on the denominator of number of missed scheduled visits.

[5] Percentage is calculated based on the denominator of number of missed unscheduled visits.

Table 19: Summary of Missed Visits in Follow-up Period by Site					
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Number of expected visits[1]	N				
Number of missed expected visits[2]	N (X.X%)				
Number of missed scheduled visits[3]	N (X.X%)				
Reason for missed visit[4]					
Participant illness	N (X.X%)				
Participant incarcerated					
Participant family issues					
Participant employment issues					
Participant refused					
Participant death					
Participant concerned about being reported for use of drugs					
COVID-19: Illness					
COVID-19: Public health measures					
COVID-19: Other					
Other					
Unknown					
Number of missed unscheduled visits[3]	N (X.X%)				
Reason for not scheduling visit[5]					
Missing; unable to contact	N (X.X%)				
Participant incarcerated					
Participant refused					
Staff error					
COVID-19: Illness					
COVID-19: Public health measures					
COVID-19: Other					
Other					
Unknown					

[1] Two follow-up visits (Weeks 12 and 16) per participant are expected. Visit documentation and reasons for missed visits is only collected for expected visits.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Percentage is calculated based on the denominator of number of missed visits.

[4] Percentage is calculated based on the denominator of number of missed scheduled visits.

[5] Percentage is calculated based on the denominator of number of missed unscheduled visits.

Table 20: Summary of Missed Visits in Follow-up Period by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Number of expected visits[1]	N		
Number of missed expected visits[2]			
Number of missed scheduled visits[3]	N (X.X%)		
Reason for missed scheduled visit[4]			
Participant illness	N (X.X%)		
Participant incarcerated			
Participant family issues			
Participant employment issues			
Participant refused			
Participant death			
Participant concerned about being reported for use of drugs			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			
Number of missed unscheduled visits[3]	N (X.X%)		
Reason for not scheduling visit[5]			
Missing; unable to contact	N (X.X%)		
Participant incarcerated			
Participant refused			
Staff error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			

[1] Two follow-up visits (Weeks 12 and 16) per participant are expected. Visit documentation and reasons for missed visits is only collected for expected visits.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Percentage is calculated based on the denominator of number of missed visits.

[4] Percentage is calculated based on the denominator of number of missed scheduled visits.

[5] Percentage is calculated based on the denominator of number of missed unscheduled visits.

17.1.2 Participant Characteristics at Baseline

Table 21: Summary of Baseline Characteristics by Site					
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Sex (at birth)					
Missing	N (X.X%)				
Male					
Female					
Don't know					
Refused to answer					
Age in years (Mean (SD))	X.X (X.XX)				
Age in years					
Missing	N (X.X%)				
< 18					
18 - < 25					
25 - < 35					
35 - < 45					
45 - < 55					
55 - < 65					
65 - < 75					
75+					
Ethnicity					
Missing	N (X.X%)				
Not Hispanic or Latinx					
Hispanic or Latinx					
Don't know					
Refused to answer					
Race					
Missing	N (X.X%)				
American Indian or Alaska Native					
Asian					
Black or African American					
Native Hawaiian or Pacific Islander					
White					
Other					
Multiracial					

Table 21: Summary of Baseline Characteristics by Site					
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Don't know					
Refused to answer					
Education completed					
Missing	N (X.X%)				
Less than high school diploma					
High school graduate					
GED or equivalent					
Some college, no degree					
Associate's degree: occupational, technical, or vocational program					
Associate's degree: academic program					
Bachelor's degree					
Master's degree					
Professional school degree					
Doctoral degree					
Don't know					
Refused					
Marital status					
Missing	N (X.X%)				
Married					
Widowed					
Divorced					
Separated					
Never married					
Living with partner					
Don't know					
Refused					
Employment					
Missing	N (X.X%)				
Working now					
Only temporarily laid off, sick leave, or maternity leave					
Looking for work, unemployed					
Retired					

Table 21: Summary of Baseline Characteristics by Site					
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Disabled permanently or temporarily					
Keeping house					
Student					
Other					
Baseline substance use (Urine Drug Screen)	N (X.X%)				
Amphetamine					
Barbiturate					
Buprenorphine					
Benzodiazepines					
Cocaine					
Ecstasy					
Fentanyl					
Marijuana					
Methadone					
Methamphetamine					
Opiates					
Oxycodone					
Phencyclidine					

Table 22: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Sex (at birth)			
Missing	N (X.X%)		
Male			
Female			
Don't know			
Refused to answer			
Age in years (Mean (SD))	X.X (X.XX)		
Age in years			
Missing	N (X.X%)		
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Missing	N (X.X%)		
Not Hispanic or Latinx			
Hispanic or Latinx			
Don't know			
Refused to answer			
Race			
Missing	N (X.X%)		
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			
Multiracial			

Table 22: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Don't know			
Refused to answer			
Education completed			
Missing	N (X.X%)		
Less than high school diploma			
High school graduate			
GED or equivalent			
Some college, no degree			
Associate's degree: occupational, technical, or vocational program			
Associate's degree: academic program			
Bachelor's degree			
Master's degree			
Professional school degree			
Doctoral degree			
Don't know			
Refused			
Marital status			
Missing	N (X.X%)		
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Don't know			
Refused			
Employment			
Missing	N (X.X%)		
Working now			
Only temporarily laid off, sick leave, or maternity leave			
Looking for work, unemployed			
Retired			

Table 22: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Disabled permanently or temporarily			
Keeping house			
Student			
Other			
Baseline substance use (Urine Drug Screen)	N (X.X%)		
Amphetamine			
Barbiturate			
Buprenorphine			
Benzodiazepines			
Cocaine			
Ecstasy			
Fentanyl			
Marijuana			
Methadone			
Methamphetamine			
Opiates			
Oxycodone			
Phencyclidine			

Table 23: Summary of Baseline Characteristics by Primary Substance of Use			
	Primary Substance of Use		
	Cocaine (N=XX)	Methamphetamine (N=XX)	Total (N=XX)
Sex (at birth)			
Missing	N (X.X%)		
Male			
Female			
Don't know			
Refused to answer			
Age in years (Mean (SD))	X.X (X.XX)		
Age in years			
Missing	N (X.X%)		
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Missing	N (X.X%)		
Not Hispanic or Latinx			
Hispanic or Latinx			
Don't know			
Refused to answer			
Race			
Missing	N (X.X%)		
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			
Multiracial			

Table 23: Summary of Baseline Characteristics by Primary Substance of Use			
	Primary Substance of Use		
	Cocaine (N=XX)	Methamphetamine (N=XX)	Total (N=XX)
Don't know			
Refused to answer			
Education completed			
Missing	N (X.X%)		
Less than high school diploma			
High school graduate			
GED or equivalent			
Some college, no degree			
Associate's degree: occupational, technical, or vocational program			
Associate's degree: academic program			
Bachelor's degree			
Master's degree			
Professional school degree			
Doctoral degree			
Don't know			
Refused			
Marital status			
Missing	N (X.X%)		
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Don't know			
Refused			
Employment			
Missing	N (X.X%)		
Working now			
Only temporarily laid off, sick leave, or maternity leave			
Looking for work, unemployed			

