Investigator Initiated Proposal: "Synchronized TMS for Posttraumatic Stress Disorder and Comorbid Depressive Symptoms"

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I. Specific Aims

i. To evaluate the safety and efficacy of synchronized transcranial magnetic stimulation (sTMS) using the NeoSync device for adults with posttraumatic stress disorder (PTSD) and comorbid depressive symptoms in a pilot sham-controlled study.
ii. To explore the relationship between frontal alpha and treatment outcomes.
iii. To generate pilot data for future trials using the device in the home setting

II. Background

The impact of Post-Traumatic Stress Disorder (PTSD) cannot be overstated in the Veteran population. PTSD is highly prevalent, affecting up to 12.5% of returning Veterans from Operation Iraqi Freedom and Operation Enduring Freedom (Hoge et al., 2008) as well as among Veterans from Operation Desert Storm and the Vietnam War (Magruder et al., 2005). Furthermore, PTSD is associated with high degrees of psychiatric and medical comorbidity (Magruder et al., 2005) and significant utilization of healthcare resources (Spiro et al., 2006). Most importantly, PTSD prevents Veterans from reintegrating into society and is associated with poor quality of life and significant occupational and social dysfunction (Thomas et al., 2010). Despite its prevalence and impact, available treatments for PTSD have limited efficacy. Evidence-based pharmacotherapy and psychotherapy approaches have had only modest success in improving symptoms and function in Veterans with PTSD (Watts et al., 2013). Therefore, there is a pressing need to identify effective adjunctive treatments for PTSD.

Despite a vastly growing body of research on the use of non-invasive neuromodulation for mental disorders, the application of these techniques to PTSD remains much less explored. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive, outpatient procedure that uses an electromagnetic field to stimulate or inhibit cortical neurons (George et al., 2002). Our group, together with others, has previously reported on rTMS efficacy for depression (Carpenter et al., 2012). Devices for rTMS are currently FDA-cleared to improve symptoms of treatment-resistant depression, are in use in over 650 outpatient locations in the U.S., and an increasing number are within the VA system. Yet in comparison to depression, there is only a small emerging literature supporting the use of rTMS for PTSD, as participants with PTSD were excluded from the original studies of rTMS for MDD (i.e., O'Reardon et al., 2007 and George et al., 2010).

After several case reports and uncontrolled studies (McCann et al., 1998; Grisaru et al., 1998; Rosenberg et al., 2002), Cohen et al. (2004) performed the first formal evaluation of rTMS for PTSD. Following this original study subsequent controlled studies have investigated

its use, including studies from Boggio et al. (2010) and Watts et al. (2012). Moreover, we recently evaluated the efficacy of rTMS in individuals suffering from comorbid depression and anxiety, which found modest outcomes (Philip et al., 2015). Karsen et al. (2014) performed a meta-analysis of rTMS for PTSD which supports that targeting the right dorsolateral prefrontal cortex (DLPFC) with either inhibitory or excitatory rTMS is safe and has a significant effect size on symptom reduction (pooled Hedges *g* 2.67; CI 1.11-4.23). Moreover, in patients with comorbid major depressive disorder rTMS also had significant effects on a reduction in depressive symptoms (pooled Hedges *g* 2.82; CI 1.99-3.65). However, this meta-analysis was based on only 3 out of the 8 trials, reflecting a relatively high proportion of uncontrolled reports, indicating that further studies are needed.

Of particular relevance to this application are the burdens associated with standard rTMS therapy. Current rTMS protocols for depression require daily sessions, each taking 45 minutes – for up to 6-8 weeks (O'Reardon et al., 2007). In our clinic this has imposed a significant burden on Veterans, as they attempt to balance treatment requirements with re-integration into society, family needs and cope with other stressors. Moreover, the trend in PTSD rTMS protocol development is to increase the number of pulses and treatment sessions to improve outcomes, supported by evidence showing a positive relationship between symptom improvement and number of pulses delivered (Karsen et al., 2014). From this perspective, future "conventional" rTMS protocols for PTSD will be longer and carry an increased treatment burden for Veterans.

