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Clinicaltrials.gov Record Summary Documents Cover Page (IRB Approved 12/13/2017)

NeoSync TMS Treatment for Bipolar I Depression (NCT02839798)

Attached document is protocol with statistical analysis plan as approved by Butler IRB.

The study had no external funding (investigational devices provided by the company Neosync, which no longer exists). This pilot trial was stopped early due to lack of funding.

IRB # 1601-004

BUTLER HOSPITAL
INSTITUTIONAL REVIEW BOARD
PROTOCOL
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TITLE OF PROJECT: Evaluation of NeoSync EEG Synchronized TMS For the Treatment of Major Depressive Episode in Bipolar Disorder and Associated Neural Response: An Open Label Trial

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Other Investigator(s): Noah S. Philip MD,

Description of Study

A. Specific Aims

The objective of this study is to establish the safety and preliminary efficacy of Synchronized Transcranial Magnetic Stimulation (sTMS) treatment, for subjects with Bipolar Disorder type I (BD-I) in a major depressive episode (BDD – bipolar depression, hereafter).

B. Background

Bipolar disorder is one of the top ten most debilitating of all illnesses. Two reports from the NIMH Collaborative Depression Study demonstrated that individuals with bipolar disorder experience depression much more frequently than hypomania or mania (Judd et al. 2002; Judd et al. 2003; Judd et al. 2012). Specifically, in these studies the hallmark symptoms of bipolar disorder (i.e. hypomanic or manic symptoms) occurred only during 9% of the time in individuals with BD-I, and in only 1% of the time in individuals with BD-II. During the depressed phase of bipolar disorder illness, affected individuals present with depressed mood, loss of interest or pleasure, feelings of guilt, low self-worth, disturbed sleep or appetite, low energy, and poor concentration.

Despite the high prevalence and cost of bipolar depression, there is a paucity of treatment options available to offer individuals struggling with this severe illness. Mood stabilizers are the mainstream option to treat bipolar depression, yet only a few choices are available. Quetiapine, olanzapine/fluoxetine combo and more recently lurasidone are few of the drugs that are FDA approved to treat bipolar depression. In comparison, depression in Major Depressive Disorder (MDD) is mainly treated with antidepressants, with several classes and options. Unfortunately, antidepressant treatment may adversely affect the overall course of bipolar illness, increasing the rates of mood destabilization and rapid cycling (Perlis et al. 2010; Valentí et al. 2012).

In addition to the psychopharmacologic treatments for depression, other therapies such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS, or simply "TMS") have been shown to have a potential therapeutic effect in MDD (for review: Noda et al. 2015). TMS uses magnetic pulses to induce excitation/inhibition of specific areas in the brain. Treatment with repetitive stimulation is intended to stimulate groups of cells in areas of the brain linked to depression. The exact mechanism by which the therapy works is still unknown (Pascual-Leone et al. 2000; Fecteau et al. 2006; Rossi et al. 2009; Noda et al. 2015). It is recognized that high-frequency rTMS can enhance cortical excitability consistently, whereas low-frequency seems to exert inhibitory effects on excitability (Fitzgerald et al. 2006). While the therapy is non-invasive, it is expensive and requires subjects to be treated daily at a treatment center because of the complexity of locating the point of stimulation as well as the potential for seizures.

On the other hand, the efficacy of rTMS for bipolar depression has not been widely investigated. From this perspective, a number of open label studies showed positive effect for rTMS (with a mixed range of parameters) in depressed patients with BDD (Dell'Osso et al. 2009; Cohen et al. 2010; Harel et al. 2011), and such result has been confirmed in few double- blind, sham-controlled studies with limited samples (Dolberg et al. 2002; Nahas et al. 2003; Tamas et al. 2007). Two of these studies were limited by small samples. Dolberg investigated a sample on 20 individuals with bipolar depression, ten in each arm (TMS parameters were not reported). In comparison, Tamas studied 5 individuals with bipolar depression (one in the sham arm and 4 in the active arm – 1Hz right frontal cortex). Nahas treated a mixed sample of 23 individual with bipolar 1 and 2, while in depressed / mixed episode (12 in the sham arm and 11 in the active arm – 5Hz left frontal cortex). However, there are case reports indicating mood destabilization leading to a manic episode after TMS treatment (Dolberg et al. 2001). It is still up to debate if rTMS using standard protocols are safe to be used in bipolar disorder.

Despite the ongoing debate regarding TMS' excitatory/inhibitory properties, it has been well established that TMS alters the oscillation of underlying brain tissue as measured with electroencephalography (EEG) (Paus et al. 2001; Klimesch et al. 2003; Fuggetta et al. 2005; Brignani et al. 2008; Fuggetta et al. 2008; Hamidi et al. 2009; Johnson et al. 2010). In particular, alpha band activity appears to exert "top down" control over broadly distributed functions in the brain, allowing selective activation of brain areas for optimal brain function (Klimesch et al. 2007). Klimesch and colleagues (2003) have proposed that one key factor determining whether TMS pulses are inhibitory or excitatory of task performance is the relationship of the frequency of TMS stimulation to the participants' intrinsic alpha frequency (IAF). Moreover, the alpha frequency range appears to be particularly involved in modulating connections among the dorsal anterior cingulate cortex, anterior insula, anterior prefrontal cortex and thalamus (Sadaghiani et al. 2010). Several of these brain areas are involved both in cognition and in regulation of mood. Furthermore, alpha frequency plays a central coordinating role in regulating brain activity. Higher mean IAF is associated with greater regional cerebral blood flow (Jann et al. 2010). In contrast, higher power and broadly synchronized alpha is associated with lower blood flow (Feige et al. 2005). Taken as a whole, these findings suggest that intrinsic alpha activity can lead to activation or inhibition of a brain region depending upon the intensity, frequency, and synchronization of the activity.