Table 23: Summary of Baseline Characteristics by Primary Substance of Use			
	Primary Substance of Use		
	Cocaine (N=XX)	Methamphetamine (N=XX)	Total (N=XX)
Retired			
Disabled permanently or temporarily			
Keeping house			
Student			
Other			
Baseline substance use (Urine Drug Screen)	N (X.X%)		
Amphetamine			
Barbiturate			
Buprenorphine			
Benzodiazepines			
Cocaine			
Ecstasy			
Fentanyl			
Marijuana			
Methadone			
Methamphetamine			
Opiates			
Oxycodone			
Phencyclidine			

Table 24: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Sex (at birth)			
Missing	N (X.X%)		
Male			
Female			
Don't know			
Refused to answer			
Age in years (Mean (SD))	X.X (X.XX)		
Age in years			
Missing	N (X.X%)		
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Missing	N (X.X%)		
Not Hispanic or Latinx			
Hispanic or Latinx			
Don't know			
Refused to answer			
Race			
Missing	N (X.X%)		
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			
Multiracial			

Table 24: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Don't know			
Refused to answer			
Education completed			
Missing	N (X.X%)		
Less than high school diploma			
High school graduate			
GED or equivalent			
Some college, no degree			
Associate's degree: occupational, technical, or vocational program			
Associate's degree: academic program			
Bachelor's degree			
Master's degree			
Professional school degree			
Doctoral degree			
Don't know			
Refused			
Marital status			
Missing	N (X.X%)		
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Don't know			
Refused			
Employment			
Missing	N (X.X%)		
Working now			
Only temporarily laid off, sick leave, or maternity leave			
Looking for work, unemployed			
Retired			

Table 24: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Disabled permanently or temporarily			
Keeping house			
Student			
Other			
Baseline substance use (Urine Drug Screen)	N (X.X%)		
Amphetamine			
Barbiturate			
Buprenorphine			
Benzodiazepines			
Cocaine			
Ecstasy			
Fentanyl			
Marijuana			
Methadone			
Methamphetamine			
Opiates			
Oxycodone			
Phencyclidine			

17.1.3 Treatment Exposure

Table 25: Summary of Early Treatment Terminations by Site

	Site 1 (N=XX)	Site 2 (N=XX)	Site 3 (N=XX)	Site 4 (N=XX)	Total (N=XX)
Number of early study treatment terminations[1]	N (X.X%)				
Reason for early treatment termination[2]					
Participant became pregnant	N (X.X%)				
Participant unable to tolerate side effects					
Participant deceased					
Participant withdrew consent					
Participant continued to experience intolerable effects after a dose reduction					
Contraindicated concomitant medication					
Participant refused, non-specific					
Participant left study and never returned					
Clinical deterioration: new onset of psychiatric or medical condition					
Physical illness or condition that precludes study intervention					
Participant feels study intervention no longer necessary, cured					
Participant feels study intervention no longer necessary, not working					
Participant terminated early from study					
Other					

[1] Percentage is out of the total number of participants randomized.

[2] Percentages are out of the total number of early treatment terminations.

Table 26: Summary of Early Treatment Terminations by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Percent of early study treatment terminations[1]	N (X.X%)		
Reason for early treatment termination[2]			
Participant became pregnant	N (X.X%)		
Participant unable to tolerate side effects			
Participant deceased			
Participant withdrew consent			
Participant continued to experience intolerable effects after a dose reduction			
Contraindicated concomitant medication			
Participant refused, non-specific			
Participant left study and never returned			
Clinical deterioration: new onset of psychiatric or medical condition			
Physical illness or condition that precludes study intervention			
Participant feels study intervention no longer necessary, cured			
Participant feels study intervention no longer necessary, not working			
Participant terminated early from study			
Other			

[1] Percentage is out of the total number of participants randomized.

[2] Percentages are out of the total number of early treatment terminations.

Table 27: Summary of Early Treatment Terminations by Primary Substance of Use			
	Primary Substance of Use		Total (N=XX)
	Cocaine (N=XX)	Methamphetamine (N=XX)	
Percent of early study treatment terminations[1]	N (X.X%)		
Reason for early treatment termination[2]			
Participant became pregnant	N (X.X%)		
Participant unable to tolerate side effects			
Participant deceased			
Participant withdrew consent			
Participant continued to experience intolerable effects after a dose reduction			
Contraindicated concomitant medication			
Participant refused, non-specific			
Participant left study and never returned			
Clinical deterioration: new onset of psychiatric or medical condition			
Physical illness or condition that precludes study intervention			
Participant feels study intervention no longer necessary, cured			
Participant feels study intervention no longer necessary, not working			
Participant terminated early from study			
Other			

[1] Percentage is out of the total number of participants randomized.
[2] Percentages are out of the total number of early treatment terminations.

Table 28: Summary of Treatment Exposure by Site						
Study Week[1]		**Site 1 (N=XX)**	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Week 1	Number of rTMS sessions performed[2]					
	N	XX				
	Mean	XX.X				
	SD	XX.XX				
	Min	XX				
	25th percentile	XX				
	Median	XX				
	75th percentile	XX				
	Max	XX				
…						
Week 8	…					
Overall	…					

[1] Study Week refers to the week as indicated by the study visit number.

[2] An rTMS session is considered performed if the rTMS Intervention (TMS) form indicates as such.

Table 29: Summary of Treatment Exposure by Treatment Arm				
		Treatment Arm		
Study Week[1]		**Sham (N=XX)**	**rTMS (N=XX)**	**Total (N=XX)**
Week 1	Number of rTMS sessions performed[2]			
	N	XX		
	Mean	XX.X		
	SD	XX.XX		
	Min	XX		
	25th percentile	XX		
	Median	XX		
	75th percentile	XX		
	Max	XX		
…				
Week 8	…			
Overall	…			

[1] Study Week refers to the week as indicated by the study visit number.

[2] An rTMS session is considered performed if the rTMS Intervention (TMS) form indicates as such.

Table 30: Summary of Treatment Exposure in Participants with rTMS Session Threshold Met[1] by Treatment Arm

		Treatment Arm		
Study Week[2]		**Sham (N=XX)**	**rTMS (N=XX)**	**Total (N=XX)**
Week 1	Number of rTMS sessions performed[3]			
	N	XX		
	Mean	XX.X		
	SD	XX.XX		
	Min	XX		
	25th percentile	XX		
	Median	XX		
	75th percentile	XX		
	Max	XX		
…				
Week 8	…			
Overall	…			

[1] Participants met the rTMS session threshold if they completed at least 20 rTMS sessions.

[2] Study Week refers to the week as indicated by the study visit number.

[3] An rTMS session is considered performed if the rTMS Intervention (TMS) form indicates as such.

Table 31: Summary of Treatment Exposure in Participants with rTMS Session Performed during Week 8 by Treatment Arm

		Treatment Arm		
Study Week[1]		**Sham (N=XX)**	**rTMS (N=XX)**	**Total (N=XX)**
Week 1	Number of rTMS sessions performed[2]			
	N	XX		
	Mean	XX.X		
	SD	XX.XX		
	Min	XX		
	25th percentile	XX		
	Median	XX		
	75th percentile	XX		
	Max	XX		
…				
Week 8	…			
Overall	…			

[1] Study Week refers to the week as indicated by the study visit number.

[2] An rTMS session is considered performed if the rTMS Intervention (TMS) form indicates as such.

Table 32: Summary of Engagement in rTMS Sessions by Treatment Arm				
		Treatment Arm		
Study Week[1]		**Sham (N=XX)**	**rTMS (N=XX)**	**Total (N=XX)**
Week 1	Number of rTMS Sessions[2]			
	Attended	N		
	Initiated and stopped prematurely	N (X.X%)		
	Performed	N (X.X%)		
…	…			
Week 8	…			
Overall				

[1] Study Week refers to the week as indicated by the study visit number.