Taken together, research on non-invasive brain stimulation for PTSD remains in its early stages, and it is critical to develop novel interventions that a) use an individual biomarker to select the treatment frequency, b) reduce the burden of care on Veterans, and c) addresses the common comorbidity of PTSD and depressive symptoms. This poises the synchronized TMS (sTMS, NeoSync Inc.) device to potentially revolutionize the treatment of PTSD with non-invasive stimulation. This is additionally informed by our own preliminary work in patients with PTSD and comorbid depressive symptoms, where we have found their IAF approximates those found in the general population (mean IAF of 9.58 ± 1.1, n = 18, unpublished data), suggesting that sTMS synchronized to the alpha range will also be feasible in the population under study.

With these considerations in mind, we propose a small, two-site, sham-controlled pilot study of sTMS in patients with comorbid PTSD and depressive symptoms. We hypothesize that sTMS will be effective for PTSD and mood symptoms in this sample.

III. Experimental Methods

1. Brief Description of Subjects

Subjects will be outpatients who meet the DSM-V criteria for PTSD (acute or chronic, confirmed by the Clinician Administered PTSD Scale [CAPS] and at least moderate severity, defined as score > 33 on the PTSD checklist [PCL-5]) and have at least moderate symptoms of depression (defined by moderate symptoms, or score ≥ 11 on the Quick Inventory for Depressive Symptomatology – Subject Rated [QIDS-SR]) and are 18 to 70 years of age (inclusive). Up to 35 participants will complete the study at the two sites, the Providence VAMC (Providence, RI) and the White River Junction VAMC (White River Junction, VT). Eligible subjects must provide written informed consent, be capable of comprehending the nature of the study, and be considered by the Investigator as likely to comply with the visit schedule. Additional inclusion/exclusion criteria are listed below.

2. Study Design

This study is a prospective, sham-controlled, trial of sTMS delivered to patients who are symptomatic despite ongoing pharmacotherapy for PTSD and mood symptoms. Serial self-report symptom assessments will take place at screening/baseline and weekly during the 4

weeks of the study. The treatment course will comprise a total of 20 double-blind treatment sessions. Treatments windows will be 10 calendar days to complete 5 treatments, with a 40-day window in total to complete 20 treatments. Post-treatment assessment sessions will take place on the last day of treatment, and again 1 month after the final treatment.

All veterans who complete the sham-controlled series will be offered open-label continuation treatment following the same administration structure (i.e., 20 open-label treatment sessions, with 10 calendar days to complete 5 treatments, within a 40-day window for all 20 treatments), with a 1-month, post-treatment visit). Of note, for patients who continue in open-label participation, the 1 final study visit (PT2, below) will occur 1 month after the final open label treatment.

3. Specific Procedures or Treatments

A. Screening: Patients who call in response to advertisements for the study or are referred by clinicians and meet preliminary demographic eligibility criteria upon phone screen will be invited to the clinic for a screening visit. Participants will also be drawn from clinical and research clinics at participating sites. After providing written informed consent, psychiatric interview and self-report measures will be used to confirm eligibility with regard to diagnosis, past psychotropic treatment history, current health history, and current symptom severity. The requirement for maintenance on a stable regimen of psychotropic medications for 6 weeks prior to baseline and during participation in the course of sTMS will be discussed.

B. Baseline/First Treatment Day: Patients meeting eligibility criteria will return within 2 weeks to begin the treatment protocol. Consent will be reviewed and confirmed with standard-of-practice forms for each institution. If indicated, women will be given a pregnancy test to make sure they are not pregnant. Clinical assessments will be updated (if more than 2 weeks have passed since screening visit), and data regarding functioning and quality of life will be collected with standardized measures. sTMS delivery will be calibrated using standard NeoSync procedures found in the device's user manual.

C. Serial Assessments: In the table below, PT1 refers to the assessment after the final sTMS treatment (i.e., after week 4 of the sham-controlled phase and, if relevant, after week 8 of the open-label phase). PT2 refers to the assessment completed 1 month after the final treatment (sham-controlled or open-label). PT1 and PT2 will include a psychiatric interview with the study PI or their designee. SC= screening visit, BL=Baseline/first treatment day, OL = open-label, with brackets indicating procedures done only in patients participating in the OL continuation phase. End-of-treatment week assessments are listed according to number of weeks of sTMS therapy completed by the time of assessment. * Indicates repeat evaluation at baseline if more than two weeks has passed since screening. Note that psychiatric assessments will occur at SC/BL, PT1, [OL PT1,] and PT2.

