Neuronetics

COMFORT START

A PROSPECTIVE, RANDOMIZED, SINGLE BLIND, CROSSOVER STUDY TO EVALUATE TREATMENT EFFECTS ASSOCIATED WITH THE NEUROSTAR SOFTSTART™ TREATMENT FEATURE

Neuronetics Protocol Number: 44-03054-000

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1 CONTACT INFORMATION

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2 INVESTIGATOR AGREEMENT

1. I have read this protocol and agree that it contains all necessary details for conducting the study as described.

2. I will conduct this investigation in accordance with the agreement, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the Institutional Review Board (IRB) and FDA.

3. I will provide a copy of my current curriculum vitae including a summary of my relevant clinical experience for the conduct of this trial.

4. I will maintain all confidentiality.

5. I will supervise all testing of the device involving human subjects.

6. I will ensure that all study personnel are appropriately trained and that they have access to all relevant documents related to the investigations, as furnished by the sponsor.

7. I will assure that all requirements of informed consent are met for subjects participating in these studies.

8. I will not enroll subjects in research under this Agreement prior to its review and approval by the IRB.

9. I acknowledge that I am primarily responsible for safeguarding the rights and welfare of each research subject, and that the subject's rights and welfare must take precedence over the goals and requirements of the research.

10. I will abide by all determinations of the Institutional Review Board (IRB).

11. I will complete any educational training required by the Institution and/or the IRB prior to initiating research covered under this Agreement.

12. The Investigator will report promptly to the IRB any unanticipated problems involving risks to subjects or any proposed changes in the research conducted under this Agreement. The investigator will not initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

_____ _____

Investigator Signature Date

_____ _____

Investigator Signature Date

3 INSTITUTIONAL REVIEW BOARD (IRB)

The name, address, and contact of the IRB used in this study is identified below.

IRB:	WCG IRB
Address:	1029 39th Ave SE, Suite120
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Contact:	clientservices@wcgirb.com 855-818-2289

5 DISCLOSURE STATEMENT

This protocol (Neuronetics protocol number 44-03054-000) contains information that is confidential and proprietary to the sponsor. It is being provided to you for the sole purpose of evaluating and/or conducting a clinical trial for the sponsor. You may disclose the contents of this document only to study personnel under your supervision, IRBs, or duly authorized representatives of the U.S. FDA for this purpose under the condition that they maintain confidentiality.

The contents of this protocol may not be used in any other device trial, disclosed to any other person or entity, and/or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsor of any such disclosure.

Any information that may be added to this protocol is also confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this protocol.

6 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
CNS	Central nervous system
CPR	Cardiopulmonary resuscitation
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
CSA	Clinical study agreement
ECT	Electroconvulsive therapy
EMG	Electromyography
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ITT	Intent-to-Treat
IRB	Institutional review board
ISTS	International Society for Transcranial Stimulation
l-DLPFC	Left dorsolateral prefrontal cortex
MDD	Major depressive disorder
MEP	Motor evoked potentials
MT	Motor threshold
NINDS	National Institute of Neurological Disorders and Stroke
NSR	Not significant risk
PRN	Pro re nata (as needed)
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious adverse event
SR	Significant risk
SOC	Standard of Care
TASS	Transcranial magnetic stimulation adult safety screen
TEAE	Treatment-emergent adverse event
TMS	Transcranial magnetic stimulation
US	United States
VAS	Visual analog scale

7 STUDY SYNOPSIS

Study Title:	Comfort Start: A Prospective, Randomized, Single Blind, Crossover Study to Evaluate Treatment Effects Associated with the NeuroStar SoftStart™ Treatment Feature
Study Rationale:	SoftStart is an exclusive feature available on the NeuroStar® Advanced Therapy System. This feature introduces a series of stepped pulses within each pulse train ramping up the pulse magnitude to the prescribed treatment level. The study hypothesizes that altering the pulse magnitude in this way will provide patients a more comfortable treatment and assist in reaching the prescribed treatment intensity with less discomfort or in a shorter time.
Trial Design:	This is a randomized, single center, single blind study conducted in an adult population being treated for MDD. Eligible subjects will have already been determined suitable to receive rTMS stimulation for MDD as assessed against the established inclusion and exclusion criteria by their independent physician. Eligible subjects will sign the informed consent form for participation. Each subject will be treated with rTMS for MDD as diagnosed and prescribed by their treating physician. Following consent and successful study qualification, study subjects will be randomized to the standard Dash protocol or the modified Dash protocol with the SoftStart feature enabled. After reaching the prescribed treatment level with the first treatment protocol per the randomization schedule, the subject will then be switched to the alternative treatment protocol for the next day's treatment. This treatment alternation will continue 3 more times. During treatments, the subject will be asked to complete several questionnaires, including comfort/pain, treatment preference, and depression questionnaires.
Approximate Duration of Subject Participation:	Up to approximately 14 days, one hour for screening and 30 minutes during each daily treatment session.
Approximate Duration of Study:	Approximately 4-6 Months

Study Objectives:	*Primary:* The Primary objective is to evaluate the comfort associated with TMS treatment when applied with the standard Dash treatment protocol vs. the Dash protocol with the SoftStart feature enabled. *Secondary:* The Secondary objectives include the ability to reach the prescribed treatment intensity, the time it takes to reach the prescribed intensity, maximum treatment intensity reached, subject treatment preference and discontinuations due to treatment discomfort between the two treatment protocols.
Criteria for Inclusion:	1. 22-70 years of age. 2. Subject qualifies to receive TMS Therapy with the NeuroStar Advanced Therapy System to treat Major Depressive Disorder (MDD) per current FDA-cleared treatment guidelines as evaluated by the treating physician. 3. Subject has MDD diagnosis according to applicable DSM-IV, DSM-IV-TR, DSM-V, ICD-9, or ICD-10 criteria. 4. Subject failed to respond to at least one prior anti-depressant medication. 5. Subject consented to receive TMS Therapy to treat MDD with his or her physician independent of potential participation in this clinical study. 6. Subject must agree not to take analgesic pain medication(s) within 8 hours prior to TMS therapy sessions. 7. Subject provides written consent to take part in the study.
Criteria for Exclusion:	1. Subject satisfies any one or more of the contraindications for TMS Therapy per current treatment guidelines as determined by the PI. 2. Physician intends to treat the subject with an off-label TMS Therapy or indication. 3. Family history of seizures or epilepsy. 4. Subject has received prior TMS. 5. Subject is currently taking analgesic medication or substances which may affect their perception or sensation of pain. 6. Known or suspected pregnancy.
Approximate Number of Subjects:	40 Subjects will be enrolled in the study: - 20 Initially Randomized to Dash Protocol - 20 Initially Randomized to Dash Protocol with SoftStart
Number of Study Centers:	1

Device Description:	NeuroStar® Advanced Therapy System is a Medical Device that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex.
Treatment Effect Evaluations:	Subject Comfort will be evaluated using the Visual Analog Scale assessing Comfort following rTMS stimulation. Depression will be evaluated by PHQ-9. Preference will be evaluated by asking the patient if they prefer the current treatment, last treatment, or if they cannot determine a difference.
Safety Evaluation:	Safety will be monitored by comparing the type, frequency, and severity of adverse events as occurring during the different treatment protocol administrations.
Statistical Analysis:	Endpoints will be analyzed for statistical and clinical significance.