NeoSync, Inc. has developed an EEG synchronized TMS (sTMS) system for the treatment of MDD (Leuchter et al. 2015). The sTMS device uses low energy alternating magnetic fields at a subject's intrinsic alpha frequency. The NeoSync sTMS device that is to be used in the proposed trial provides therapy by generating an alternating magnetic field in close proximity to the head of the subject using diametrically magnetized cylindrical neodymium magnets. These magnets rotate to generate a sinusoidal magnetic field set at the average individualized alpha frequency calculated from the subject's EEG. The magnetic field generated is less than 2% of that required for active depolarization of neurons and approximately only 10% of conventional TMS output. In comparison, the total amount of magnetic field exposure for a full course of sTMS therapy is approximately only a minimal fraction of the exposure from a single scan with an MRI, which is widely used to study brain function in the psychiatric population, including children and infants. NeoSync's sTMS device is not an implantable device, is not used in supporting or sustaining human life, and does not present a potential for serious risk to the health, safety, or welfare of a subject. Based upon the profile of the product, the FDA considers the low energy emitting NeoSync sTMS device to be a "non-significant risk" (NSR) device. However, sTMS has not been studied in bipolar disorder; sTMS might be particularly safe due its low magnetization protocol, with potentially low risk for mood destabilization and manic episode induction.

Furthermore, bipolar depression is associated with a range of emotional and affective disturbances, coupled with deficiencies in cognitive and reward function (Almeida and Phillips 2013; Phillips and Kupfer 2013; Nusslock et al. 2014). Moreover, bipolar disorder is associated with hypersensitivity to reward cues that may lead to increased approach or goal-directed motivation to stimuli or life events involving reward pursuit; which, in the extreme, might be reflected in manic symptoms. By contrast, MDD is characterized by reduced sensitivity to reward cues, which has been related to anhedonic symptoms. Current neuroimaging findings suggest that bipolar depression can be modeled as dysfunction in two neural systems: 1) increased attention bias to emotional rather than neutral stimuli associated with abnormally increased activity in an amygdala-centered system associated with anterior cingulate dysregulation underlying emotion processing; and 2)hypersensitivity to reward stimuli associated with abnormally increased activity in ventral striatum and ventro-lateral pre-frontal cortex within the fronto-striatal neural circuit implicated in reward system. The former (1) may underlie the emotional lability, the latter (2) the hypersensitivity to positive stimuli, and the combination of both abnormalities are core clinical features of bipolar depression. Furthermore, resting state connectivity studies in adults with bipolar disorder suggests a decoupling between frontal, temporal and subcortical regions.

The proposed research will evaluate (1) the safety and preliminary efficacy of sTMS as adjunct treatment in bipolar depression; and (2) the extent to which task performance impairments and associated functional abnormalities within these two main neural systems may predict and moderate treatment response in bipolar depression using sTMS.

C. Experimental Method

C1. Brief Description of Subjects

Approximately 20 male and female subjects aged 18 to 80 years who present with a primary diagnosis of bipolar disorder type 1 currently in a major depressive episode (i.e. bipolar depression) and taking at least one mood stabilizer will receive open label treatment with sTMS. Furthermore, subjects will also complete weekly EEGs and some of the subjects will complete baseline and follow-up brain fMRI. 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. Subjects will be recruited from self-referral, clinician referral, and through contacts with the Mood Disorders Research Program. Additional inclusion/exclusion criteria are listed below.

C2. Study Design

This clinical trial is a prospective, open label, single center study (Butler Hospital). This study is designed to evaluate the safety and effectiveness of sTMS for symptoms of major depressive episode in subjects with bipolar disorder type I. A total of 20 subjects will receive 5 daily treatments per treatment week for 6 treatment weeks (total of 30 treatments) or when remission is achieved.

After providing written informed consent, subjects will start the assessment phase. Subjects must be on a stable dose of at least one mood stabilizer for at least 4 half-lives. Subjects will be assessed using clinician based interviews and self-rating scales (to determine baseline clinical characteristics). Subjects will also complete a baseline EEG.

Treatment will be initiated on Day 1 of the study and will be delivered daily for 6 weeks or when remission is achieved. Remission will be defined by Inventory of Depressive Symptomatology, Self-

Report Version (IDS-SR) score <14 for at least 14 calendar days. Subjects will be evaluated at the end of each treatment week during the treatment period.

At the end of each treatment week, subjects will repeat self-rating scales (see study flow chart, below).

A subset of the subjects will also complete a baseline and follow-up fMRI to investigate brain functioning (pending additional funding to support the scans); participation in the brain imaging at baseline and at endpoint will be optional. fMRI procedures will consist of a one hour session in the scanner during which subjects will complete protocols for assessing resting state, emotional processing, and reward processing, which are considered core components of bipolar disorder psychopathology. fMRI procedures will occur within one week of baseline assessments and study endpoint.

The end point assessments will be completed within 5 days of the final treatment day. In final evaluation, subjects will be assessed using clinician-based interviews and self-rating scales to evaluate efficacy of the treatment. Side effects will be recorded as described by study participants at any visit or during any contact with the subjects.

Two weeks after the last sTMS treatment, subjects will be contacted by telephone for a brief follow-up safety assessment

C3. Specific Procedures or Treatments

C3a. Open Label Trial:

This study is an open label pilot study, to determine effect size for sample estimation, and determine safety and preliminary efficacy. Subjects will start treatment after baseline assessments are completed; treatment will continue for 6 treatment weeks (or until subject remits per IDSSR criterion score sustained for 14 days). A treatment week will consist of 5 treatment days within 8 calendar days. Furthermore, all subjects must have at least 5 treatments within 10 calendar days; and 30 treatments within 6 treatment weeks (plus 3 days grace period), which will lead to 45 calendar days.