Table 1: Serial Assessments

Abbrev:	Assessment Title:	Administered at:
CAPS	Clinician Administered PTSD Scale	SC, BL*, PT1, [OL PT1,] PT2
CTQ	Childhood Trauma Questionnaire	SC, BL*
CGI-S	Clinical Global Impression - Severity	SC, BL*, PT1, [OL PT1,] PT2
QIDS-SR	Quick Inventory of Depressive Symptoms – Self Report	SC, BL*, Weeks 1-3,PT1, [OL Weeks 5-7, OL PT1,] PT2
PCL-5	PTSD Checklist	SC, BL*, Weeks 1-3,PT1, [OL Weeks 5-7, OL PT1,] PT2
GAD7	7 Item Generalized Anxiety Disorder Scale	SC, BL*, PT1, [OL PT1] PT2
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire	SC, BL*, PT1, [OL PT1] PT2
CGI-I	Clinical Global Impression – Improvement	PT1, [OL PT1,] PT2
PGI-I	Patient Global Impression - Improvement	PT1, [OL PT1,] PT2

D. sTMS Treatment Administration: sTMS will be delivered following NeoSync administration guidelines using the device user manual. Acting under the direct supervision of a TMS-credentialed physician, trained sTMS operators will supervise all treatments.

Treatment emergent side effects associated with stimulation (during treatments) and emerging between treatment sessions will be queried on each treatment day and recorded.

E. Serial Imaging: Participants (at Providence VAMC site) found eligible at SC may undergo three MRI scanning sessions during the course of this study. Scans may occur prior to BL/first treatment day and after completing each study phase (i.e., after PT1 and PT1 OL). Scans will be completed at Brown University MRI Facility (MRF) or Providence VAMC; with scanner location remaining consistent for each participant (i.e., a participant BL screened at Brown will undergo PT1 scan at Brown, not PVAMC). Eligible participants will be scheduled to arrive at either facility 1 hour prior to MRI start time. At that time research staff will review MRI safety and study procedures, and discuss any changes in mood, sleep, and/or medication since their last visit. Additionally, participants will be asked to complete the Perceived Stress Scale prior to entering the scanner. Once in the magnet, research staff will ensure that the participant is comfortable, able to view the task screen, and has been provided the necessary instructions regarding communication with research staff during the scan (e.g., using emergency squeeze ball). After each scan, the participant will be queried about their experience in the scanner to assess for anxiety and/or discomfort.

Images will be acquired using either a Siemens (Erlangen, Germany) TIM TRIO or VERIO 3.0 Tesla scanner located at Brown MRF and PVAMC (Building 1), respectively. Imaging acquisition and procedures are well established at both scanner locations. The scan session will start with a T1 anatomic scan for reference, followed by blocks of n-back tasks (working memory) during BOLD imaging in between BOLD and multi-band EPI resting blocks (resting state image acquisition), and finish with a DTI sequence. We have experience using this sequence order (see Table 2) in similar research projects, and have found that is effective in minimizing in-scanner fatigue. Total in-scanner time will be approximately 42 minutes.

Table 2. MRI Sequence

Run	Duration (sec)	Sequence	Task	Volumes (TRs)
1	250	MPRAGE	N/A	N/A
2	480	EPI	Rest-Fixation Cross	192
3	300	EPI	2-Back	116
4	300	EPI	2-Back	116
5	480	MB-EPI	Rest-Fixation Cross	480

6	720	DTI	N/A	N/A

Total time: 2530 sec (42.2 min)

Imaging Sequences. High-resolution (1 mm^3) whole brain T1 images will be acquired for anatomic reference using MPRAGE sequence, and pulse oximetry and respiratory bellows will be measured for use as potential covariates during processing and analyses. Functional connectivity during tasks will be evaluated with multi-band and BOLD echoplannar imaging (EPI) sequences. Diffusion tensor imaging (DTI) parameters will utilize double spin echo echo-planar DWI, with diffusion gradients applied in 64 non-collinear directions (b = 1000), one DWI for each gradient direction and 10 non-weighted (b = 0) normalization images, using Siemens MDDW protocol with partial echos and interpolation on. All parameters are outlined in the table below.