8 SCHEDULE OF EVENTS

			Dose Ramp Phase					Crossover Phase			
Study Visits	**Screening and Baseline**		**1[AB]**	**2[F]**	**3[F]**	**4[F]**	**5[F]**	**1[C,D]**	**2[C,D]**	**3[C,D]**	**4[C,D]**
Patient Visit SOC	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Informed Consent	X		X								
Medical History & Medications	X										
Inclusion and Exclusion Criteria	X										
Randomization			X								
Motor Threshold Determination[E]			X								
Study Exit											X
TMS Treatment Session - SOC			X	X	X	X	X	X	X	X	X
Efficacy Assessments											
VAS (comfort and pain)[G]			X	X	X	X	X	X	X	X	X
Subject Preference [H]				X	X	X	X	X	X	X	X
PHQ-9 [H]			X								X
Safety Assessments											
Adverse Events			X	X	X	X	X	X	X	X	X
Medication changes				X	X	X	X	X	X	X	X

[A] The stimulation dose for the DLPFC is determined by the physician

[B] The stimulation protocol is randomized to treatment X or Treatment Y

[C] The stimulation protocol is alternated between treatment X or Treatment Y

[D] The stimulation protocol preference of treatment X or Treatment Y is determined by the subject

[E] Motor Threshold Determination will be completed as SOC and not dictated by the study procedures

[F] Study procedures for treatment visits 2-5 are only completed if the patient does not achieve target %MT and sustain that intensity for 3:45 min; Once achieved, subject will begin Crossover phase at the next visit

[G] Assessments completed at minute 3:45 of treatment and end of treatment

[H] Assessments completed at the end of treatment visits

9 CLINICAL SECTION

9.1 Introduction TMS and SoftStart

Repetitive transcranial magnetic stimulation (rTMS) is defined as the administration of a series of magnetic stimuli to the brain for the purpose of altering brain function. NeuroStar transcranial magnetic stimulation (TMS) Therapy was FDA cleared in 2008 for the treatment of major depressive disorder in adult patients who have not received benefit from prior medication. This procedure is non-invasive, does not require anesthesia, and may be delivered in an appropriately staffed outpatient setting. Although generally regarded as safe and without lasting adverse effects, patients treated with rTMS may experience minor side effects. The most common side effects are discomfort due to stimulation of the scalp musculature under the site of stimulation and muscle tension headaches which may persist for 1-2 hours post stimulation.[8,9] These effects are thought to be due to the direct activation of muscles and nerves near the stimulating coil and both duration and intensity of stimulation impact the incidence of these effects.

Stimulus intensity is based on individually determined resting motor threshold (RMT or MT, minimum intensity to elicit muscle twitches at relaxed upper or lower extremities, by visual inspection or electromyography). The recommended stimulation intensity range is 110-120% MT. [21] According to the original NeuroStar protocol, after determining the MT, a treatment session included stimulation at 120% motor threshold with a pulse sequence of 10 Hz for 4 seconds, followed by a 26 second inter-train interval (quiet period). A session lasted for a total of 37.5 minutes with a total of 3,000 pulses. A full NeuroStar treatment includes 30 daily sessions over 6 weeks with an additional 6 session ramp down over 3 weeks for a total of 9 weeks.[15] In clinical practice, during the first 5-10 treatment sessions clinicians typically “ramp up” patients to the prescribed treatment intensity (% MT) to minimize side effects. Treatment sessions often start at 80-90% MT and stimulation intensity is increased to the prescribed level based on individual patient tolerance.

Over time, cumulative clinical trial experience has revealed that a variety of alterations to the stimulation protocols, delivering different doses and timing of stimulation, can produce beneficial antidepressant effect without jeopardizing safety.[10] In 2016, FDA cleared a new treatment protocol termed “Dash”. The Dash protocol was introduced to improve the acceptability and convenience of TMS therapy by reducing the duration of a 3000-pulse session to as short as 18.75 minutes, which is half the time required for the Standard protocol FDA cleared in 2008.

In 2021, several optional features were added to the NeuroStar TMS system including a feature called “SoftStart”. When enabled, SoftStart introduces a series of stepped pulses within each pulse train which alters the pulse magnitude during the beginning and ending of a treatment pulse train. The pulse train gradually increases (ramps up) in magnitude (MT Level) until the prescribed MT treatment level has been obtained. At the conclusion of the 40 pulses in the train at the prescribed MT level, a series of pulses ramp down before the intertrain interval rest period begins. For some patients, sensitivity at the treatment site can cause discomfort and studies have been conducted to investigate ways to improve patient comfort and prevent dropout due to intolerance of treatment.[21] Patient intolerance can not only increase drop-out but also prevent patients from reaching the prescribed dose or reduce the number of treatments delivered at the prescribed dose. For accurate, safe, and effective application of brain stimulation, it is essential that an appropriate level of electric current be induced within a target region. Under stimulation reduces the probability of detecting significant results and deprives patients of necessary treatment dosages.[20] By ramping pulses from 60% to 100% of the programmed treatment level, SoftStart was designed to improve treatment comfort, which could also allow patients to reach the prescribed treatment intensity more easily or reach that intensity in a shorter time which will provide patients with a greater percentage of their pulses at the full prescribed dose.

The objective of this study is to evaluate the effect of SoftStart on patient comfort when treated with TMS for major depression. The impact of SoftStart on the ability and the time taken to reach the prescribed dose of TMS and other secondary factors associated with patient comfort will also be evaluated.

10 STUDY DESIGN

10.1 General Description

This study is a prospective, randomized, single blind study to be conducted in 40 adults who have been prescribed treatment for MDD with rTMS. The study will be performed at a single site, where MDD patients, if eligible, may provide consent and participate. Prior to rTMS stimulation, the Motor Threshold (MT) will be established for each subject individually. Each subject will be evaluated for up to 2 weeks during their normal TMS treatment protocol, then exited from the study. The total study duration is expected to be approximately 6 months depending upon enrolment rate. The goal of the study is to monitor and compare patient comfort (treatment area sensitivity) using two different treatment protocols at the start of TMS

therapy where the stimulation intensity is typically escalated over 1-10 treatments until the patient is comfortable with the prescribed treatment dose (% MT; typically, 120%).

Each subject will be treated with rTMS for MDD as diagnosed and prescribed by their treating physician. All study visits will occur during the subject's normal pre-treatment evaluation and within the first 10 TMS treatment sessions. Study questionnaires will be administered during screening and during each treatment to evaluate the subject's perception of comfort specifically related to the TMS therapy provided that day.