Study Occasion – Open Label, not sham controlled												
	Assessment Phase			Treatment Phase (week)						Termination Phase		
Rating or procedure	Screening	MRI	Baseline	1	2	3	4	5	6	MRI	End Point	Phone Check-in
CONSENT/ELIGIBILITY	X											
SCID-5-RV	X											
Consent/MRI	X											
EEG: IAF	x											
CTQ	x											
HRSD/MADRS	X		X								X	
YRMS	X		X								X	X
BAS/BIS			X								X	
PCGI-I											X	
CGI-Bipolar			X	X	X	X	X	X	X		X	X
IDS-SR		X	x*	X	X	X	X	X	X	x*	X	
ASRM		X	x*	X	X	X	X	X	X	x*	X	
PHQ9		X	x*	X	X	X	X	X	X	x*	X	
EEG: Resting			x								X	
MRI – resting state, cerebral blood flow, reward processing, emotion processing, cognitive processing		X								X		

x* Baseline measures repeated, if needed
only if >3 days from MRI or first treatment

Altman Self-Rating Mania Scale (ASRM)
Behavioral Activation System / Behavioral Inhibition System (BAS/BIS)
Childhood Trauma Questionnaire (CTQ)
Clinical Global Impressions - Bipolar Version (CGI-Bipolar)
Hamilton Rating Scale for Depression (HRSD)
Electroencephalogram (EEG) Recording: Individual Alpha Frequency (IAF)
Inventory of Depressive Symptomatology, Self-Report Version (IDS-SR)
Montgomery–Asberg Depression Rating Scale (MADRS)
Magnetic Resonance Imaging (MRI)
Patient Clinical Global Impression – Improvement (PCGI-I)
Patient Health Questionnaire-9 (PHQ-9)
Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV)
Electroencephalogram (EEG) Recording: Resting State
Young Rating Mania Scale (YRMS)

C3b: Clinical Assessments:
(1) Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV) diagnoses at Screening (First et al. 2015); **(2) Hamilton Rating Scale for Depression (HRSD) 17 items,** standard depression severity rating scales by clinician interview at Baseline and End Point (Hamilton 1960); **(3) Young Mania Rating scale (YMRS),** standard mania severity rating scales by clinician interview at Baseline and End Point (Young et al. 1978); (**4) Childhood Trauma Questionnaire (CTQ),** self-report measure of child abuse and neglect at Baseline (Bernstein et al. 2003); **(5) Patient Clinical Global Impression for Improvement,** standard self-rating scale at End Point; **(6) Clinical Global Impressions for Severity (CGI-S)** scores by clinical rater at Baseline, Week 1-6 and End Point **and Improvement (CGI-I) Bipolar Disorder version** at End Point only (Spearing MK et al 1997); **(7) Inventory of Depressive Symptomatology (IDS-SR),** standard self-rating scale for depressive symptoms at Baseline, Week 1-6 and End Point (Rush et al. 1996; Trivedi et al. 2004); **(8) Altman Self-Rating Mania Scale (ASRM),** standard self-rating scale for manic symptoms at Baseline, Week 1-6 and End Point (Altman et al. 1997); **(9) Patient Health Questionnaire-9 (PHQ-9),** standard self-rating scale for depressive symptoms at Baseline, Week 1-6 and End Point (Kroenke et al. 2001); **(10) Release of Health Information,** subject will sign releases of information for their last appointment with their PCP for medical comorbidities/ general health and for psychiatric care inpatient/outpatient for chart review for documented manic episodes**;(11) Behavioral Activation System / Behavioral Inhibition System (BAS/BIS)**, self rating scale for measures of the sensitivity of incentive and aversive motivational systems at Baseline and End Point (Carver, C. S., & White, T. L. 1994), (12) Montgomery–Asberg Depression Rating Scale (MADRS), standard depression severity rating scales by clinician interview at Baseline and End Point (Montgomery and Asberg 1979)

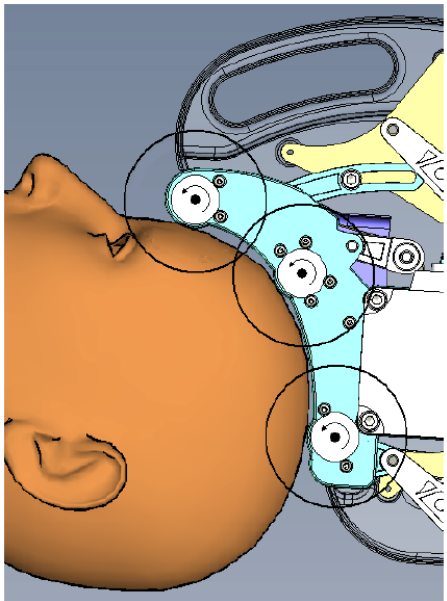
C3c: Electroencephalogram (EEG):
EEG data will be acquired using a research grade wireless EEG headset designed for rapid application of multiple sensors at locations corresponding to the 10-20 International System. The EEG recording system uses dry electrodes and is comfortable, portable, and easy to set up for recording EEG in under 5 minutes. In this study, brain waves will be recorded during 20 minutes while the patient has eyes closed and relaxes. After the recording session, the headset will be removed and cleaned.

C3d: Magnetic Resonance Imaging (MRI), optional measure pending extra funding:
Neuroimaging data will be collected in some of the subjects at the Brown University MRI Research Facility (MRF). The MRF includes a research dedicated Siemens 3 Tesla PRISMA scanner with a 32 channel head coil that improves signal to noise ratio. Participants will complete the MRI safety