Table 3. Imaging Parameters

Parameter/Sequence	Sagittal MPRAGE	Axial BOLD (EPI)	MB-EPI	DTI (DWI)
Slice (mm)	1	3	2	1.8
TE (ms)	2.98	28	30.2	10060
TR (ms)	1900	2500	1050	103
FOV (mm)	2562	1922	1922	226

Tasks. During resting state image acquisition, participants will be instructed to keep their eyes open and view a grey fixation cross against a black background. Working memory will be tested using a standard n-back task as used in previous studies. During the DTI sequence participants will be instructed to remain awake, but given the option as to whether they prefer keeping their eyes opened or closed.

4. Power Calculations and Data Analysis

We aim to maximize power through collaborative analyses including data collected from the two sites of the study. De-identified data will be shared for final analyses. At least 20 subjects will be completed in total. The sample size for this pilot controlled study is based on estimations regarding the appropriate amount of information required to inform next steps in trial design rather than on statistical significance calculations for any primary safety or efficacy endpoint. Previous studies of different TMS parameters for PTSD (without comorbid MDD) have utilized sample sizes of ~ N = 20. By employing a comparable sample size we anticipate having sufficient power to detect significant differences between baseline and endpoint. This sample size will be adequate to determine the appropriate sample size for a subsequent trial.

For the primary efficacy endpoint, we will analyze change in total scores on both PCL-5 scores from baseline to end point PT1. Categorical response (empirically defined as 50% decrease from pre-treatment baseline) and remission (below threshold score, per published standards for each scale) will be calculated for each scale, and these will be reported in a descriptive manner for the sample. Secondary efficacy endpoints will utilize pre- and post-treatment scores on the self-report scales and CAPS. Open-label results, potentially informing issues related to duration of treatment, will be reported descriptively.

IV. Material Inducements

Participants will be offered payments in the form of gift cards, for completion of three milestones in the study: $25 giftcard for completion of all baseline procedures, $25 giftcard for completion of all PT1 procedures, and $50 giftcard for completion of PT2 procedures. There is a maximum total payment of $100 to offset time and travel expenses incurred as a result of participation in the research assessments that are not standard of care for non-research patients who undergo sTMS therapy. Participants who undergo open-label treatment will receive an additional $25 for completing OL PT1 procedures, bringing the maximum total of $125

(inclusive of acute phase and open-label inducements). Additionally, participants who undergo serial MRI imaging will receive an additional $50 at each scanning session. There is a maximum total payment of $150 for completing 3 serial MRI sessions. Thus, participants that complete all primary study procedures and serial imaging procedures may receive a maximum of $275. Payments may occur via gift cards or EFT.

V. Training of Research Personnel

All research staff will receive study specific training from their site PI prior to their involvement in the study, and all staff will receive device-specific training from NeoSync. Research staff meetings will be scheduled as needed for further training, especially if the protocol is amended. Study PIs will be available to research staff by phone and email to answer any study related questions. Study PIs or their designees will train and supervise research assistants to process and analyze the research data. Study PIs will be responsible for documentation of all training that will be placed in the study's regulatory files. Study PIs or providers with experience in neuromodulation will supervise delivery of sTMS during the study.

VI. Human Participants

1. Participant Population

Up to 35 male and female subjects , age 18 to 70 years, who are suffering from PTSD and comorbid depressive symptoms, will complete the study.

Inclusion Criteria:
(1) To ensure subjects can safely receive sTMS, eligible subjects must meet all established screening criteria for safety during MRI (magnetic resonance imaging). These are conservative measures require a patient not having the following (unless MRI-safe): Cardiac pacemaker, implanted device (deep brain stimulation) or metal in the brain, cervical spinal cord, or upper thoracic spinal cord;
(2) Outpatients 18-70 years of age (inclusive);
(3) Meet DSM-V criteria for PTSD (acute or chronic) at the time of the screening and/or baseline visit; AND report at least moderate symptom severity of depressive symptoms. Participants with bipolar II or otherwise unspecified, who are currently in a depressed episode, will be eligible to participate;
(4) Have a baseline score of "Moderately Ill" or worse on the CGI-S;
(5) Be on a stable psychotropic regimen for at least 6 weeks prior to baseline, or no psychotropic medication at all (for at least 6 weeks prior to baseline), and be willing to maintain the current regimen and dosing for the duration of the study (unless medically necessary to make changes with notification of research staff);
(7) If female and of child bearing potential, agree to use an acceptable method of birth control for the duration of the study treatment period;
(8) Be willing and able to comply with all study related procedures and visits;
(9) Be capable of independently reading and understanding patient information materials and giving written informed consent.