Patients will be randomized after consent to receive either the standard Dash protocol (Treatment Y) or the modified Dash protocol with the SoftStart feature enabled (Treatment X). During all treatments, the subject will be blinded to whether they are receiving "Treatment X" or "Treatment Y".

Ramp Phase:

Since during the first few treatment sessions patients are typically ramped up to the desired treatment intensity (%MT) in a subjective manner by the treater, this process will be standardized during the study to minimize this confounding factor on perception of comfort. For all treatments, the first session will begin at 90% MT and the treater will ask the subject if they can tolerate the treatment intensity at 5 equal time intervals per treatment session (a treatment interval is 3 minutes and 45 seconds (3:45)). If tolerance is acceptable, the treater will increase the treatment intensity by 10% with the objective of reaching 120% by the end of the first treatment session. Dosage escalations during treatment will be limited to these 5 equal time intervals; however, dosage decreases can be done at any point due to patient intolerance. Treatment intensity changes will not be communicated to the subject. The treatment intensity achieved at each interval will be logged and documented in the study CRF. After the first interval (3:45), and after each stimulation session the subject will be asked to complete a "Comfort/Pain" VAS scale from (0-10cm). Once the subject completes the last 3:45 of a treatment session at 120%MT, they will begin their Crossover phase at the start of the next session. If a subject does not reach 120% MT by the end of the fifth treatment session, dose escalation attempts will continue, but they will transition to the Crossover phase. Refer to Attachment D for details of the Dose Escalation process.

Crossover Phase:

At the start of the 6th Treatment session or the session after the subject reaches the prescribed dose, the subject will be crossed over to the alternative treatment protocol and continue to alternate treatment each day for the next 3 treatments. Each day of these 4 treatment sessions,

at the first time interval (3:45) and the end of the session the subject will complete the comfort/pain questionnaire and be asked whether they preferred the current treatment, or the treatment received at the previous session (Todays Treatment, Last Treatment, No Difference).

After the final study treatment, the treatment protocol planned for remaining TMS sessions, and reason for choosing it, will be documented as a secondary study endpoint and the subject will be exited from the study. All further treatments will be conducted at the discretion of the treating physician. After the full study is over, subjects may be informed of the actual difference in treatments they received but will be informed that other patients may have received different treatments and the assignment was randomized.

Subjects will be encouraged to complete the study, however, upon request, subjects may discontinue the study and protocol assigned treatment at any time. The treatment protocol for further TMS sessions will be determined by the clinician and the patient as part of their normal care.

10.2 Treatment Selection, Risk and Discontinuation

In this study, only patients who are prescribed and treated with the Dash protocol (rTMS stimulation in the Left Dorsolateral Prefrontal Cortex (L-DLPFC)) are eligible to participate the study. In clinical practice the choice to utilize the SoftStart feature with Dash is up to the treating physician.

In this study, initial treatment with the Dash protocol or Dash with the SoftStart feature enabled will be assigned by randomization. Both these treatment options are commercially available, and none of the treatment parameters required by the study are experimental. The protocol requirement of randomization and all subjects alternating between SoftStart and standard Dash treatments will not impose additional risk to the subject other than the potential for minor additional discomfort for those patients who receive the first few treatments with the standard Dash protocol when they may have been treated with the SoftStart feature if not part of this study.

MT determinations and rTMS stimulation sessions will be administered under the supervision of the study physician. Patients may discontinue the study, in consultation with their treating physician, at any time. All personnel performing these specific activities must have clinical experience sufficient to provide immediate clinical support in the event of a seizure, or other adverse events.

11 STUDY OBJECTIVES

11.1 Primary Objective

The Primary objective is to evaluate the comfort associated with TMS treatment when applied with the standard Dash treatment protocol vs. the Dash protocol with the SoftStart feature enabled.

11.2 Secondary Objectives

The Secondary objectives are to evaluate the ability to reach the prescribed treatment intensity, the time it takes to reach the prescribed treatment intensity, maximum treatment intensity reached, patient treatment preference and other treatment effects between the two treatment protocols.

12 STUDY POPULATION

12.1 Number of Subjects

40 subjects will be enrolled and randomized to one of two treatment arms.

12.2 Inclusion Criteria

To be eligible to participate in this study, healthy volunteers must meet the following criteria:

1. Subject is 22 years of age to 70 years of age.
2. Subject qualifies to receive TMS Therapy with the NeuroStar Advanced Therapy. System to treat Manic Depressive Disorder (MDD) per current FDA-cleared treatment guidelines as evaluated by the treating physician.
3. Subject has MDD diagnosis according to applicable DSM-IV, DSM-IV-TR, DSM-V, ICD-9, or ICD-10 criteria.
4. Subject failed to respond to at least one prior anti-depressant medication.
5. Subject consented to receive TMS Therapy to treat MDD with his or her physician. independent of potential participation in this clinical study.
6. Subject must agree not to take analgesic pain medication(s) within 8 hours prior to TMS therapy sessions.
7. Subject provides written consent to take part in the study.

12.3 Exclusion Criteria

Any of the following will exclude a subject from the study:

1. Subject satisfies any one or more of the contraindications for TMS Therapy per current treatment guidelines as determined by the treating physician.
2. Physician intends to treat the subject with an off-label TMS Therapy or indication.
3. Subject has a family history of seizures or epilepsy.
4. Subject has received prior TMS therapy.
5. Subject is currently taking analgesic medication or substances which may affect their perception or sensation of pain.
6. Known or suspected pregnancy.

13 STUDY PROCEDURES

13.1 Study Visits

This is a prospective, randomized, single blind, cross-over study in an adult population. Only patients who have already consented to treatment with rTMS for MDD as diagnosed and prescribed by their treating physician will be enrolled in this study.

The study consists of up to 10 visits; Visit 1 for subject screening and Visits 2-10 for treatment administration which will be conducted concurrently with the subjects scheduled rTMS stimulation sessions. Study visits are estimated to take approximately 30 minutes in addition to the patient's regular rTMS treatment visits.

The study visits will be conducted in 2 phases:

Ramp Phase: The intent of the first 1-5 treatment visits is to evaluate the differences between treatment groups on subject comfort as the subjects are ramped to the prescribed treatment dose. This phase will also evaluate the impact of the two treatments on the ability and the time to achieve the prescribed treatment dose.

Crossover Phase: The intent of the crossover phase is to evaluate comfort differences and subject treatment preference between treatment groups and within subjects. In addition, the ability, and the time to reach the prescribed dose for those subjects who may not have reached it in the first 5 treatment sessions will continue to be assessed.

Details of the study visits are described below and on the subject flow diagram in section 14.2.