form, and a 60-minute multi-modal MRI session. The session will include a 1) 3 plane localizer scan for slice positioning; (2) high-resolution T1-weighted MPRAGE anatomical scan with whole-brain coverage for structural MRI analysis and fMRI spatial normalization; (3) BOLD EPI scans for event-related fMRI and task-dependent activity/connectivity; (4) 1 EPI scan while the participant is at rest for task-independent (default mode network) analyses; and (5) ASL scan while the participant is at rest for cerebral blood flow analyses. MRI scan parameters will be per facility protocol. All participants will be studied awake and without sedation. Procedures will be stopped immediately at the participant's request or for any signs of significant distress. All standard procedures for ensuring safety during scanning will be followed (e.g., exclusions due to pregnancy, metal fragments in the body). Before the scan session, subjects will receive brief training in each task to ensure adequate performance. After scanning, participants will be debriefed about task content. **Emotion Processing Task (EPT):** The EPT is an emotional Stroop task to probe implicit emotion regulation processes during the presentation of conflicting emotional information. Stimuli consists of 148 pictures of emotional faces (happy or fearful), and participants will be asked to label the expression while ignoring an emotion word ("happy" or "fear") that overlays the image. The emotion words either matchs (congruent trials) or conflicts (incongruent trials) with the emotional face. Stimuli will be presented for 1000ms, with a variable inter-stimulus interval (3000-5000ms, M=4000ms), in a pseudo-random order, counterbalanced as a function of expression, word, gender, and response button; **Monetary Incentive Delay (MID) Task:** The MID task assesses both anticipation and feedback phases of reward and loss processing unbiased by performance or success rate. The task consists of 24 reward trials, 24 loss trials, and 24 neutral trials in random order. During each trial, participants are shown a geometric shape cue to signal trial type (circles for reward, squares for loss, and triangles for neutral trials; 2000 msec), followed by a fixation-crosshair (variable interval: 2000–2500 msec) and then a white square target to which participants are supposed to respond by pressing a button during its presentation. The target duration time is adapted throughout the task based on the success rate, such that participants would succeed on approximately 66% of the trials. After a jittered delay (700–2100 msec), participants receive feedback (1920 msec) notifying them about their present trial and total score, followed by an intertrial interval of 4000 milliseconds. On reward trials, participants can win $0.50 when pressing in time but will never lose money when failing to do so. Conversely, loss cues signas that participants could prevent losing money by successful button press or lose $0.50 upon failure. Finally, neutral trials result in $.00, irrespective of performance. **The money won during the particiapation is not actual money but rather imaginary money, only used as an incentive for the participant. Default Mode Network (BOLD and ASL):** eight-minute scan sessions in which subjects will be instructed to keep their eyes open looking at a fixation cross.

Total scan time will be approximately 60 minutes, and total subject involvement will be approximately 2 hours.

C3e. NeoSync Investigational Device: The NeoSync sTMS device provides therapy via an alternating magnetic field in close proximity to the head of the subject, generated by diametrically magnetized cylindrical neodymium magnets (each 1 inch diameter and length, with a surface field of 6,430 Gauss or 0.64 Tesla). These magnets rotate to generate a sinusoidal magnetic field set at precisely the average individualized alpha frequency (IAF, see below) calculated from the subject's EEG. The device contains three magnets in the saggital line above the subject's scalp, which



rotate along a transverse axis. sTMS is delivered broadly over the prefrontal and frontal regions of the brain.

The NeoSync sTMS device is powered by a medical-grade power supply that plugs into any 110-220VAC wall socket. A housing structure encloses the 3 rotating magnets of the device and keeps them in close proximity to the subject's scalp. The housing ("treatment arm") can be raised and lowered so that it rests on the subject's head while the subject lies in the device. The Figure (right side) shows a schematic of the device positioned on a subject's head, with the approximate area of stimulation indicated for each magnet.

The treatment arm can be latched in the fully raised position to allow the subject to position his/her head in the device. The base of the device extends under the treatment arm and an ergonomic pillow rests on the base to provide the subject with a comfortable, stable platform that keeps his/her head in the correct position during therapy. To administer therapy, the subject lays with his/her head under the treatment arm, face up. The treatment arm is gently lowered so that Magnet #1 rests on the subject's forehead and the other magnets are in the correct position against the scalp. The magnet housing can be tilted up to 10 degrees to provide the most comfort to the subject. Also, if the subject indicates that the pressure on his/her forehead is uncomfortable, the Head Size Adjustment Knob may be used to reduce the pressure.

C3f: Individualized Alpha Frequency:

(1) Electroencephalogram (EEG) (by NeoSync device) to measure Individualized Alpha Frequency (IAF) at Screening. To determine each subject's baseline IAF, the NeoSync sTMS device includes an EEG recording module. A single channel (sensing lead, reference lead, and a ground reference) pre-treatment EEG will be recorded to determine each subject's Alpha Frequency in a Patient Passport Module (PPM). To record EEG, 2 disposable patch Ag-AgCl snap-type electrodes are affixed to the subject's head, one high on the right forehead and the other above the mastoid bone behind the left ear. A finger-clip electrode is used as a ground reference. EEG recording is done automatically at the push of the START button. This recording takes approximately 5-10 minutes while the subject lies still, relaxed, awake, with eyes closed. The NeoSync sTMS device uses a proprietary algorithm to determine the IAF and records the value to the PPM, then indicates to the user that EEG recording has completed. EEG recording at the screening visit is done to verify that the subject's IAF can be determined, as a very small percentage of the population (<5%) do not have a strong enough alpha strength to capture using EEG. After this, the PPM is considered valid and may be used whenever the subject undergoes therapy. The IAF obtained at baseline is used to determine parameters for sTMS delivered throughout the study.

C3g. The sTMS Treatment Procedure:
Each patient's IAF is stored on their PPM, which is inserted into the USB port on the NeoSync sTMS device to program the sTMS parameters. During therapy, the subject lies still, relaxed, awake with eyes closed. Each therapy session lasts 30 minutes. If the treatment arm is raised to the latched position or drops to the bottom, the session will pause, and will resume only when the treatment arm is moved back into position. The therapy is intended to target "whole brain" rather than discrete anatomical regions, so minor shifting of the subject's head or body will not affect the efficacy of the therapy. A backlit LCD screen displays the current Patient ID and the status of the system. In order to prevent a subject from undergoing therapy more than once per day, a 12-hour lockout of the device occurs after a therapy session has ended or is cancelled.

C4. Data Analysis:
A total of 20 subjects will be enrolled and treated. The sample size for this open-label 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. For the primary efficacy endpoint, we will analyze change in total scores on the IDS-SR, HRSD, and MADRS scores from baseline to End Point. Categorical response (50% decrease from pre-treatment baseline on IDS-SR) and Remission (IDS-SR score <14) will be calculated to determine treatment efficacy.

Neuroimaging data will be pre- processed and analyzed using statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm). For both experiments, a first-level effect model will be constructed with conditions entered separately in the design matrix.

D. Material Inducements
Subjects will not compensated for the sTMS treatment but rather receive it free of charge. Subjects that participate in each neuroimaging session will receive a gift card with value of $25 for each MRI scan they complete.

E. Training of Research Personnel
Clinical data will be collected, entered and analyzed by Dr. Almeida in the Mood Disorders Research Program and research assistants trained under his supervision. Neuroimaging data will be processed and analyzed by Dr. Almeida and research assistants trained under his supervision. Dr. Linda Carpenter will provide overall supervision and oversight for the study.