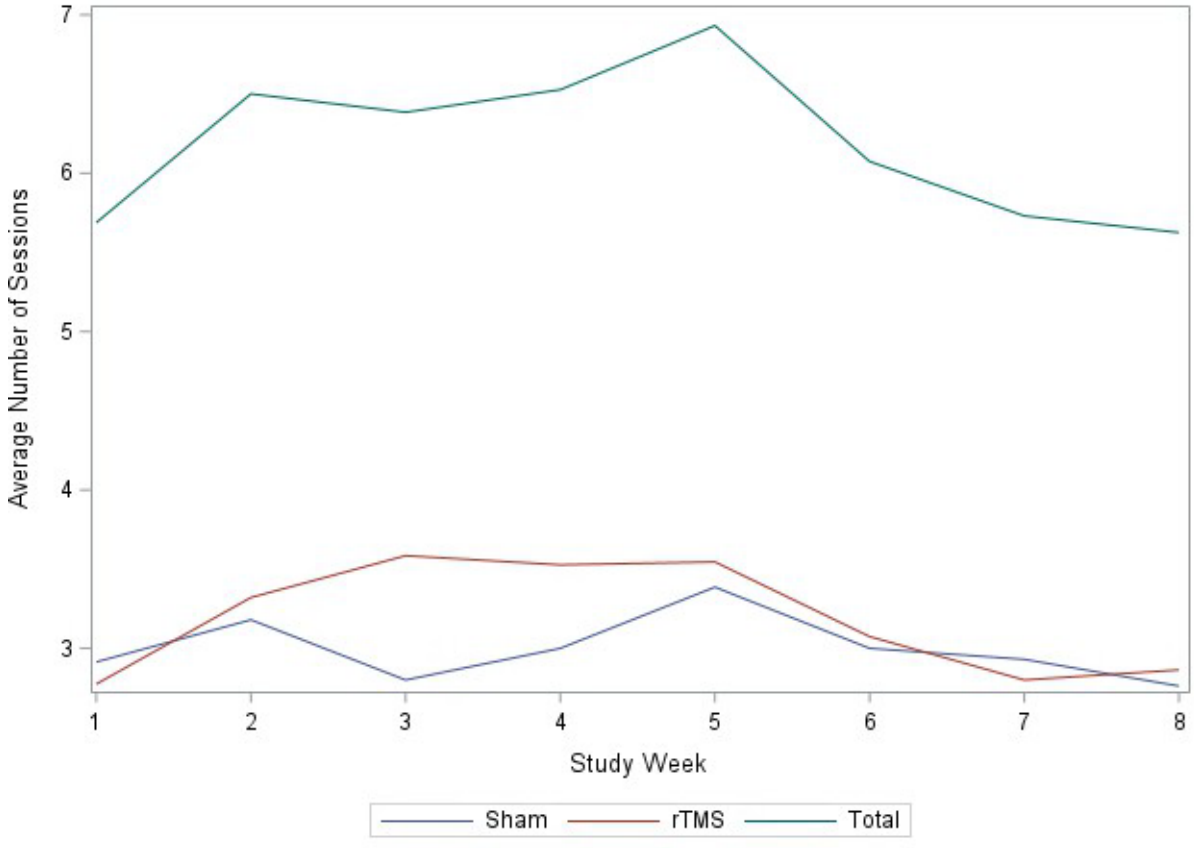
[2] rTMS session attendance, whether the session was stopped prematurely, and whether the session was performed was captured on the rTMS Intervention (TMS) form. Percentages are calculated based on the denominator of the number of attended sessions.

Table 33: Summary of Engagement in rTMS Sessions by Primary Substance of Use				
Study Week[1]		**Primary Substance of Use**		**Total (N=XX)**
		Cocaine (N=XX)	**Methamphetamine (N=XX)**	
Week 1	Number of rTMS Sessions[2]			
	Attended	N		
	Initiated and stopped prematurely	N (X.X%)		
	Performed	N (X.X%)		
…	…			
Week 8	…			
Overall				

[1] Study Week refers to the week as indicated by the study visit number.

[2] rTMS session attendance, whether the session was stopped prematurely, and whether the session was performed was captured on the rTMS Intervention (TMS) form. Percentages are calculated based on the denominator of the number of attended sessions.

Figure 4: Average Number of rTMS Sessions Attended by Treatment Arm and Week



Example figure provided.

17.1.4 Primary Outcome

Table 34: Summary of Primary Outcome Analysis

Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
		Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Upper Confidence Limit
N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method.

17.1.5 Supportive Analyses of the Primary Outcome

Table 35: Summary of Primary Outcome by Sex

Subgroup	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Upper Confidence Limit
Male	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
Female					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the subgroup.

Table 36: Summary of Primary Outcome by Race

Subgroup	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
Black	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
White					
Other[4]					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the subgroup.

[4] Other includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other, and Multiple Race. Missing or refused responses are not included in the analysis (N=X).

Table 37: Summary of Primary Outcome by Ethnicity

Subgroup	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
Not Hispanic or Latinx	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
Hispanic or Latinx					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the subgroup.

Table 38: Summary of Primary Outcome by Age

Subgroup	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
18-44 years	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
45 years or greater					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the subgroup.

Table 39: Summary of Primary Outcome by Employment Status

Subgroup	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
Employed[4]	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
Unemployed					
Other[5]					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the subgroup.

[4] Employed includes working now, temporarily laid off, sick leave, or maternity leave.

[5] Other includes retired, disabled (permanently or temporarily), keeping house, student, and other. Missing or refused responses are not included in the analysis (N=X).

Table 40: Summary of Primary Outcome Analysis by Primary Substance of Use

Primary Substance of Use	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]			
			Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit	p-value
Cocaine	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%	0.xxx
Methamphetamine						

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Confidence limits results are obtained by the Wilson method within the primary substance of use. P-value is obtained from the Fisher's exact test.

Table 41: Summary of Primary Outcome Analysis by Treatment Arm						
			Results[3]			
Treatment Arm	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit	p-value
Sham	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%	0.xxx
rTMS						

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Confidence limits results are obtained by the Wilson method within the treatment arm. P-value is obtained from the Fisher's exact test.

Table 42: Summary of Primary Outcome Analysis by Primary Substance of Use and Treatment Arm

Primary Substance of Use	Treatment Arm	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Results[3]		
				Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
Cocaine	Sham	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
	rTMS					
Methamphetamine	Sham					
	rTMS					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Confidence limits results are obtained by the Wilson method within the primary substance of use and treatment arm.

Table 43: Primary Outcome Analysis by Primary Substance of Use and Treatment Arm: Conditional Results

Variable of Interest	Conditional Variable	Results[3]	
		Number of Participants with at Least 20 Sessions[1,2] N (%)	p-value
Primary Substance of Use: Cocaine	Treatment Arm: Sham	N (XX.X%)	0.xxx
	Treatment Arm: rTMS		
Primary Substance of Use: Methamphetamine	Treatment Arm: Sham		
	Treatment Arm: rTMS		
Treatment Arm: Sham	Primary Substance of Use: Cocaine		
	Primary Substance of Use: Methamphetamine		
Treatment Arm: rTMS	Primary Substance of Use: Cocaine		
	Primary Substance of Use: Methamphetamine		

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] P-value results are obtained from the Fisher's exact test for independence of the outcome and the variable of interest conditional on the given variable.