Screening/Baseline Study Visit

During Visit 1, the subject will be informed about the study and will be screened for eligibility to participate against the inclusion and exclusion criteria (including medication and medical

history). Eligible subjects will have the study and consent process explained to them and be provided the informed consent form to sign, or to return signed on Day 1 of TMS Treatment.

Ramp Phase:

Treatment Visit 1

Once signed consent is obtained, in addition to the treating clinicians' normal TMS instruction, subjects will receive instruction about the study procedures including the completion of comfort, preference and depression scales at the time of treatment for up to 9 treatments. Medication changes and recent medical history, including adverse events will be reviewed.

Next, the PHQ-9 questionnaire will be completed, and subjects will have their Motor Threshold determined by the standard of care practice of the treating clinician and be randomized to receive their first rTMS stimulation with either treatment X or treatment Y.

The %MT treatment goal of 120% will be established by the physician. Subjects will have their Motor Threshold determined by the standard of care practice of the treating clinician and the first stimulation will be programmed to begin at 90% MT. Subjects will then be randomized to rTMS stimulation with either treatment X or treatment Y and have their first randomized stimulation treatment with the NeuroStar TMS Therapy System. Subject MT may be re-established and documented at the discretion of the treating physician at any time.

Treatment Assessments: Once TMS therapy begins, adjustments to lower the stimulation intensity can begin immediately, as needed, for subject tolerance. Every 3:45 minutes the TMS treater will assess if the subject can tolerate escalating the treatment MT by 10%. At each interval and the end of treatment, the treater will record the current %MT achieved. The goal will be to reach and sustain the target MT established by the treating physician of 120%MT. Once the target MT has been achieved and sustained for 3:45 minutes, recording and increases of %MT may be discontinued, but re-started at 3:45 minute intervals if %MT is subsequently reduced.

At minute 3:45, and at the end of the treatment session, the subject will be asked to complete a Visual Analog Scale (VAS), for Comfort/Pain.

If the subject reaches the prescribed %MT at Treatment Visit 1, the next study visit will be the start of the crossover phase of the study (Crossover Treatment 1), if not, they will continue to the next visit of the Ramp Phase.

Treatment Visits 2-5

Subjects will start treatment at the %MT established in the previous session and all study treatment procedures completed on Treatment Visit 1 will be repeated and documented for Treatment Visits 2-5. In addition, at the first time interval of 3:45, subjects will be asked a preference question - if they prefer the current treatment, last treatment, or if they cannot determine a difference. This question will be repeated at the end of the treatment visit.

If the subject reaches the prescribed %MT at any of these visits and sustains that MT through the final 3:45 minute time interval, the next study visit will be the start of the crossover phase of the study (Crossover Treatment 1). If the subject does not achieve the prescribed MT by the end of the 5th Treatment session, they will continue to Crossover Treatment 1 at the next visit, however, attempts to achieve the prescribed %MT should continue and be documented.

Crossover Phase

Visit 1

Subjects will be crossed over to the alternative treatment protocol, those who had received treatment X will then receive treatment Y and vice versa. Subjects will start treatment at the %MT established in the previous session and all study treatment assessments completed on Treatment Visits 2-5 of the Ramp Phase will be repeated and documented for each visit of the Crossover Phase.

Visits 2-4

Subjects will be crossed over to the alternative treatment protocol, those who had received treatment X will then receive treatment Y and vice versa. At the start of treatment, subjects will start treatment at the %MT established in the previous session and all study treatment assessments completed on Crossover visit 1 will be repeated.

Visit 4: Final Crossover Visit

At the start of treatment for Crossover visit 4, subjects will be crossed over to the alternative treatment protocol, subjects will start treatment at the %MT established in the previous treatment and all study treatment assessments completed on Crossover visit 1 will be repeated.

At the end of the final treatment, the treatment protocol for further TMS sessions will be determined by the clinician and the patient as part of their normal care. The treatment choice will be documented, and the subject will be exited from the study. See subject flow diagram in section 14.2 for additional information.

13.2 Discontinuation and Withdrawal of Subjects

Subjects may withdraw voluntarily from the study at any time. They may be withdrawn from the study by the Investigator if:

- A serious adverse event (SAE) occurs.
- The Investigator believes that for safety reasons it is in the best interest of the subject to be withdrawn.
- The subject withdraws consent.
- A positive urine drug screen at any visit.
- A positive pregnancy test at any visit; the subject reports pregnancy.
- Inability to locate and quantify a motor threshold as defined in the protocol or a motor threshold above 1.6 SMT.
- Investigator sets a treatment goal below 120% of MT.

Discontinuation information [e.g., date and the reason(s) for discontinuation] must be recorded in the subject's CRF (i.e., Study Termination Record page).
Follow-up information will be obtained for subjects who experience an SAE.
Subjects withdrawn from the study will not be replaced.

13.3 Compensation

As an incentive to complete the study and compensation for their time and effort, participants will be offered a $50 stipend if they complete all study treatment visits or discontinue due to intolerance of treatment.

14 DEVICE DESCRIPTION AND RTMS ADMINISTRATION

14.1 Device Description

The NeuroStar TMS Therapy System is a computerized electromechanical instrument that produces and delivers brief duration, rapidly alternating (pulsed) magnetic fields to induce electrical currents in localized regions of the cerebral cortex. The NeuroStar TMS Therapy System is offered in the following configurations:

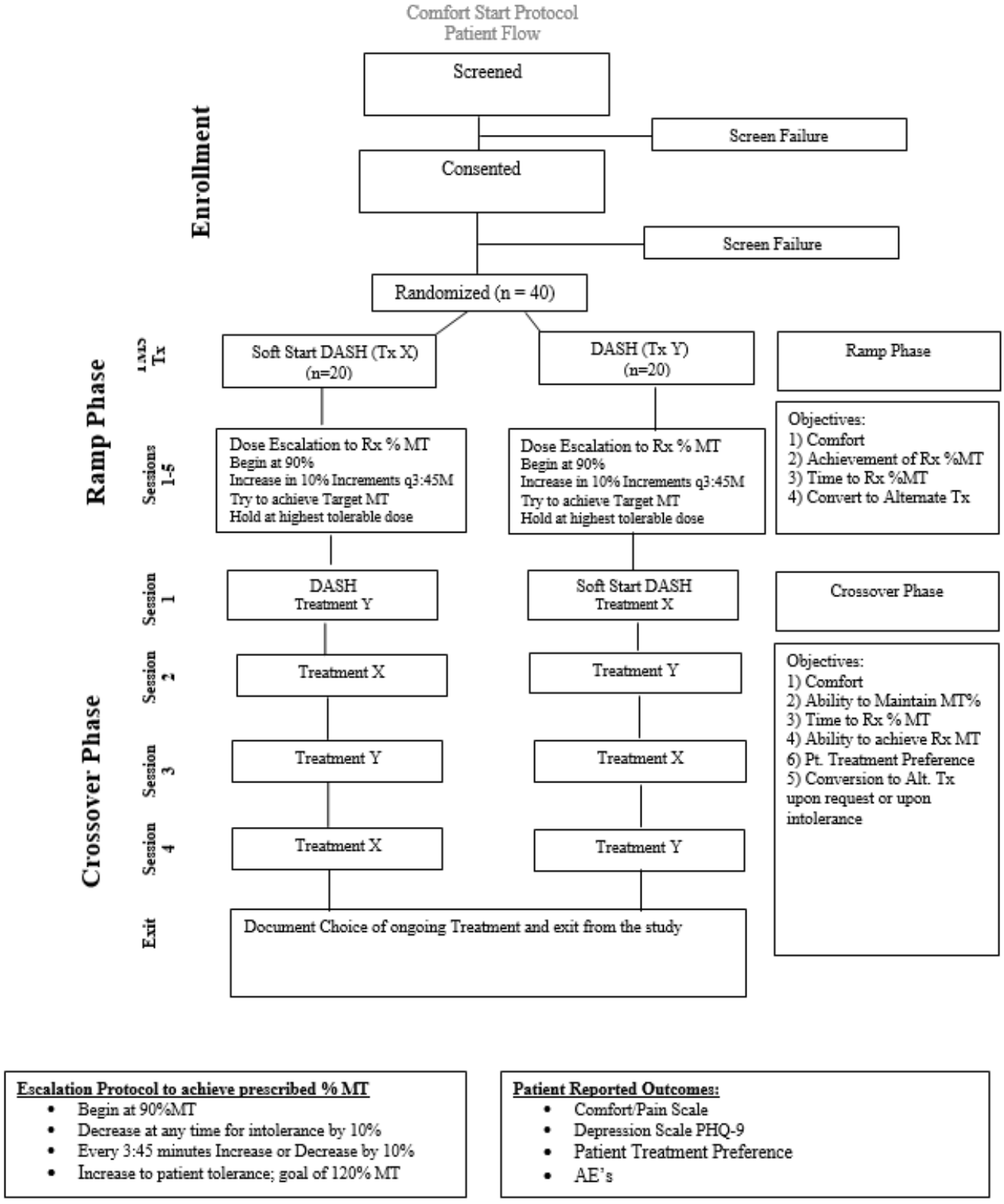
- Single mobile console configuration: mobile console, rTMS stimulation coil, head support system, chair, and TMS TrakStar practice data management system.

- Multiple mobile consoles/TMS TrakStar system configurations to address the needs of facilities with large subject populations.

During TMS, the conductive substance of interest is the brain, in particular the region of the cortex that lies beneath the NeuroStar TMS Therapy System treatment coil. This is the NeuroStar TMS Therapy System component that rests against the subject's head and transmits magnetic pulses to the subject's brain. The induced current is tangential to the scalp at the cortical surface and diminishes in magnitude with increasing depth.

For further detailed description on the NeuroStar TMS Therapy System, see the User Manual.

14.2 Subject Flow



15 MEASURES TO AVOID STUDY BIAS

15.1 Subject Identification

Each subject will be assigned a unique screening number after signing the study consent. This number will consist of an assigned unique, 3-digit subject identifier. For example, the first subject screened would be subject 001.

Subjects should be identified to the Sponsor only by their assigned number, age and sex. The Investigator must maintain a master list linking subject names and the identifying information indicated above.

15.2 Randomization

A randomization schedule will be generated by Neuronetics or a designated contract research organization (CRO). Eligible subjects will be randomly assigned to the Dash treatment protocol (Y) or Dash with the SoftStart feature enabled (X). Randomization numbers will be recorded in the screening log and on the subject's CRF. Randomization numbers may not be reassigned.

15.3 Blinding

Subjects will be blinded to all treatments. Subjects will be randomized to begin with either treatment X or treatment Y. Treaters and Clinicians will be aware of the treatment protocol assignments once assigned to subjects. Treaters will administer the Comfort scale but will not score the scales. Subjects will not be able to view previous responses to the Comfort, Preference or Depression questionnaires. Treater scripts will be used to administer the TMS changes and subject questionnaires.

15.4 Treatment Consistency

The same treater and same TMS treatment unit will be utilized for each subject whenever possible over the course of the study treatments.

16 COMFORT EVALUATIONS

Primary endpoint: The difference in the change in VAS scores for Comfort after rTMS stimulation between treatments administered with the Dash protocol and treatments administered with the Dash protocol with SoftStart feature enabled. Comfort will be evaluated as a change for all observations between groups, observations from Baseline to end of escalation phase, observations between groups during the crossover phase and observations

within a patient between treatments in the cross-over phase. Comfort will also be analyzed over time and by number of treatments between groups. See also section 18.

In the event that adverse events occur, those data will be summarized using standard descriptive statistics (frequency distributions, percentages, listings).

17 SAFETY EVALUATIONS

A medical history will be obtained at the screening visit including a list of medications and history contraindicated for TMS therapy and this protocol.

All spontaneous adverse events, serious or non-serious will be recorded during and after the rTMS stimulation procedures. Serious Adverse Events will be reported to Neuronetics by the study center within one business day of notification. Neuronetics will report any and all SAEs and other safety events, as applicable, to the IRB and/or the FDA within the pre-specified timeframes, as applicable.

17.1 Adverse Event Definitions

An *adverse event* is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person who has received rTMS stimulation with a Neuronetics device or in a Neuronetics clinical study. The event need not be causally related to the Neuronetics device or Neuronetics clinical trial. An AE includes, but is not limited to:

- Any clinically significant worsening of a pre-existing condition.
- An AE occurring from overdose (i.e., a dose higher than that described in the protocol) of a Neuronetics device, whether accidental or intentional.
- An AE occurring from abuse (e.g., use for non-clinical reasons) of a Neuronetics device.
- An AE that has been associated with the discontinuation of the use of a Neuronetics device;

A *preexisting condition* is a clinical condition (including a condition being treated) that is diagnosed before an informed consent form is signed and is documented as part of the subject's medical history.

A *serious adverse event* (SAE) is defined by Neuronetics as an AE that:

- Results in death:
- Is life threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization.

- Results in permanent impairment of a body function or permanent damage to a body structure.
- Necessitates medical or surgical intervention to preclude such impairment.
- Results in a congenital anomaly or birth defect.

Additionally, *important medical events* that may not result in death, be life-threatening, or require hospitalization, may be considered SAEs, based upon appropriate medical judgment.

Life threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death.

Hospitalization is to be considered only as an overnight admission. Hospitalization or prolongation of a hospitalization constitutes an AE to be classified as serious.

Note that hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).

Anticipated adverse events:

Anticipated events such as Headache, Dizziness, and Ear popping do not need to be recorded unless they are higher in frequency, severity, or duration than considered normal for TMS therapy. For this study, these events should be noted on the patient treatment form in the comments area.