3) Human Subjects

A. Subject Population *(include number; gender; age; diagnosis; inpatient vs. outpatient; physical health; inclusion/exclusion criteria; rationale for use of special groups)*

A total of 20 male and female subjects, age 18 to 80 years, who are suffering from bipolar disorder type 1, currently depressed, will be enrolled into the study and treated. All subjects will receive open label sTMS treatment. Subjects will be recruited from outpatient setting and in stable physical health.

Inclusion Criteria: Subjects must meet all of the following inclusion criteria to qualify for enrollment into the study:
(1) 18 – 80 years of age;
(2) DSM-5 primary diagnosis of Bipolar Disorder type 1 (with a documented diagnosis of the disorder on medical record), currently in a Major Depressive Episode by diagnostic criteria elicited by structured clinical interview (SCID-5-RV);
(3) MADRS score $\geq$ 20;
(4) Duration of current episode $\geq$4 weeks
(5) YMRS score $\leq$ 12;
(6) baseline EEG of sufficient quality for quantitative analysis processing;
(7) willing and able to adhere to the intensive treatment schedule and all required study visits;
(8) currently on adequate dose of mood stabilizer with significant evidence base or FDA approval for maintenance therapy of bipolar disorder (valproic acid/divalproex, carbamazepine, lamotrigine, lithium, aripiprazole, ziprasidone, risperidone, quetiapine, olanzapine, asenapine, haloperidol, chlorpromazine, paliperidone, cariprazine).

Exclusion Criteria: Subjects will be excluded from study participation if one of the following exclusion criteria applies:
(1) unable or unwilling to give informed consent;
(2) diagnosed with current primary psychotic disorder (rather than BD);
(3) diagnosed with current mania or hypomanic mood episode;
(4) history of moderate to severe substance use disorder within the past 6 months (except nicotine and caffeine);
(5) currently being treated with a stimulant;
(6) clinically defined major neurological disorder; including, but not limited to, seizure disorder and history of loss of consciousness due to head injury for greater than 10 minutes, or with documented evidence of brain injury;
(7) increased risk of seizure for any reason, including diagnosis of increased intracranial pressure, comorbid neurological disorder, use of certain medications, highly unstable use of alcohol or benzodiazepines;
(8) Initiation of new antidepressant treatments (new medication, new device-based stimulation, or new psychotherapy) within 6 weeks prior to baseline;
(9) 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;
(10) presence of implanted cardiac pacemakers, implanted medication pumps, or intracardiac lines;
(11) intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, stents, or electrodes) or any other metal object within or near the head (excluding the mouth), which cannot be safely removed;
(12) clinically significant unstable medical condition;
(13) if female: pregnant, not using medically acceptable means of birth control, or currently breastfeeding;
(14) other condition, which in the judgment of the Investigator could prevent the subject from completion of the study.
(15) for participants in the MRI study: ferromagnetic metal implant or other contraindication to imaging in a 3 Tesla MRI (see Brown MRF consent for MRI included with this protocol);

B. <u>Recruitment and Consent Procedures</u>
Community psychiatrists and other physicians will be made aware of this study to facilitate referral of potentially appropriate candidates. Postings describing the study and basic eligibility criteria may be advertised through local print, internet, radio, or other media. Subjects interested in participating will be grossly assessed for eligibility through basic phone screen queries. If a potential participant is found to be eligible for enrollment, the study consent form will be reviewed with the subject and the study methods and requirements will be explained. Written informed consent will then be obtained. A pre-screening log will be maintained to record data about subjects who are screened for enrollment, but either do not qualify or decide not to participate in the study. A copy of the signed consent form will be provided to the study participant and the original signed consent form will be maintained in the subject's files.

Once a subject has been consented, the screening process will include review of past treatments. This process may include a detailed interview with the patient to obtain history of illness and treatments; a phone consultation with the subject's attending physician/psychiatrist or prescribers, and/or a full review of the subject's relevant past medical records, including pharmacy records, if available. Participants may be asked to provide written permission for the researchers to request medical record documentation supporting past history of manic episode. This process will specifically ensure eligible subjects have the correct diagnosis and are currently taking a mood stabilizer.

C. Potential Risks

Risk of Mood Destabilization: Risks associated with participation in this trial include possible lack of positive response to the treatment, and/or worsening of depressive symptoms and/or mood destabilization. In addition, occasionally some emotional discomfort may occur while filling out questionnaires or being interviewed about matters pertaining to emotions, mental health, functioning and other relevant experiences.

Risk of Side Effects from sTMS: Risk related to treatment with the NeoSync device is minimal. In a recently completed sham controlled trial with the same device and similar treatment schedule, both active and sham treatments were well tolerated, with no significant difference between the active and sham arms in the incidence, severity, or clinical significance of adverse events (or relationship to treatment of adverse events) reported with an incidence rate of >2%. Headache was most common, occurring in 21% of active and 19% of sham subjects, followed by back pain (8.7% active v. 4.0% sham), insomnia (6.8% active v. 5.1% sham), respiratory infection (7.8% active v. 5.1% sham), paresthesia (3.9% active v. 0% sham), nonspecific GI discomfort (3.9% active v. 3.0% sham). The Severity of these events was considered mild, and none of them resulted in a subject dropping out of the research trial. There was no significant difference in treatment discontinuation due to reported adverse events in the active versus sham groups (2 and 5 subjects, respectively). The only suicide attempt reported during the blinded trial occurred in a sham-treated subject. No SAEs were attributable to either active or sham treatment. Upon review of the available preliminary data, the FDA classified the NeoSync sTMS device as a "nonsignificant risk" device and as such there are abbreviated IDE requirements and no FDA requirement for IDE filing for the current investigator-initiated study in bipolar depression.

Risk of discomfort during EEG: Subjects may feel areas of pressure on their scalp at the location of the recording electrodes during collection of EEG data.

Risk during MRI procedures: MRI imaging is generally considered to be safe if participant does not have metallic objects in the body. Some people experience anxiety, panic or a sensation of claustrophobia when lying in the MRI machine. A separate consent form associated with use of the Brown MRI Facility will be reviewed with the subject and signed prior to participating in the scan. Subjects will also be informed that the scan provided does not constitute a clinical scan and that researchers are not board-certified neuroradiologists. The scanner also makes loud noises during imaging.