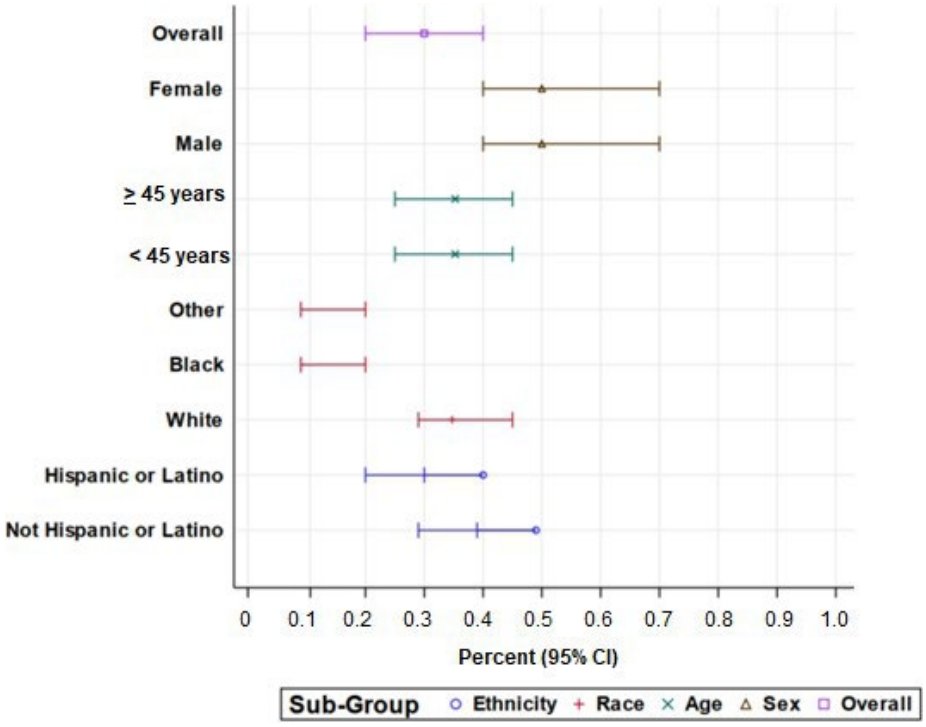
Table 44: Summary of Primary Outcome Analysis by Site					
			Results[3]		
Site	Number of Participants Randomized	Number of Sessions Performed Per Participant[1] Mean (SD)	Number of Participants with at Least 20 Sessions[1,2] N (%)	95% Lower Confidence Limit	95% Lower Confidence Limit
Site 1	N	X.X (X.XX)	N (XX.X%)	XX.XX%	XX.XX%
Site 2					
Site 3					
Site 4					

[1] A rTMS or sham session was considered performed if indicated as such on the rTMS Intervention (TMS) form.

[2] Percentage is calculated out of the total number of participants randomized.

[3] Results are obtained by the Wilson method within the site.

Figure 5: Forest Plot of Primary Outcome Results



Example figure provided.

17.1.6 Secondary Outcomes

Table 45: Summary of Secondary Outcome Availability[1] by Site					
Study Week	**Site 1 (N=XX)**	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Site 4 (N=XX)**	**Total (N=XX)**
Week 1	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)
Week 2					
Week 3					
Week 4					
Week 5					
Week 6					
Week 7					
Week 8					
Overall					

[1] The secondary outcome is available if there is at least one UDS with a result for the participant's respective primary substance of use (cocaine or methamphetamine). Primary substance of use is designated at randomization. Percentage is calculated as the number of participants with secondary outcome available divided by the number of participants randomized.

Table 46: Summary of Secondary Outcome Availability[1] by Treatment Arm					
	Primary Use Cocaine		**Primary Use Methamphetamine**		
	Treatment Arm		**Treatment Arm**		
Study Week	**Sham (N=XX)**	**rTMS (N=XX)**	**Sham (N=XX)**	**rTMS (N=XX)**	**Total (N=XX)**
Week 1	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)	N (X.X%)
Week 2					
Week 3					
Week 4					
Week 5					
Week 6					
Week 7					
Week 8					
Overall					

[1] The secondary outcome is available if there is at least one UDS with a result for the participant's respective primary substance of use. Primary substance of use is designated at randomization. Percentage is calculated as the number of participants with secondary outcome available divided by the number of participants randomized.

Table 47: Summary of Secondary Outcome Analysis by Treatment Arm							
Primary Substance of Use	Treatment Arm	Number of Participants Randomized	Results[2]				
			Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Sham	N	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	rTMS						
Methamphetamine	Sham						
	rTMS						

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the treatment arm term of the generalized linear mixed model.

Table 48: Summary of Negative UDS Results[1] by Treatment Arm					
	Primary Use Cocaine[2]		Primary Use Methamphetamine[2]		
	Treatment Arm		Treatment Arm		
Study Week	Sham (N=XX)	rTMS (N=XX)	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Week 1	n/N (X.X%)	n/N (X.X %)	n/N (X.X %)	n/N (X.X %)	n/N (X.X %)
Week 2					
Week 3					
Week 4					
Week 5					
Week 6					
Week 7					
Week 8					
Overall					

[1] The number of participants with a negative UDS in the participant's respective primary substance of use (cocaine or methamphetamine) on the last UDS administered per study week. Percentage is calculated as the number of participants with a negative UDS divided by the number of participants with a UDS available for that week within the primary substance of use subgroup. Missing UDS are not imputed.

[2] Primary substance of use is designated at randomization.

17.1.7 Supportive Analyses of the Secondary Outcomes

Table 49: Summary of Secondary Outcome by Sex and Treatment Arm

Primary Substance of Use	Subgroup	Number of Participants Randomized	Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Male	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Female							
Methamphetamine	Male							
	Female							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the treatment arm and subgroup interaction term. Missing UDS are not imputed.

Table 50: Summary of Secondary Outcome by Race and Treatment Arm

Primary Substance of Use	Subgroup	Number of Participants Randomized	Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Black	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	White							
	Other[3]							
Methamphetamine	Black							
	White							
	Other[3]							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the treatment arm and subgroup interaction term.

[3] Other includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other, and Multiple Race. Missing or refused responses are not included in the analysis (N=X).

Table 51: Summary of Secondary Outcome by Ethnicity and Treatment Arm								
			Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
Primary Substance of Use	Subgroup	Number of Participants Randomized	Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Not Hispanic or Latinx	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Hispanic or Latinx							
Methamphetamine	Not Hispanic or Latinx							
	Hispanic or Latinx							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the treatment arm and subgroup interaction term.

Table 52: Summary of Secondary Outcome by Age and Treatment Arm								
			Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
Primary Substance of Use	Subgroup	Number of Participants Randomized	Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	18-44 years	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	45 years or greater							
Methamphetamine	18-44 years							
	45 years or greater							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the treatment arm and subgroup interaction term.

Table 53: Summary of Secondary Outcome by Employment Status and Treatment Arm

Primary Substance of Use	Subgroup	Number of Participants Randomized	Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Employed[3]	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Unemployed							
	Other[4]							
Methamphetamine	Employed[3]							
	Unemployed							
	Other[4]							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the treatment arm and subgroup interaction term.

[3] Employed includes working now, temporarily laid off, sick leave, or maternity leave.