Adverse Events of Special Interest:

An adverse event of special interest is a device-specific adverse event designated by Neuronetics to be reported in the same time frame as an SAE, even if it does not meet serious reporting criteria. For this protocol, seizure should be reported as an adverse event of special interest.

If there is any doubt whether the information constitutes an SAE, the information should be treated as an SAE for the purpose of this study.

Definition of Severity

The seriousness and severity must be evaluated independently when documenting the AEs in the records. There are three definitions of AE severity:

Mild: Awareness of sign or symptom, but easily tolerated

Moderate: Discomfort enough to cause interference with usual activity

Severe: Incapacitating with inability to work or do usual activity

Determining the Relationship: (if any) Between an Adverse Event and the Study Device:

Not related: The AE is unlikely to have been caused by study device.
Possibly related: It is unclear whether the AE may have been caused by study device.
Related: The AE is likely to or definitely have been caused by study device.
When assessing the relationship between an investigational product/protocol and an AE, the following parameters are considered:

- Temporal relationship between the investigational device/protocol and the AE
- Biologic plausibility of relationship
- Subjects' underlying clinical state or concomitant agents/therapies
- Where applicable, whether the AE abates on discontinuation of the investigational device (dechallenge)

SAEs that are not device-related may nevertheless be considered by the participating Investigator or Neuronetics Medical Affairs to be related to the conduct of the clinical study, i.e., to a subject's participation in the study.

17.2 Timing for Reporting of Serious Adverse Events

Any SAE (as defined above) regardless of causal relationship, must be reported immediately to Neuronetics Medical Affairs (within one business day) by emailing to Neuronetics a completed serious adverse event form to customersupport@neurostar.com and then confirming by telephone (870-600-7555) that the email was received. If no direct phone contact is made, the investigator should repeat attempts to notify Neuronetics Inc. or designated representative until receipt is acknowledged. The SAE may be reported using IRB required forms, or Neuronetics forms 25-44028-000, Serious Adverse Event Form, or 25-80031-000, Medical Event Form. Compliance with this time requirement is essential so that Neuronetics may comply with its regulatory obligations.

Follow-up information relating to an SAE must also be reported to Neuronetics Medical Affairs within one (1) business day after the information is received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified. Any emergency must be reported to the Neuronetics Medical Affairs immediately (within one business day).

For all other inquiries and information about this study, contact the Clinical Operations representative identified in Section 1.1 of this protocol.

17.3 Reportable Events

All AEs and SAEs, regardless of relationship to the protocol or rTMS device, that are collected during the rTMS stimulation procedure will be recorded on source documents and recorded on the subject's CRFs. Neuronetics will instruct the Investigator to follow all AEs, SAEs, and other reportable events until the event has subsided or values have returned to baseline, or in case of permanent impairment, until the condition stabilizes.

The Investigator will provide all documentation pertaining to an SAE (e.g., additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the medical monitor in a timely manner. Reports relative to the subject's subsequent course must be submitted to the Sponsor until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Other information reportable to Neuronetics, while not meeting the definition of an AE, is reportable to Neuronetics with the timeliness of an SAE. This includes:

- Pregnancy occurring during the study period in which the subject was exposed to the rTMS device.
- Overdose (e.g., a dose higher than that prescribed by a healthcare professional for clinical reasons) with or without AEs.
- Abuse (e.g., use for non-clinical reasons) with or without an AE.
- Inadvertent or accidental exposure with or without an AE.
- Device malfunction that would likely result in death, serious injury or other significant adverse event.

17.4 Reporting Procedures

All AEs collected during stimulation visits will be recorded in the adverse event record of the subject's CRF. The information recorded should be based on the signs or symptoms detected during the physical examination and clinical evaluation of the subject. Signs and symptoms should be recorded using standard medical terminology.

The following AE information must be included (when applicable): the specific condition or event and direction of change; whether the condition was preexisting (i.e., an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (e.g., in severity and/or frequency); the dates and times of occurrence; duration; severity; causal relationship to the product under study ; action taken; and outcome.

IRB Reporting:

Any AE's/SAE's should also be reported in writing to the reviewing IRB, per their requirements.

MDR Reporting:

As the study device is commercially available, all adverse events also need to be reported through FDA's MDR reporting system. https://www.accessdata.fda.gov/scripts/medwatch/

Follow-up of Adverse Events

All AEs recorded during the study are to be followed in accordance with good medical practice until they are:

- resolved, stabilized, or judged no longer clinically significant, or
- if a chronic condition, until fully characterized, or
- for 30 days, which may extend through the follow-up phase for treatment related AEs or SAEs that occur or are ongoing at the last treatment session.

17.5 Safety Monitoring for Potential Seizure Risk

All treatment protocols in this study do not deviate from FDA cleared treatment parameters for NeuroStar TMS. All subjects will be assessed during the screening phase for neurologic disease, concurrent medication use, or other clinical factors that may contribute to the risk of seizure. Stimulation parameters maintain a safety level within the guidelines consistent with the 1998 NINDS workshop recommendations.

All personnel involved in the administration of rTMS in this study will be required to participate in individual site initiation visits and/or complete other sponsor training requirements and be able to demonstrate understanding of these issues for the sponsor prior to initiation of subject enrollment at the site.

18 STATISTICAL ANALYSIS PLAN

Statistical analyses will be performed by the Biostatistics Section of the Sponsor or its designee. Any additional or supplemental data analyses performed independently by the Investigator should be submitted to the Sponsor for review and approval.

18.1 Sample Size Considerations

A sample size of 40 total subjects, twenty to begin treatment with each of Treatments X and Y was selected as sufficient to perform a preliminary assessment of the differences between the two repetitive transcranial magnetic stimulation (rTMS) therapies for MDD. The sample size is

not based on formal power requirements for a statistical hypothesis test but is based on a desire to obtain a reasonable initial data set for exploratory and planning purposes.

18.2 Analysis Plan

The primary outcome is the difference in comfort and pain observed between rTMS stimulation protocols using VAS comfort scores. The analysis will be performed on the sample of evaluable subjects, meaning those subjects with at least one post-treatment time point.

- Descriptive analysis of subject demographics and other baseline variables.
- Primary Outcome Assessment:
  The Primary study outcome will be determined based on differences in the mean VAS ratings on a 0-10cm VAS scale for comfort between treatment arms.
- Secondary Outcome Assessment:
  The Secondary objectives are to evaluate the ability to reach the prescribed treatment intensity, the time it takes to reach the prescribed treatment intensity, maximum treatment intensity reached, patient treatment preference and discontinuations due to treatment discomfort. Other treatment effects between the two treatment protocols will be explored.
  - Comparison of the incidence, severity, and frequency of Adverse Events (AE) between the experimental and the control group will be made descriptively.
  - Statistical methods employed to detect differences between the experimental and the control groups, for the above outcomes, may include a t-test, Chi-Square test, and Fisher's Exact test. For assessments including crossovers, a relevant method accounting for period effect, repeated measures, and randomized order will be utilized.
  - Subgroup analysis will be performed based on initial comfort scores, group assignments or other variables.
  - More detailed descriptions of the statistical methodology and analyses will be supplied in a separate SAP (statistical analysis plan).