Exclusion Criteria:
Subjects will be excluded from participation if they meet any of the following:
(1) Are pregnant or lactating or planning to become pregnant within the next three months;
(2) Have a lifetime history of loss of consciousness due to head injury for greater than 10 minutes, or any lifetime history of loss of consciousness due to a head injury with documented evidence of brain injury (including brain atrophy);
(3) Current (or past if appropriate) significant neurological disorder, or lifetime history of a) seizure disorder b) primary or secondary CNS tumors c) stroke or d) cerebral aneurysm;

(4) Unstable medical illness, or, in the opinion of the investigator, significant absence of appropriate medical care;
(5) Current Axis 1 primary psychotic disorder, or bipolar I disorder, active moderate/severe substance use disorders (within the last month, excluding nicotine/caffeine). Veterans on stable (>3 months), monitored opiate agonist therapy may be included at the investigator's discretion;
(6) Past failed treatment with rTMS or ECT; any past treatment with deep brain stimulation or vagus nerve stimulation;
(7) Have active suicidal intent or plan as detected on screening assessments, or in the Investigator's opinion, is likely to attempt suicide within the next six months;
(8) Demonstrate the presence of any other condition or circumstance that, in the opinion of the investigator, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.
(9) Inability to obtain EEG of sufficient quality and duration that can be processed for use to calibrate the study device.

2. Recruitment and Consent Procedures
Potential participants will be recruited through advertisements in the community. Announcements to hospital and community clinicians will be made to facilitate referrals. Research assistants will provide preliminary screening with callers who express interest. Written informed consent will take place as described above, during the screening visit.

3. Potential Risks to Participants

A. Risk of side effects from sTMS treatments: The U.S. Food and Drug Administration has designated this device as a "non-significant risk device" in MDD patients, and in the largest sTMS trial to date for MDD, there were no statistically significant differences in side effects between active and sham sTMS (Leuchter et al., 2015). The most commonly side effect reported was headache (21.4% in active sTMS, 19.2% in sham sTMS). Over-the-counter pain medications such as acetaminophen or ibuprofen may be helpful for reducing discomfort associated with sTMS. Because sTMS remains investigational, study staff will assess subjects' well being and functioning before and after each treatment to minimize the risk of experiencing these or any other side effects.

B. Risk of Worsening PTSD/Depression Symptoms or Lack of Improvement: Risks associated with participation in this trial include possible lack of positive response to sTMS treatment. Worsening of PTSD/Depressive symptoms is also a risk. There is no guarantee that the treatment will lead to improvement of symptoms. During the course of sTMS treatments or after finishing the final session in an sTMS treatment series, symptoms may worsen. The research staff will evaluate subjects at every sTMS treatment session, and the study physician will be available at all times to ensure that participation in this research continues to be safe and reasonable for them.

C. Risk of Inconvenience and Burden of Required Time/Travel: Subjects may engage in screening procedures and learn they are not eligible for participation in the research treatment trial. Emotional discomfort may be associated with completing the assessments and questionnaires. Frequent visits to the research clinic for the sTMS treatments (5 days per week) for up to 10 weeks may represent a considerable inconvenience, especially if a subject travels a great distance or has other constraints on their time or transportation. A small payment will be offered to cover part of the subject's expenses related to participation in this research study, but subjects will not be offered reimbursement for all of the expenses they may incur.