[4] Other includes retired, disabled (permanently or temporarily), keeping house, student, and other. Missing or refused responses are not included in the analysis (N=X).

Table 54: Summary of Secondary Outcome Analysis by Major Depressive Episode

Primary Substance of Use	Major Depressive Episode[1]	Number of Participants Randomized	Treatment Arm		Results[3]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[2]	Percentage Negative UDS[2]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Present	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Absent							
Methamphetamine	Present							
	Absent							

[1] Major Depressive Episode is assessed for current MDE at baseline.

[2] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[3] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the MDE term.

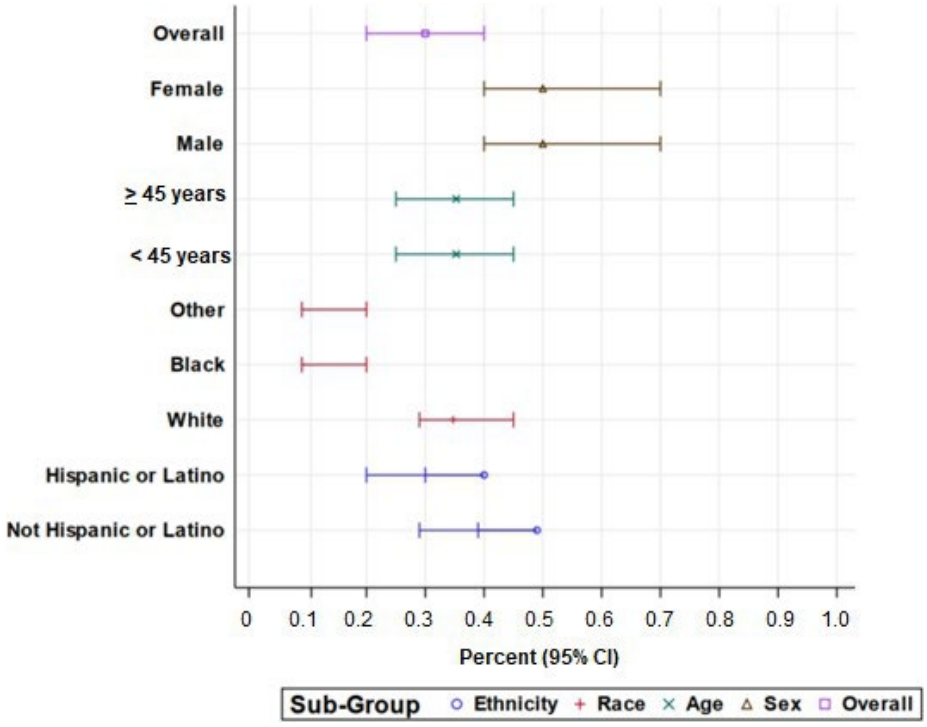
Table 55: Summary of Secondary Outcome Analysis by Site

Primary Substance of Use	Site	Number of Participants Randomized	Treatment Arm		Results[3]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[2]	Percentage Negative UDS[2]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Site 1	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Site 2							
	Site 3							
	Site 4							
Methamphetamine	Site 1							
	Site 2							
	Site 3							
	Site 4							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the generalized linear mixed model. The odds ratios and p-values result from the site term.

Figure 6: Forest Plot of Secondary Outcome Results



Example figure provided.

Table 56: Summary of Secondary Outcome Analysis: Participant Effect

Primary Substance of Use	Number of Participants Randomized	Within Participant Correlation Results[1]			
		Estimate	Standard Error	95% Lower Confidence Limit	95% Upper Confidence Limit
Cocaine	N	X.XX	X.XX	X.XX	X.XX
Methamphetamine	N				

[1] Results are obtained from the generalized linear mixed model.

Table 57: Summary of Secondary Outcome Analysis: Week by Treatment Arm

Primary Substance of Use	Study Week	Number of Participants Randomized	Treatment Arm		Results[2]			
			Sham (N=XX)	rTMS (N=XX)				
			Percentage Negative UDS[1]	Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Week 1	N	n/N (XX.X%)	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	Week 2							
	Week 3							
	Week 4							
	Week 5							
	Week 6							
	Week 7							
	Week 8							
Methamphetamine	Week 1							
	Week 2							
	Week 3							
	Week 4							
	Week 5							
	Week 6							
	Week 7							
	Week 8							

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Odds ratio and confidence limit results are obtained from the generalized linear mixed model treatment arm and study week interaction term test for marginal significance. The p-value is obtained from the Type III test for joint significance.

Table 58: Summary of Secondary Outcome Supportive Analyses by Treatment Arm

UDS Results	Treatment Arm	Number of Participants Randomized	Results[2]				
			Percentage Negative UDS[1]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Negative for all substances[3]	Sham	N	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	rTMS						
Negative for stimulants[4]	Sham						
	rTMS						
Negative for primary substance of use[5]	Sham						
	rTMS						

[1] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[2] Results are obtained from the treatment arm term of the generalized linear mixed model.

[3] Substances include: amphetamine, barbiturate, buprenorphine, benzodiazepines, cocaine, ecstasy, fentanyl, marijuana, methamphetamine, methadone, opiates, oxycodone, and phencyclidine.

[4] Substances include: amphetamine, cocaine, and methamphetamine.

[5] Primary substance of use (cocaine or methamphetamine) is assessed at randomization.

Table 59: Summary of Negative UDS Results in Participants with rTMS Session Threshold Met[1] by Treatment Arm

Primary Substance of Use	Treatment Arm	Number of Participants with Threshold Met	Results[3]				
			Percentage Negative UDS[2]	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Cocaine	Sham	N	n/N (XX.X%)	X.XX	X.XX	X.XX	0.xxx
	rTMS						
Methamphetamine	Sham						
	rTMS						
Overall	Sham						
	rTMS						

[1] Participants met the rTMS session threshold if they completed at least 20 rTMS sessions.

[2] Outcome is defined as the percentage calculated by the number of negative UDS divided by the number total UDS performed; it includes the last UDS per study week over the 8-week treatment period in the participant's primary substance of use assessed at randomization. Missing UDS are not imputed.

[3] Results are obtained from the treatment arm term of the generalized linear mixed model.

Table 60: Summary of Secondary Outcome Sensitivity Analysis by Treatment Arm

Method	Results	N	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Protocol defined secondary outcome	Secondary outcome (missing UDS not imputed)	N	X.XX	X.XX	X.XX	0.xxx
Sensitivity analysis: Time	Study Week defined as strict 7-day window					
	Time defined using Study Day					
Imputation of missing UDS	Missing UDS imputed as negative					
	Missing UDS imputed as positive					
	Missing UDS imputed based on self-reported use (TLFB)					
	Multiple imputation					

17.1.8 Safety Outcomes

Table 61: Summary of Adverse Events by Treatment Arm

	Treatment Arm		
	Sham (N=XX)	**rTMS (N=XX)**	**Total (N=XX)**
Number of participants with at least one adverse event (AE)[1]	N (X.X%)		
Maximum severity of AE for participants with at least one AE[2]			
Grade 1 – Mild	N (X.X%)		
Grade 2 – Moderate			
Grade 3 - Severe			
Number of AEs	N		
Severity of AEs[3]			
Grade 1 – Mild	N (X.X%)		
Grade 2 – Moderate			
Grade 3 – Severe			

[1] The percentage is calculated based on the denominator of the number of randomized participants.