ADMINISTRATIVE SECTION

19 INVESTIGATOR OBLIGATIONS

19.1 Institutional Review Board (IRB) Approval

No subjects will be enrolled at the investigational site until full approval is obtained from the institutions IRB for both the protocol and the informed consent document.

The protocol and the informed consent document must have the initial and at least annual (when required) approval of an IRB. The signed IRB approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document).

19.2 Pre-study Documentation

The Investigator must provide the Sponsor with the following documents prior to enrolling any subjects:

- Protocol Investigator Agreement/Investigator Signature (see p. 6 of protocol)
- Current signed and dated curricula vitae for the Investigator, sub-Investigators, and all key personnel listed on the clinical study information form.
- Copy of the IRB approval letter for the protocol and informed consent. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB must also be provided to the sponsor. Any changes in this study or unanticipated problems involving risks to the subjects must be reported promptly to the IRB. An Investigator must not make any changes in a study without IRB and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. All protocol amendments must be submitted to the IRB and approved.
- Copy of the IRB-approved informed consent document to be used.
- When applicable, a list of the IRB members and their qualifications, and a description of the committee’s working procedure.
- Financial disclosure statement.
- Fully executed clinical study agreement (CSA).

19.3 Informed Consent and HIPAA Authorization

Subject's written informed consent will be obtained prior to enrolment in the study, disclosing all known and potential risks, including societal, of rTMS. A copy of the consent form will be given to each subject.

Subject confidentiality will be protected throughout the course of the study.

The informed consent document shall contain all of the elements of informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the subject and/or inclusion of additional information in an informed consent document. Copies of the regulations relating to informed consent and the protection of human subjects in clinical studies are available from the Sponsor.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, some regulations require the permission of regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

The delegation of Investigator responsibilities including informed consent will be documented on the clinical study information form. Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed by all study subjects prior to any procedures for the study being conducted.

19.4 Case Report Forms (CRFs)

CRFs will be created for each subject participating in the study to ensure consistent data collection. The Investigator or his/her authorized designee must ensure that all information has been accurately entered and that correct dates and required signatures are present.

19.5 Review of Source Records

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the subject will be maintained unless disclosure is required by regulations.

Accordingly, the following statement (or similar statement) will be included in the informed consent document: Representatives of regulatory agencies, IRBs and the sponsor may review your medical records and all information related to this study as permitted by law. Identifying

information will not appear on any record received by the sponsor. Each subject's identity will remain confidential unless disclosure is required by law.

19.6 Monitoring of the Study

Clinical monitoring visits will be scheduled prior to the commencement of the study and at regular intervals thereafter. The Investigator shall cooperate with the study monitor. This includes, but is not limited to, allowing the inspection of facilities utilized by the Investigator for this clinical investigation, providing access to subject medical records for review and verification purposes; providing all required reports; and providing all other reports, including any subject report forms reasonably requested by Neuronetics. The Investigator shall also permit, at reasonable times, an authorized officer or employee of the FDA to inspect the facilities utilized by the Investigator for the clinical investigation. The Investigator will also permit this representative to inspect, copy and verify records required, as part of, or relevant to the investigation.

Clinical monitoring visits will be scheduled in advance to ensure that the Investigator and other appropriate staff have sufficient time available to meet with the monitor and discuss all relevant findings. In addition to regular visits by the monitor, more frequent follow-up visits will be scheduled if the Investigator fails to provide adequate subject data or if otherwise deemed necessary. Subject data will be reviewed and/or verified, and all deficiencies corrected on site, if possible. A complete report will be made of all monitoring visits. If the study is terminated, a monitor will visit the site to ensure that all records are complete, the IRB is notified, and all Neuronetics materials are retrieved.

The monitor will review the study conduct to determine compliance with the study protocol. Protocol deviations are not permitted without prior written approval from Neuronetics and, if necessary, the reviewing IRB and/or FDA. The monitor will review and/or verify all case report forms and source documents as appropriate to ensure that correct and adequate copies are available for the investigational study. The monitor will review the subject informed consent forms to ensure that no forms were signed prior to the date of IRB approval of the study. The monitor will inspect the facilities and equipment used in the investigation to ensure that they are appropriate for use and properly maintained.

The monitor will assess the site to assure the Principal Investigator is properly overseeing the study activities of associate Investigators, if applicable.

19.7 Protocol Amendments

Any significant change in this protocol requires a protocol amendment. The Investigator and the medical monitor will indicate their approval by signing the approval page of the amendment. After sponsor approval of a protocol amendment, the Investigator will submit the amendment to the IRB for written approval. The approval letter must refer specifically to the Investigator, the sponsor protocol number, the protocol title, the protocol amendment number, and the date of the protocol amendment. The Sponsor will submit a copy of the protocol amendment to the appropriate regulatory agency.

A protocol amendment may be implemented following IRB approval. In some cases, an amendment must receive a favorable opinion from the regulatory agency. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB within 5 working days, and submitted to the appropriate regulatory agency in the required time frame.

19.8 Change in Investigator

If any Investigator retires, relocates, or otherwise withdraws from conducting this study, the responsibility for maintaining records may be transferred to the Sponsor, IRB, or other Investigator. The Sponsor must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation.

19.9 Termination by the Sponsor

The sponsor may terminate the study at any time for any of the following reasons:

1. Failure to enrol subjects.
2. Protocol violations.
3. Inaccurate or incomplete data.
4. Unsafe or unethical practices.
5. Questionable safety of the test article.
6. Suspected lack of efficacy of the test article.
7. Administrative decision.

19.10 Termination by the Investigator

If the Investigator terminates the study prematurely, he/she must:

1. Return all investigational devices, CRFs, and related study materials to the Sponsor.
2. Provides the IRB and the sponsor with a written statement describing why the study was terminated prematurely. **Note:** Prompt compliance with this requirement is essential so that the sponsor may comply with its regulatory obligations.

19.11 Final Study Report

The Investigator will complete a report notifying the IRB of the conclusion of the clinical study. This report should be made within 3 months of completion or termination of the study. The final report sent to the IRB will also be sent to Neuronetics and, along with the completed CRFs, will constitute the final summary to Neuronetics, thereby fulfilling the Investigator's regulatory responsibility.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

19.12 Confidentiality

All unpublished information provided to the Investigator by the Sponsor shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the sponsor unless otherwise specified in the study agreement.

19.13 Publications

The institution and Investigator shall not publish or present data from the study center until the study has been presented in full or for two years after the termination of the study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator shall submit reports, abstracts, manuscripts and/or other presentation materials to the Sponsor for review prior to submission for publication or presentation.