D. Confidentiality: There is some risk to patient confidentiality associated with participation in research clinical trials, as more data are collected than would happen in usual medical practice. Steps will be taken to protect privacy of patient health information. Participants' records/assessments will not become a part of their permanent medical record. All

study forms and data will be identified only by code numbers, and will be stored in locked file cabinets or on secure research servers. Identifying information (contact information, name, consent documents) will be separated from the research data and be stored separately in a different locked file cabinet. All computerized data will be de-identified and stored on secure, password-protected files. No personal participant information will be presented in any publication or presentations resulting from this research. Only the PI and study team will have access to materials gathered during the study. Patients will be told that information about their sTMS therapy will be shared with their prescribing psychiatrist and primary care provider, per best-practice standards. De-identified EEG data may be acquired, downloaded to and stored via NeoSync-provided utilities and recording equipment. De-Identified data may be shared with NeoSync, Inc., the device manufacturer. De-identified data from study sites will be entered into a shared database for analysis at the completion of the study.

E. There may be other risks that are currently unknown. Although sTMS is a designated a non-significant risk device in an MDD population, the long-term effects of sTMS on individuals are not completely known. The research team will notify subjects if anything new is learned about the safety of sTMS that might make them change their mind about participating in this study.

3. Further Detail of Protection Against Risks

A. sTMS: A licensed study physician with experience and training in neuromodulation will be available throughout all sTMS sessions. Study technician (defined as a non-LIP) will be within the sTMS treatment area during all sTMS sessions. Spontaneous report of side effects of sTMS will be used to identify and address any sTMS-emergent adverse effects. Risk of other serious adverse events related to stimulation will be mitigated by careful screening of past health history, identification of underlying risk factors, and application of the study inclusion/exclusion criteria.

B. Confidentiality, privacy and security: Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following: What protected health information (PHI) will be collected from subjects in this study; Who will have access to that information and why; Who will use or disclose that information; The rights of a research subject to revoke their authorization for use of their PHI.

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

If a potential participant is found ineligible on phone pre-screen or elects not to participate prior to signing a consent form, all their identifying information will be maintained only with age and gender. To protect participant's confidentiality all study data collected at each site will be labeled with a unique code and have none of the eighteen personal identifiers on them. The link to this code will be stored on a VA secure server with access only by research staff designated by the PI. Consent forms and participant demographic data will be stored separate from the study data. All research data and study documents collected at the VA site will be stored in locked files in an office at that location.

4. Potential Benefits and Importance of Knowledge to Be Gained

For Subjects: Benefits to subject participating in this trial include a thorough evaluation of mood and anxiety symptoms at no cost, and possible relief from PTSD and depressive symptoms from sTMS, a treatment with a very favorable safety profile.

For Society: The potential benefits of this project to society may include enhanced knowledge about treatment options for PTSD, about EEG-synchronized brain stimulation, and outcomes among the type of patients often encountered in clinical practice but excluded from participation in most large clinical trials – those with comorbid PTSD and depressive syndromes with chronic and often disabling symptoms

5. Risk-Benefit Ratio

The risk-benefit ratio of this study is favorable, particularly since the US FDA designated this device as non-significant risk. As such, it is considerably safer than a current study of standard rTMS therapy. Risks of adverse events associated with the use of the sTMS device are minimal and minimized by study design. Risk of potential nonresponse is managed through oversight by trained physicians. Patients will be under the care and supervision of experienced research psychiatrists and will be seen in by research clinic staff five days per treatment week for treatment and assessment of worsening of symptoms/adverse events.

6. Data Safety and Monitoring Plan

The site principal investigators will review all data collected and will report any adverse events to the IRB, as appropriate. To ensure the integrity of the data the site PI will review all the data for errors or inaccuracy within one week after it is obtained. All data will be entered into a research database as it is collected using RedCap, and study personnel will meet weekly or as appropriate to review ongoing subject data. All research staff members are trained in basic first aid and CPR. Following standard practice, serious and unexpected adverse events will be reported to the relevant IRBs within the designated IRB guidelines. For example, a serious adverse event will be reported by fax or e-mail within 1 business day, followed by a written report within 7 days. NeoSync will be notified immediately after IRB notification. If a pattern or potential pattern of unexpected adverse events emerges during the course of the study, the site PI will discuss this pattern with the other study PI and other physicians with expertise in brain stimulation in this population, and review whether the creation of a formal data safety and monitoring board would be indicated.

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