[2] The percentage is calculated with the denominator as the number of participants with AEs.

[3] The percentage is calculated with the denominator as the number of AEs.

Table 62: Summary of MedDRA-coded Adverse Events by Treatment Arm

System Organ Class/Preferred Term (MedDRA V26.1)	Treatment Arm		Total (N=XX)
	Sham (N=XX)	rTMS (N=XX)	
Participants with at least one adverse event (AE)	**N (X.X%)**		
Psychiatric disorders	**N (X.X%)**		
Suicidal ideation	N (X.X%)		
Suicide attempt			
Self injurious behavior			
Psychotic disorder			
Depression suicidal			
Depression			
Delirium			
Anxiety			
Affective disorder			
Injury, poisoning and procedural complications	**N (X.X%)**		
Overdose	N (X.X%)		
Multiple fractures			
Burns third degree			
Infections and infestations	**N (X.X%)**		
Cellulitis	N (X.X%)		
Abscess limb			
Pneumonia			
Influenza			
Nervous system disorders	**N (X.X%)**		
Syncope	N (X.X%)		
Seizure			
Facial paresis			
Respiratory, thoracic and mediastinal disorders	**N (X.X%)**		
Respiratory depression	N (X.X%)		
Asthma			
Musculoskeletal and connective tissue disorders	**N (X.X%)**		
Back pain	N (X.X%)		
Metabolism and nutrition disorders	**N (X.X%)**		
Dehydration	N (X.X%)		

Percentages are calculated based on the number of participants experiencing the adverse event at least once as the numerator and the number of participants randomized as the denominator.

Example SOC and PT provided.

Listing 1: Adverse Events by Treatment Arm											
Treatment Arm = Sham											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Alternative Etiology**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None apparent Study disease Concomitant medication Other pre-existing disease or condition Accident, trauma, or external factors Concurrent illness/condition (not pre-existing) Study procedures Other	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxx	xxxxxxxx

SAEs are highlighted in grey.

Listing 1: Adverse Events by Treatment Arm											
Treatment Arm = rTMS											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Alternative Etiology**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None apparent Study disease Concomitant medication Other pre-existing disease or condition Accident, trauma, or external factors Concurrent illness/condition (not pre-existing) Study procedures Other	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxx	xxxxxxxx

Table 63: Summary of Serious Adverse Events by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Number of participants with at least one serious adverse event (SAE)[1]	N (X.X%)		
Number of participants with at least one SAE of the following type[2]			
Congenital anomaly or birth defect	N (X.X%)		
Persistent or significant disability or incapacity			
Death			
Initial or prolonged hospitalization			
Life threatening			
Other serious event (Important Medical Event)			
Number of SAEs	N		
Type of SAE[3]			
Congenital anomaly or birth defect	N (X.X%)		
Persistent or significant disability or incapacity			
Death			
Initial or prolonged hospitalization			
Life threatening			
Other serious event (Important Medical Event)			

[1] The percentage is calculated based on the denominator of the number of randomized participants.

[2] The percentage is calculated with the denominator as the number of participants with SAEs.

[3] The percentage is calculated with the denominator as the number of SAEs.

Table 64: Summary of MedDRA-coded Serious Adverse Events by Treatment Arm

System Organ Class/Preferred Term (MedDRA V26.1)	Treatment Arm		Total (N=XX)
	Sham (N=XX)	rTMS (N=XX)	
Participants with at least one serious adverse event (SAE)	**N (X.X%)**		
Psychiatric disorders	**N (X.X%)**		
Suicidal ideation	N (X.X%)		
Suicide attempt			
Self injurious behavior			
Psychotic disorder			
Depression			
Injury, poisoning and procedural complications	**N (X.X%)**		
Overdose	N (X.X%)		
Multiple fractures			
Burns third degree			
Infections and infestations	**N (X.X%)**		
Cellulitis	N (X.X%)		
Abscess limb			
Pneumonia			
Influenza			
Nervous system disorders	**N (X.X%)**		
Syncope	N (X.X%)		
Seizure			
Facial paresis			
Respiratory, thoracic and mediastinal disorders	**N (X.X%)**		
Respiratory depression	N (X.X%)		
Asthma			
Musculoskeletal and connective tissue disorders	**N (X.X%)**		
Back pain	N (X.X%)		
Metabolism and nutrition disorders	**N (X.X%)**		
Dehydration	N (X.X%)		

Percentages are calculated based on the number of participants experiencing the adverse event at least once as the numerator and the number of participants randomized as the denominator.

Example SOC and PT provided.

Listing 2: Serious Adverse Events by Treatment Arm											
Treatment Arm = Sham											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Alternative Etiology**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None apparent Study disease Concomitant medication Other pre-existing disease or condition Accident, trauma, or external factors Concurrent illness/condition (not pre-existing) Study procedures Other	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxx	xxxxxxxx

Listing 2: Serious Adverse Events by Treatment Arm											
Treatment Arm = rTMS											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Alternative Etiology**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None apparent Study disease Concomitant medication Other pre-existing disease or condition Accident, trauma, or external factors Concurrent illness/condition (not pre-existing) Study procedures Other	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxx	xxxxxxxx

Table 65: Summary of Adverse Device Reactions by Treatment Arm			
	Treatment Arm		
	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Number of participants with at least one adverse device reaction (ADR)[1]	N (X.X%)		
Maximum severity of ADE for participants with at least one ADR[2]			
Grade 1 – Mild	N (X.X%)		
Grade 2 – Moderate			
Grade 3 – Severe			
Number of ADEs	N		
Severity of ADEs[3]			
Grade 1 – Mild	N (X.X%)		
Grade 2 – Moderate			
Grade 3 – Severe			

[1] An adverse device reaction is any adverse event caused by the study device. The percentage is calculated based on the denominator of the number of randomized participants.

[2] The percentage is calculated with the denominator as the number of participants with ADRs.

[3] The percentage is calculated with the denominator as the number of ADRs.

Table 66: Summary of MedDRA-coded Adverse Device Reactions by Treatment Arm			
	Treatment Arm		
System Organ Class/Preferred Term (MedDRA V26.1)	Sham (N=XX)	rTMS (N=XX)	Total (N=XX)
Participants with at least one adverse device reaction	**N (X.X%)**		
General disorders and administration site conditions	**N (X.X%)**		
Medical device site pain	N (X.X%)		
Medical device site discomfort			
Application site discomfort			
Medical device site paraesthesia			
Application site pain			
Chills			
Nervous system disorders	**N (X.X%)**		
Headache	N (X.X%)		
Paraesthesia			
Head discomfort			

Percentages are calculated based on the number of participants experiencing the adverse event at least once as the numerator and the number of participants randomized as the denominator.

Example SOC and PT provided.

Listing 3: Adverse Device Reactions by Treatment Arm											
Treatment Arm = Sham											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Action Taken with the Study Device**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None Decreased rTMS/sham "dose" Temporarily stopped rTMS/sham Permanently stopped rTMS/sham	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxxx	xxxxxxxxx

SAEs are highlighted in grey.

Listing 3: Adverse Device Reactions by Treatment Arm											
Treatment Arm = rTMS											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Action Taken with the Study Device**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None/ Decreased rTMS/sham "dose" Temporarily stopped rTMS/sham Permanently stopped rTMS/sham	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxxx	xxxxxxxxx

SAEs are highlighted in grey.