The Sponsor shall have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The principal Investigator shall act in good faith upon requested revisions, except the Investigator shall delete any confidential information from such proposed publication. The Investigator shall delay submission of such publication or

presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

19.14 Subject Injury

A study-related injury is a physical injury that is directly caused by the study device or procedures required and described in the study protocol or by medical procedures that are required by the study and that are not standard of care.

Other than questionnaires, there are no study procedures or medical procedures required in this study that are not standard of care so no compensation for study related injury will be provided.

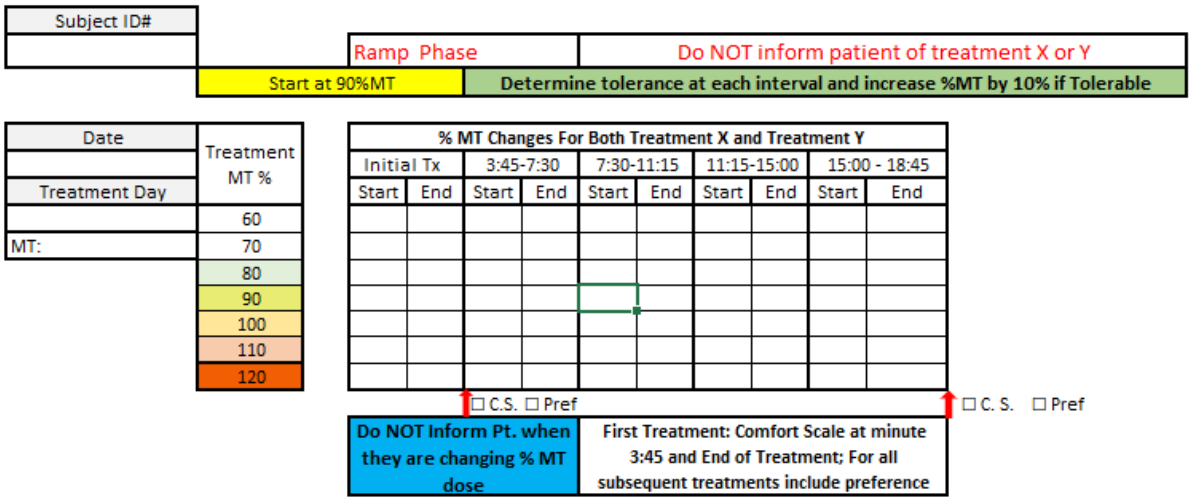
If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation. Where applicable, the Sponsor has taken specific national insurance.

19.15 Record Retention

Consistent with federal regulations, Investigators shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those documents defined by GCP as essential documents, for the longer of: (i) 2 years after the last marketing authorization for the investigational device has been approved or the Sponsor has discontinued its research with respect to such device or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor, in writing, of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator’s notice, and the Sponsor shall have a further opportunity to retain such materials at the sponsor’s expense.

20 ATTACHMENTS

Attachment A – Treatment MT Escalation and Tracking Worksheet



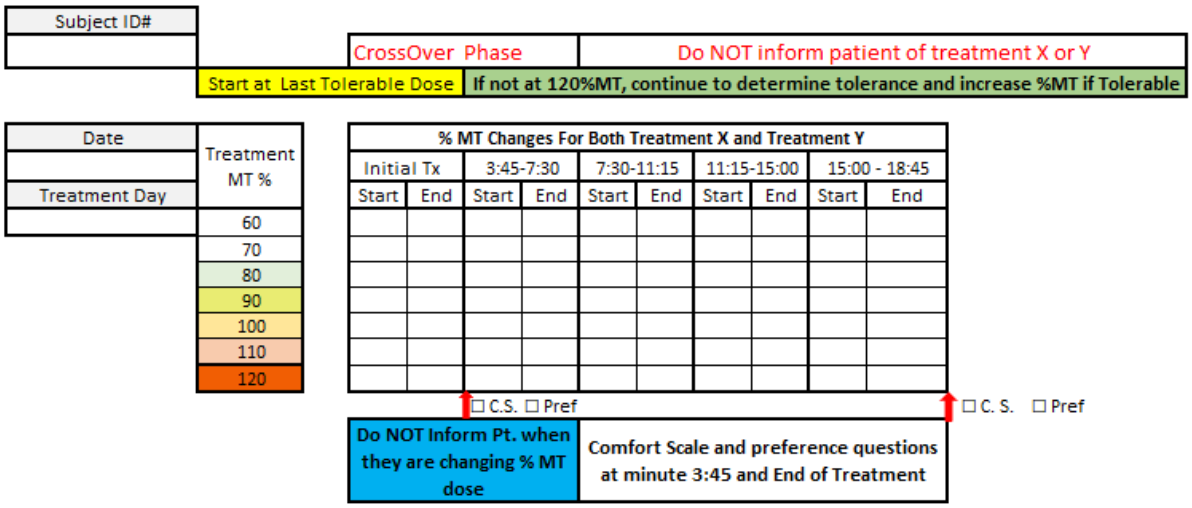
Subject ID#		Ramp Phase	Do NOT inform patient of treatment X or Y
		Start at 90%MT	Determine tolerance at each interval and increase %MT by 10% if Tolerable

Date	Treatment MT %
	60
Treatment Day	70
	80
MT:	90
	100
	110
	120

% MT Changes For Both Treatment X and Treatment Y									
Initial Tx		3:45-7:30		7:30-11:15		11:15-15:00		15:00 - 18:45	
Start	End	Start	End	Start	End	Start	End	Start	End

☐ C.S. ☐ Pref ☐ C. S. ☐ Pref

Do NOT Inform Pt. when they are changing % MT dose	First Treatment: Comfort Scale at minute 3:45 and End of Treatment; For all subsequent treatments include preference



Subject ID#		CrossOver Phase	Do NOT inform patient of treatment X or Y
		Start at Last Tolerable Dose	If not at 120%MT, continue to determine tolerance and increase %MT if Tolerable

Date	Treatment MT %
	60
Treatment Day	70
	80
	90
	100
	110
	120

% MT Changes For Both Treatment X and Treatment Y									
Initial Tx		3:45-7:30		7:30-11:15		11:15-15:00		15:00 - 18:45	
Start	End	Start	End	Start	End	Start	End	Start	End

☐ C.S. ☐ Pref ☐ C. S. ☐ Pref

Do NOT Inform Pt. when they are changing % MT dose	Comfort Scale and preference questions at minute 3:45 and End of Treatment

Attachment B – Comfort Visual Analogue Scale: (VAS)

"Mark just ONE spot on the line below that best shows the level of discomfort/pain you may have felt during the treatment, where '0' means you didn't feel any discomfort/pain at all and '100' means you felt extreme discomfort/worst pain you can imagine. Please mark only ONE spot on the line with an X that looks about right for your pain level during treatment. Do not think of or write in a number."

No discomfort or pain Extreme discomfort or worst pain imaginable

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