The alternatives to participation in this study: (1) not receiving treatment for bipolar depression, or (2) receiving standard treatment administered by a clinician and/or prescribed by a physician or nurse outside of this research study. The primary risk of untreated BDD is prolonged disability and suffering, or if the condition becomes severe/worsens, possibly attempting or completing suicide. Risks related to obtaining treatment for depression outside of this study are the ones typically associated with available antidepressant and mood stabilizer pharmacotherapies, somatic therapies, or psychotherapy (side effects unique to each), and the risk of non-response to treatment interventions.

D. Protection of the Subject *(include: D.1. measures to minimize potential risks; D.2 measures to ensure confidentiality; D.3. data safety monitoring plan)*

D1. Measures to minimize potential risks:

Risk of Mood Destabilization: As part of inclusion criteria, subjects are required to receive stable and therapeutic doses of mood stabilizers, which should minimize TMS related mood destabilization. Furthermore, sTMS is potentially well suited to be used in bipolar disorder due to the relatively low intensity of stimulation, compared to standard rTMS. The magnetic field generated by sTMS is approximately only 10% of conventional TMS output. Moreover, in comparison, the total amount of magnetic field exposure for a full course of sTMS therapy is approximately only a minimal fraction of the exposure from a single scan with an MRI, which is widely used to study brain function in the psychiatric population, including children and infants. Furthermore, mood stability will be assessed weekly with Altman Self-Rating Mania Scale as a screening tool, and values above 6 on that screening scale will prompt further clinical evaluation that will include assessment with YRMS. Subjects will also be assessed weekly with self-rating scales for depression.

Risk of Side Effects from sTMS: A trained member of the research staff will administer each treatment and be present throughout treatment sessions to observe the participants. Moreover, all procedures will occur as part of the Butler Hospital's neuromodulation clinic, and a physician will be available at all times during treatments. Serial assessments side effects and contacts with research staff and study physicians will be used to identify and address any treatment-emergent side effects.

Risk of discomfort during EEG: The EEG headset allows adjustments to reduce scalp pressure if it is uncomfortable. EEG recording will be aborted if it cannot be done comfortably for any subject.

Risk during MRI procedures: Subjects will fill out standard questionnaires and informed consent provided by the Brown MRI research facility (MRF). Subjects will be screened for metallic objects or exposure that would preclude them from participation in the study. Investigators and research technicians associated with the MRF will screen for claustrophobia. If there is concern for a physical abnormality on structural scan, the principal investigator will provide an appropriate clinical referral. Ear protection will be provided to reduce the noise level. Participant may stop during the procedure for any reason by telling the technician through the intercom or by squeezing a ball that we will place in the participant's left hand.

Subjects will be told the following, which is reiterated in the ICF: "during the scan itself, you will lie on a table that slides into a horizontal cylinder slightly wider than your body. You will be asked to lie still, but you will be able to hear and speak to the MRI personnel. If you feel uncomfortable for any reason before or during the procedure, please tell the researcher. If for any reason during the procedure you want to stop, you may do so at any time by telling the technician through the intercom or by squeezing a ball that we will place in your left hand. This ball is connected to a buzzer that tells us you want to stop."

D2. Measures to ensure confidentiality:
Subjects will be told that their participation in this study is strictly voluntary and that they can change their minds at any time without impacting their present or future research participation. They will be assured of confidentiality in the handling of data generated by their participation in this study.

Subjects will also be informed that their participation in this study and the clinical information relevant to safe treatment with sTMS will be documented in the Butler Hospital medical record. Other research-related information will be stored in locked research files in the Mood Disorders Research Clinic and subject names will not appear on any research forms (only identification

numbers). Data will be stored on secure hospital servers and in secure, password-protected REDCAP databases.

Confidentiality: 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. that the subject is alive) at the end of their scheduled study period.

Ethical Considerations: This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study.

D.3. data safety monitoring plan:

Study Monitoring Plan: This study will be monitored with regard to progress, adverse events, and other unexpected events at weekly research staff meetings with the investigators. The Butler IRB will provide review and oversight of progress through continuing review and through review of Serious/Unexpected Adverse Events. A data safety monitoring board will be convened annually to review the progress. Together these measures will act to ensure its scientific integrity, the quality of data, the safety of human subjects, and compliance with the ethical principles that have their origin in the Declaration of Helsinki, the ICH guideline for Good Clinical Practice (GCP), applicable local regulatory requirements, and Sponsor regulations, guidelines, and policies.

E. Potential Benefits

For Subjects: Benefits to subject's participation in this trial include a thorough evaluation of depressive symptoms at no cost, and possible relief from BDD symptoms from an investigational treatment with a favorable side effect profile.

For Society: The potential benefits of this project to society may include enhanced knowledge about treatment options for BDD.

F. Risk-Benefit Ratio

The risk-benefit ratio of this study is favorable. Risks of adverse events associated with the use of this device (rated as nonsignificant risk by FDA) are minimal. Risk of potential non-response associated with lack of efficacy is managed through oversight by a trained physician. Patients will be under the care and supervision of experienced research psychiatrists and will be seen in by research clinic staff five (5) days per treatment week for treatment and assessment of worsening of symptoms/adverse events.

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5) CRITERIA FOR WAIVER OF AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION (PHI)

5A. Does the requested use of PHI involve more than minimal risk to privacy?
☐ **YES** ***[if "YES," project is not eligible for PHI Waiver]***
☒ **NO** ***[if "NO," address 1-3 below]***

Plan to Protect Patient Identifiers from Improper Use and Disclosure:
Data obtained from screening phone calls, faxed referral documents, and chart reviews will be treated confidentially and at the earliest possible point, be given anonymous numerical designations to protect PHI and stored on spreadsheets in secured locations. All research personnel have completed appropriate research ethics training.

Plan to Destroy Identifiers or Justification for Retaining Identifiers:
All unique subject identifiers will be removed from the final data set.

Assurances that the PHI will not be Re-used or Disclosed:
Protected health information will not be re-used or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study. Co-investigators will review the data for accuracy.