Table 67: Summary of Unanticipated Adverse Device Effects by Treatment Arm

	Treatment Arm		
	Sham (N=XX)	**rTMS (N=XX)**	**Total (N=XX)**
Number of participants with at least one unanticipated adverse device effect (UADE)[1]	N (X.X%)		
Number of participants with at least one UADE of the following type[2]			
Congenital anomaly or birth defect	N (X.X%)		
Persistent or significant disability or incapacity			
Death			
Initial or prolonged hospitalization			
Life threatening			
Other event (Important Medical Event)			
Number of UADEs	N		
Type of UADE[3]			
Congenital anomaly or birth defect	N (X.X%)		
Persistent or significant disability or incapacity			
Death			
Initial or prolonged hospitalization			
Life threatening			
Other event (Important Medical Event)			

[1] The percentage is calculated based on the denominator of the number of randomized participants.

[2] The percentage is calculated with the denominator as the number of participants with UADEs.

[3] The percentage is calculated with the denominator as the number of UADEs.

Table 68: Summary of MedDRA-coded Unanticipated Adverse Device Effects by Treatment Arm

System Organ Class/Preferred Term (MedDRA V26.1)	Treatment Arm		Total (N=XX)
	Sham (N=XX)	rTMS (N=XX)	
Participants with at least one unanticipated adverse device effect	**N (X.X%)**		
General disorders and administration site conditions	**N (X.X%)**		
Medical device site pain	N (X.X%)		
Medical device site discomfort			
Application site discomfort			
Medical device site paraesthesia			
Application site pain			

Percentages are calculated based on the number of participants experiencing the adverse event at least once as the numerator and the number of participants randomized as the denominator.

Example SOC and PT provided.

Listing 4: Unanticipated Adverse Device Effects by Treatment Arm											
Treatment Arm = Sham											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Action Taken with the Study Device**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None Decreased rTMS/sham "dose" Temporarily stopped rTMS/sham Permanently stopped rTMS/sham	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxxx	xxxxxxxxx

SAEs are highlighted in grey.

Listing 4: Unanticipated Adverse Device Effects by Treatment Arm											
Treatment Arm = rTMS											
										MedDRA V26.1	
Site	**Participant ID**	**Date of Randomization**	**Onset Date**	**AE Description**	**Severity of AE**	**Action Taken with the Study Device**	**Outcome**	**Date of Resolution/ Medically Stable**	**SAE Associated With**	**Preferred Term**	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxx	Grade 1 – Mild Grade 2 – Moderate Grade 3 – Severe	None Decreased rTMS/sham "dose" Temporarily stopped rTMS/sham Permanently stopped rTMS/sham	Recovering/ resolving Recovered/ resolved Recovering/ resolved with sequelae Not recovered/ not resolved Fatal Unknown	mm/dd/yyyy	Congenital anomaly or birth defect Persistent or significant disability or incapacity Death Initial or prolonged hospitalization Life threatening Other serious event (Important Medical Event)	xxxxxxxxx	xxxxxxxxx

SAEs are highlighted in grey.

Table 69: Summary of CHRT – Participant Rated by Treatment Arm				
Major Depressive Episode[1]	**Number with suicide ideation/intent on CHRT-SR[2,3]**	**Treatment Arm**		**Total (N=XX)**
		Sham (N=XX)	**rTMS (N=XX)**	
Absent	During screening	N (X.X%)	N (X.X%)	N (X.X%)
	During treatment period			
	During follow-up period			
Present	During screening			
	During treatment period			
	During follow-up period			
Overall	During screening			
	During treatment period			
	During follow-up period			

[1] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

[2] Concise Health Risk Tracking-Participant Rated (CHRT-SR). Suicide ideation/intent on CHRT is defined as a response of “Agree” or “Strongly Agree” on any of CHRT-SR questions 14, 15 or 16: In the past week “I have been having thoughts of killing myself”, “I have thoughts about how I might kill myself” or “I have a plan to kill myself”.

[3] Unique randomized participants with suicidal ideation/intent, at least once during the treatment and/or follow-up period. Denominator is the number randomized.

Listing 5: CHRT[1] Participant Rated by Treatment Arm								
Treatment Arm = Sham								
Site	**Participant ID**	**Date of Randomization**	**Major Depressive Episode[2]**	**Visit**	**Date of Assessment**	**I have been having thoughts of killing myself**	**I have thoughts about how I might kill myself**	**I have a plan to kill myself**
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	Absent/ Present	Screening Week 1 A1 Week 1 A2 etc.	mm/dd/yyyy	Strongly Disagree Disagree Neither Agree nor Disagree/ Agree Strongly Agree	Strongly Disagree Disagree Neither Agree nor Disagree Agree Strongly Agree	Strongly Disagree Disagree Neither Agree nor Disagree Agree Strongly Agree

All visits are included for randomized participants who answered, 'Agree' or 'Strongly Agree'. Responses of 'Agree' are highlighted in orange and 'Strongly Agree' are highlighted in red.

[1] Concise Health Risk Tracking – Participant Rated (CHRT-SR) form.

[2] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

Listing 5: CHRT[1] Participant Rated by Treatment Arm								
Treatment Arm = rTMS								
Site	**Participant ID**	**Date of Randomization**	**Major Depressive Episode[2]**	**Visit**	**Date of Assessment**	**I have been having thoughts of killing myself**	**I have thoughts about how I might kill myself**	**I have a plan to kill myself**
xxxxxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	Absent/ Present	Screening Week 1 A1 Week 1 A2 etc.	mm/dd/yyyy	Strongly Disagree Disagree Neither Agree nor Disagree Agree Strongly Agree	Strongly Disagree Disagree Neither Agree nor Disagree Agree Strongly Agree	Strongly Disagree Disagree Neither Agree nor Disagree Agree Strongly Agree

All visits are included for randomized participants who answered 'Agree' or 'Strongly Agree'. Responses of 'Agree' are highlighted in orange and 'Strongly Agree' are highlighted in red.

[1] Concise Health Risk Tracking – Participant Rated (CHRT-SR) form.

[2] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

Table 70: Summary of CHRT – Clinician Rated by Treatment Arm					
Major Depressive Episode[1]	**Time Period**	**Suicidal Ideation/Attempt**	**Treatment Arm**		**Total (N=XX)**
			Sham (N=XX)	**rTMS (N=XX)**	
Absent	Screening	Number with passive suicide ideation	N (X.X%)	N (X.X%)	N (X.X%)
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Treatment Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Follow-up Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
Present	Screening	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Treatment Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Follow-up Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			

Table 70: Summary of CHRT – Clinician Rated by Treatment Arm

Major Depressive Episode[1]	Time Period	Suicidal Ideation/Attempt	Treatment Arm		Total (N=XX)
			Sham (N=XX)	rTMS (N=XX)	
Overall	Screening	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Treatment Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			
	Follow-up Period	Number with passive suicide ideation			
		Number with active/non-specific suicidal ideation			
		Number with active suicidal ideation with method			
		Number with active suicidal ideation with method and intent			
		Number with active suicidal ideation with method, intent, and plan			
		Number with suicide attempt reported			

Concise Health Risk Tracking- Clinician Rated Module (CHRT- CR) will be performed by the Medical Clinician only if a participant endorses any of questions 14 -16 on the CHRT-SR as “Agree” or “Strongly agree”. Percentage within the time period is calculated as the number of unique randomized participants with the specified type of suicidal ideation/attempt at least once during the week prior to the visit where the assessment occurs, divided by the number of participants randomized.