5B. Could the research be practicably conducted without a waiver?
☐ **YES** ☒ **NO**
5C. Could the research be practicably conducted without access to and use of the PHI?
☐ **YES** ☒ **NO**
5D. PHI is only needed for activities preparatory to research
☐ **YES** ☒ **NO**

DESCRIPTION OF PHI TO BE COLLECTED UNDER WAIVER

We will collect screening information from potential participants (who are referred or screened prior to signing informed consent for participation) from their verbal report, their medical records, or from their referring clinicians, including: 1) Name, 2) Date of Birth, 3) Phone Number, 4) Treatment History 5) Diagnosis. The PHI information will be kept in a separate file from the participant's research data, and only selected and authorized staff will have access to PHI on an as needed basis.

ADVERTISEMENTS

See attached.

8) INFORMED CONSENT FORM (ICF)

See attached

BUTLER HOSPITAL CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

Evaluation of NeoSync EEG Synchronized TMS For the Treatment of Major Depressive Episode in Bipolar Disorder and Associated Neural Response: An Open Label Trial

Sponsorship

This study is supported by internal funds at Butler Hospital/The company that makes the investigational treatment device (NeoSync) has loaned equipment to Butler Hospital for this study.

Research Project Summary

You are invited to participate in a study designed to assess efficacy, tolerability and safety of synchronized transcranial magnetic stimulation (abbreviated "sTMS") for the treatment of depression and associated brain functioning changes. You have been invited to participate because you have a diagnosis of Bipolar I Disorder and symptoms of a major depressive episode that are not relieved by medication.

If you decide to participate, your participation in the study will last for approximately 30 treatment days plus clinical evaluations before and after the treatment procedures. You may be asked to participate in a magnetic resonance imaging (abbreviated "MRI") scan before starting and after finishing the series of sTMS treatments.

A series of treatment will require approximately 30minutes per day, five days a week, for 6 weeks. Additionally, once a week, you will participate in self-rating. There will be a clinical assessment and recording of brainwaves before starting the first treatment (approximately 4 hours). When you complete the study there will be a final 1 hour assessment and another brain wave recording session. The main risks related to participation are lack of efficacy (the device doesn't work to relieve your symptom), and risks related to MRI scans. These are described in more detail below.

Description of Procedures

If you decide to participate, you will participate in clinical assessments, brainwave recordings (called electroencephalograms, abbreviated "EEG"), a procedure to take pictures of your brain (called MRI scan) and investigational brain stimulation treatments.

Clinical Assessments: you will participate in clinical interviews during which you will be asked about your depression symptoms and health history. You will also be asked to complete questionnaires or self-rating scales to measure the severity of your depression. Assessments may be done with paper and pencil, or through a computer screen. You will repeat the clinical assessments at multiple visits in this study. Finally, you will also perform a safety follow-up assessment or phone call two weeks after your final treatment.

EEG: your brain waves will be recorded using an EEG system with a cap and/or sticky patches. Several disposable, adhesive, snap-type electrode "patches" will be temporarily stuck on your head so your "brainwaves" can be recorded for about 5-10 minutes. You will not feel anything happening during the EEG recording procedure, other than the electrode patches stuck or

clipped to your body. You will be asked to be still and remain quiet while the EEG recording is taking place.

MRI scan: you may participate up to two (at the beginning and at the end of the study) brain scans in a MRI scanner located at Brown University campus.

sTMS: is a noninvasive method used to stimulate the brain by a series of magnetics that move in a device close to your head. The device can be raised and lowered so that it rests gently on your head while you lay flat on a table. Adjustments can be made to the device if you find the pressure on your forehead uncomfortable. You will remain quiet and awake during each 30-minute session. All participants will receive "active" or "real" stimulation from the sTMS device. There are no "sham" or "fake" treatments in this study. A pillow rests on the base of the device to provide you with a comfortable, stable platform that keeps your head in the correct position during sTMS treatment sessions. You will hear some subtle sounds and feel some subtle mechanical vibration as the 1-inch cylinder-shaped magnets rotate in the device over your forehead.

Risks and Inconveniences In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, risks associated with the procedures, possible benefits of participation, and possible alternatives. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form. In preparation of this consent form, it was necessary to use several technical words. Please ask for an explanation of any that you do not understand.

Risk of Mood Destabilization: Risks associated with participation in this trial include possible lack of positive response to the treatment, and/or worsening of depressive symptoms and/or mood destabilization. Furthermore, there is a theoretical risk of mood swing from depression to hypo/mania episode with the treatment. In addition, occasionally some emotional discomfort may occur while filling out questionnaires or being interviewed about matters pertaining to emotions, mental health, functioning and other relevant experiences.

Risk of Side Effects from sTMS: Risks related to treatment with the NeoSync device is minimal. In a previous study, common side effects included back pain (8.7%) and paresthesia, or numbness/tingling (3.9%).

Upon review of the available preliminary data, the US Food and Drug Administration, who regulates these devices, classified the NeoSync sTMS device as a "nonsignificant risk" device, which means that the device does not present a potential for serious risk to health.

Risk of discomfort during EEG: Subjects may feel areas of pressure on their scalp at the location of the recording electrodes during collection of EEG data.

Risk during MRI procedures: MRI imaging is generally considered to be safe if the participant does not have metallic objects in the body. Some people experience anxiety, panic or a sensation of claustrophobia when lying in the MRI machine. A separate consent form associated with use of the Brown MRI Facility will be reviewed with you prior to participating in the scan. The MRI in this study does not constitute a clinical scan, which means the MRI cannot be used for diagnostic purposes. The scanner also makes loud noises during imaging.

Any intervention may have unforeseen side effects. You should know that the prediction of treatment effects in any individual cannot be done with certainty, and unexpected potentially harmful effects occasionally occur with the administration of any type of intervention. If you have questions about magnetic stimulation, or if you experience any disturbing side effects during the study, inform study personnel. In the event of any unexpected, potentially harmful effects of any treatment administered in this study, we will monitor your condition closely and institute appropriate treatment.