[1] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

Listing 6: CHRT[1] Clinician Rated by Treatment Arm											
Treatment Arm = Sham											
						Suicidal Ideation					
Site	**Participant ID**	**Date of Random-ization**	**Major Depressive Episode[2]**	**Visit**	**Date of Assessment**	**Passive**	**Active/ Non-specific**	**Active with Method**	**Active with Method and Intent**	**Active with Method, Intent and Plan**	**Suicide Attempt Reported**
xxxxxxxxx	xxxxxxxxxx	mm/dd/yyyy	Absent/ Present	Screening Week 1 A1 Week 1 A2 etc.	mm/dd/yyyy	No/Yes	No/Yes	No/Yes	No/Yes	No/Yes	No/Yes

All visits are included for randomized participants who answered, 'Agree' or 'Strongly Agree' to any of the Concise Health Risk Tracking - Participant Rated (CHRT-SR) questions 14, 15 or 16: In the past week "I have been having thoughts of killing myself", "I have thoughts about how I might kill myself" or "I have a plan to kill myself".

[1] Concise Health Risk Tracking – Clinician Rated Module (CHRT-CR) form.

[2] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline.

Listing 6: CHRT[1] Clinician Rated by Treatment Arm											
Treatment Arm = rTMS											
						Suicidal Ideation					
Site	**Participant ID**	**Date of Random-ization**	**Major Depressive Episode[2]**	**Visit**	**Date of Assessment**	**Passive**	**Active/ Non-specific**	**Active with Method**	**Active with Method and Intent**	**Active with Method, Intent and Plan**	**Suicide Attempt Reported**
xxxxxxxxx	xxxxxxxxxx	mm/dd/yyyy	Absent/ Present	Screening Week 1 A1 Week 1 A2 etc.	mm/dd/yyyy	No/Yes	No/Yes	No/Yes	No/Yes	No/Yes	No/Yes

All visits are included for randomized participants who answered, 'Agree' or 'Strongly Agree' to any of the Concise Health Risk Tracking - Participant Rated (CHRT-SR) questions 14, 15 or 16: In the past week "I have been having thoughts of killing myself", "I have thoughts about how I might kill myself" or "I have a plan to kill myself".

[1] Concise Health Risk Tracking – Clinician Rated Module (CHRT-CR) form.

[2] Current Major Depressive Episode is assessed via the Mini International Neuropsychiatric Interview at baseline'.

Listing 7: Pregnancies by Treatment Arm							
Treatment = Sham							
Site	**Participant ID**	**Date of Randomization**	**Date Staff Aware of Pregnancy**	**Date Pregnancy Confirmed**	**Date of Pregnancy Outcome**	**Pregnancy Outcome**	**Normal Infant?**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	Vaginal delivery Cesarean delivery Miscarriage Termination Other Unknown	Yes/No

Listing 7: Pregnancies by Treatment Arm							
Treatment = rTMS							
Site	**Participant ID**	**Date of Randomization**	**Date Staff Aware of Pregnancy**	**Date Pregnancy Confirmed**	**Date of Pregnancy Outcome**	**Pregnancy Outcome**	**Normal Infant?**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	Vaginal delivery Cesarean delivery Miscarriage Termination Other Unknown	Yes/No

Listing 8: Deaths by Treatment Arm					
Treatment Arm = Not Randomized					
Site	**Participant ID**	**Date of Death**	**Description**	**MedDRA V26.1**	
				Preferred Term	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxx

Listing 8: Deaths by Treatment Arm						
Treatment Arm = Sham						
Site	**Participant ID**	**Date of Randomization**	**Date of Death**	**Description**	**MedDRA V26.1**	
					Preferred Term	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxx

Listing 8: Deaths by Treatment Arm						
Treatment Arm = rTMS						
Site	**Participant ID**	**Date of Randomization**	**Date of Death**	**Description**	**MedDRA V26.1**	
					Preferred Term	**System Organ Class**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxx

17.1.9 Data Quality

Table 71: Summary of Data Audits

Site	Date of Audit	Total Fields Audited[1]	Total Data Discrepancies[2]	Error Rate
Site 1	mm/dd/yyyy	N	N	X.XX%
	Subtotal			
Site 2				
Site 3				
Site 4				
Total				

[1] Fields reviewed at monitoring visit comparing the database to source documentation.

[2] Fields discrepant between database and source documentation.

17.1.10 Protocol Deviations

Table 72: Summary of Protocol Deviations

	Site 1	Site 2	Site 3	Total
Total number of protocol deviations	N			
Number of participants impacted per protocol deviation				
None	N (X.X%)			
One				
More than one				
Total number of major protocol deviations	N			
Type of major protocol deviation				
No consent/assent obtained	N (X.X%)			
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent				
Non-IRB approved/outdated/obsolete informed consent/assent documents used				
Ineligible participant randomized/inclusion/exclusion criteria not met or eligibility not fully assessed prior to randomization				
Study assessments/procedures not followed in accordance with the study protocol				
Inappropriate unblinding				
AE not reported				
SAE not reported				
AE/SAE reported out of protocol specified reporting timeframe				
AE/SAE not elicited, observed and/or documented as per protocol				
Safety assessment (e.g., labs, ECG, clinical referral to care) not conducted per protocol				
Stratification error				
Participant use of protocol prohibited medication				
Study behavioral intervention was not provided/performed as per protocol				
Study devices dispensed to ineligible participant				
Destruction of study materials without prior authorization from sponsor				
Breach of Confidentiality				
Other informed consent/assent procedures issues				
Other inclusion/exclusion criteria issues				
Other laboratory assessments issues				
Other study procedures/assessments issues				
Other adverse events issues				
Other randomization procedures issues				

Table 72: Summary of Protocol Deviations				
	Site 1	**Site 2**	**Site 3**	**Total**
Other study behavioral intervention issues				
Other study device issues				
Other significant deviations issues				
Total number of minor protocol deviations	N			
Type of minor protocol deviation				
No consent/assent obtained				
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent				
Non-IRB approved/outdated/obsolete informed consent/assent documents used				
Ineligible participant randomized/inclusion/exclusion criteria not met or eligibility not fully assessed prior to randomization				
Study assessments/procedures not followed in accordance with the study protocol				
Inappropriate unblinding				
AE not reported				
SAE not reported				
AE/SAE reported out of protocol specified reporting timeframe				
AE/SAE not elicited, observed and/or documented as per protocol				
Safety assessment (e.g. labs, ECG, clinical referral to care) not conducted per protocol				
Stratification error				
Participant use of protocol prohibited medication				
Study behavioral intervention was not provided/performed as per protocol				
Study devices dispensed to ineligible participant				
Destruction of study materials without prior authorization from sponsor				
Breach of Confidentiality				
Other informed consent/assent procedures issues				
Other inclusion/exclusion criteria issues				
Other laboratory assessments issues				
Other study procedures/assessments issues				
Other adverse events issues				
Other randomization procedures issues				
Other study behavioral intervention issues				
Other study device issues				
Other significant deviations issues				

Listing 9: Protocol Deviations												
Deviation Category = Category Name 1												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Major PDs are Highlighted in grey.

Listing 9: Protocol Deviations												
Deviation Category = Category Name 2												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Major PDs are Highlighted in grey.

Listing 9: Protocol Deviations												
Deviation Category = …												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Major PDs are Highlighted in grey.