Women Please Note:
sTMS is not recommended for use during pregnancy. sTMS may be harmful to a developing fetus. Therefore, you may be tested for pregnancy at the time of your admission to the study. Prior to your beginning the study we will discuss with you in more detail the importance of avoiding pregnancy. We will specifically ask you to let us know if you change your mind and decide to become pregnant during the study.

Benefits
If you decide to participate in the study, you will receive a thorough evaluation of your depressive symptoms at no cost to you, and possible relief from bipolar depression symptoms from an investigational treatment with a favorable side effect profile. Furthermore, it will also help to advance the understanding of treatment options for bipolar depression in general.

Economic Considerations
You will not receive payment for your participation in the study. However, you will receive investigational sTMS treatments and clinical assessments at no cost to you. If you participate in the MRI scans, you will receive a gift card in the value of $25.00 for each of the MRI scans.

NeoSync is providing the devices to Butler Hospital so the researchers can offer the study intervention at no cost to you. sTMS treatments and all of the tests and procedures that will be done only for this research will be paid for by the study funds.

In Case of Injury
We will offer you services in Care New England facilities as needed to treat any injury that results directly from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for any injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed on the last page of this consent form.

Alternative Treatments

sTMS is an investigational treatment and it is not known if it will help relieve symptoms of depression in patients with bipolar disorder. If you choose not to participate in this study, there are standard treatments for bipolar depression such as medication and psychotherapy, which can be administered by a clinician and/or prescribed by a physician or nurse outside of this research study. The primary risk of untreated BD is prolonged disability and suffering, or if the condition becomes severe or worsens, possibly attempting or completing suicide.

Alternative to Participation

As an alternative to participating, you may choose not to participate in these research procedures and have usual care for bipolar depression as directed by community healthcare providers. Your current or future care at Butler Hospital will not be affected in any way if you decide not to participate in this research study.

Financial Disclosure

Butler Hospital has received research funding from NeoSync, Inc. to conduct research trials with the device used in this study. The study physicians and research staff are employees of Butler Hospital and have no direct personal financial relationships with the company that makes the sTMS device (NeoSync, Inc.).

Voluntary Participation

You are free to decide whether or not to participate in this study, and you are free to withdraw from the study at any time. A decision not to participate or to withdraw from the study will not adversely affect your current or future interactions with Butler Hospital or Care New England. Your participation in the study may be terminated by the researchers without regard to your consent; in that case, you are entitled to an explanation of the circumstances leading to that decision.

Confidentiality

Personal identifiers will be removed from any identifiable private information about you in the final research dataset created by this study. The de-identified information may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you. You will not be personally identified in any reports or publications that may result from this study. The confidentiality of the information you provide to us will be maintained in accordance with state and federal laws. If you tell us something that makes us believe that you or others have been or may be physically harmed, we may report that information to the appropriate agencies.

To keep your information safe, research data will be captured in a de-identified way (without your name or other information that identifies you personally) and a list linking your identity with a coded ID number for this study will be kept in a restricted-access file on a password-protected server maintained by CNE. Any paper documents that contain personal health information about you will be stored in locked cabinets or secure spaces dedicated for research records. General information about this study has been or will be submitted to the federal

clinical trial registry databank, which can be accessed on the Internet at www.ClinicalTrials.gov

Authorization for use/disclosure of Health Information that Identifies you for a Research Study
If you sign this document, you give permission to researchers at Butler Hospital to use and share your health information that identifies you, for the purpose of conducting the research study described above. Your health information related to this study may also be shared with and used by individuals outside of Butler Hospital, including your psychiatric clinicians or other healthcare providers involved in your medical care, the Butler Hospital Institutional Review Board, the Brown MRI facility staff.

The health information that we may use or share with others for research purposes includes your diagnosis and medications, current and past medical and treatment history.

Your health information may also be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions. The U.S. Food and Drug Administration (FDA) may inspect all study records to ensure that the study is being conducted in accordance with FDA regulations.

Butler Hospital is required by law to protect your health information. Individuals outside of Butler that receive your health information may not be required by Federal privacy laws (such as the HIPAA Privacy Rule) to protect it, so we cannot guarantee that they will not share it without your permission.

Please note that:

- You do not have to sign this consent form, but if you do not, you may not participate in or receive research-related treatment in this study.
- Butler Hospital may not withhold treatment or refuse to treat you, based on whether you sign this consent form.
- You may change your mind and revoke (take back) this consent and authorization at any time. If you no longer want to give us permission to use your health information for this research study, you must contact the Principal Investigator, Dr. Linda Carpenter, and you will be instructed to provide a written statement.
- Even if you revoke (take back) this consent and authorization, Butler researchers may still use or share health information about you that they already have obtained, when doing so is necessary to maintain the integrity or reliability of the current research.
- You generally will not have access to your personal health information related to this research until the study is completed. At the conclusion of the research and at your request, you will have access to your health information that Butler Hospital maintains in a designated record set, according to the Notice of Privacy Practices provided to you by Butler Hospital. The designated record set includes medical information or billing records used by doctors or other health care providers at Butler Hospital to make decisions about individuals.
- Your health information will be provided to you or to your physician if it is necessary for your care.
- This Authorization does not have an expiration date.

Questions
In preparation of this consent form it was necessary to use several technical words. Please ask for an explanation of any that you do not understand.

Authorization:
I have read this form and decided that _____
(name of participant)
will participate in the project described above. Its general purposes, the nature of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. I have received a copy of this consent form.

_____ _____
Signature Date
Relationship: (self, parent, guardian)_____

_____ _____
Signature of Principal Investigator Date

~or~

_____ _____
Signature of Person Obtaining Consent Date

Telephone Number of Principal Investigator or Person Obtaining Consent_____

If you have further questions about this project or about research-related injuries, please contact Linda Carpenter at 401-455-6537. If you have questions about your rights as a research subject, please contact Paul F. Malloy, Ph.D., Associate Chair, Butler Hospital Institutional Review Board, at 401-455-6355.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE IRB OFFICE

THIS FORM IS VALID UNTIL:

DATE: December 31, 2018

IRBNET ID# 839938

BUTLER IRB REFERENCE# 1601-004

BY (ADMINISTRATOR): CCordeiro