CT-DBS for Traumatic Brain Injury Using the Medtronic Activa PC+S System

Study Protocol and Statistical Analysis Plan

NCT02881151

January 30, 2020

Study Protocol

Title:	**CT-DBS for Traumatic Brain Injury Using Medtronic Activa PC and Percept PC**
Type and Phase:	Single arm, single center feasibility study
Study Product:	Medtronic Activa PC system, Medtronic Percept PC system and Medtronic Nexus-E system for central thalamic deep brain stimulation (CT-DBS)
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
SAE	Serious Adverse Event
UADE	Unanticipated Device Event
CT-DBS	Central Thalamus-Deep Brain Stimulation
GOSE	Glasgow Outcome Scale-Extended
MCS	Minimally Conscious State
IPG	Implantable Pulse Generator
EMCS	Emergence from Minimally Conscious State
SMTBI	Moderate to severe Traumatic Brain Injury
GPi	Internal Globus Pallidus
STN	Subthalamic Nucleus
VPM	Ventral Posterior Medial
CRF	Case Report Form
eCRF	Electronic Case Report Form
INS	Implantable Neurostimulator
IC	Integrated Circuit
PIC	Algorithm Microprocessor
ANT	Attention Network Test
PRO	Patient-Reported Outcomes

1. SYNOPSIS

Table 1: Protocol Synopsis

Title	Central Thalamic Deep Brain Stimulation for the Treatment of Traumatic Brain Injury
Study Groups	Single arm study of 6 subjects
Study Objective	Pilot study to inform the safety and efficacy of central thalamic-deep brain stimulation (CT-DBS) in the treatment of chronic cognitive impairment and residual disability caused by traumatic brain injury (TBI).
Study Device	Medtronic Percept PC system for central thalamic deep brain stimulation (CT-DBS)
Clinical Hypothesis	CT-DBS will be safe in the study population and will enhance cognitive function as indexed by the primary outcome measure
Study Population	Adult patients with a history of moderate to severe TBI (GCS ≤12) who continue to demonstrate neuropsychological impairment and functional disability (Glasgow Outcome Scale- Extended = 5-7) at least 24 months post-injury. The 6 participants will be separated into three pairs.
Study Design	Single arm, open-label, sponsor-investigator study
Number of Sites	1 site
Total Number of Subjects	18 subjects screened with a total of 6 subjects enrolled for randomization and implantation
Duration of Study	The total duration of the study is 12 to 14 months depending on cohort.
Inclusion Criteria	• History of moderate to severe TBI based on worst GCS score within first 48 hours of injury (acceptable GCS range = 3-12) • Age 22-60 • At least 24 months from date of onset • Fluent in English and able to independently provide consent • Retains decision-making capacity and is able to function independently (i.e., unsupervised) in the home setting • Multiple unsuccessful attempts to sustain competitive employment or complete an academic degree-granting program of study • Either receives no CNS stimulants or other medications known to affect cognitive function, or on stable doses of these medications for the last three months (see additional information regarding concomitant medications below)

Exclusion Criteria	• History of major developmental, neurologic, psychiatric or substance use disorder with evidence of disability prior to onset of TBI • Major medical co-morbidities including: end stage renal failure, severe heart failure, coagulopathy, severe respiratory problems, severe liver failure, uncontrolled hypertension or other significant medical co morbidities • Have had a documented seizure within 3 months of study screening (subjects may re-screen if seizure free after initial screen failure) • Malignancy with < 5 years life expectancy • Untreated / uncontrolled (severe at the time of enrollment) depression or other psychiatric disorder • Women of childbearing age who do not regularly use an accepted contraceptive method • Inability to stop anticoagulation therapy or platelet anti-aggregation therapy before, during and after surgery • Previous DBS or other brain implants • Previous ablative intracranial surgery • Implantable hardware not compatible with MRI • Condition requiring diathermy after DBS implantation • Hardware, lesions or other factors limiting placement of electrodes in optimal target location in the judgment of the operating surgeon • Concurrent enrollment in any other clinical trial • Any condition or finding that, in the judgment of the PI, significantly increases risk or significantly reduces the likelihood of benefit from DBS
Main Study Phases/Activities	• Pre-screening Evaluation and Informed Consent • Randomization to 1of 3 baseline conditions lasting 30, 44 or 58 days. Each participant will also be randomly assigned to a treatment withdrawal or continuation condition for 21 days following the 90-day unblinded treatment phase • Baseline physical and neurological pre-operative examinations • Hospitalization and surgical implantation of DBS system • Post-operative washout (30-day surgical washout for resolution of any transient physiological or behavioral effects of surgery) • DBS Stimulation Titration/Optimization (14 days, optimize settings to be used during treatment phase) • Unblinded Treatment Phase (90 days) • Randomization to treatment withdrawal or continuation • 6-month open label follow up
Outcome Measures	Primary outcome measure: o Trail Making test Secondary outcome measures include: • Measures of Cognition o Ruff 2 & 7 • Physical Symptoms (self-report)

	○ Rivermead Post-Concussion Symptom Questionnaire (RPQ) • Psychological Health (Self-report) ○ Patient Health Questionnaire-9 (PHQ-9) ○ Columbia Suicide Severity Rating Scale (C-SSRS) • Quality of Life ○ Traumatic Brain Injury Quality of Life (TBI-QoL subscales) • Measure of Global Function ○ Glasgow Outcome Scale – Extended (GOSE)
Safety Endpoints	Rate of adverse events, serious adverse events and adverse device effects
Statistical Methods and Sample Size Determination	This is a single center, feasibility study to be performed by a sponsor investigator at an academic institution. All baseline, procedural, and safety and effectiveness follow-up data will be summarized with appropriate descriptive statistics. For continuous variables, we will summarize data by the mean, median, standard deviation, minimum and maximum. For non-continuous variables we will summarize by percentages and frequency distributions. We will tabulate data for all enrolled patients.

2. INTRODUCTION

This study involves the treatment of cognitive impairment secondary to traumatic brain injury (TBI) using the Medtronic Percept PC for central thalamic deep brain stimulation (CT-DBS). The proposed study, if successful, will provide supporting evidence for the development of a novel therapeutic approach utilizing CT-DBS to improve these enduring cognitive impairments arising in persons with multi-focal structural brain injuries. This research will address the critical gap of the lack of any available treatments. CT-DBS targets well-defined neuronal populations within the central thalamus that have known anatomical and physiological specializations, which not only provide a key role in arousal regulation during cognitively-mediated behaviors, but also exhibit a particular vulnerability to dysfunction in the setting of multi-focal, non-selective brain injuries.

The proposed study builds on a previous clinical study of CT-DBS in subjects with very severe traumatic brain injuries (Schiff et al. 2007 [22]; Giacino et al. 2012 [10]). In the preliminary clinical and preclinical studies, we have identified that CT/DBS acts through specific circuit and cellular mechanisms that counter the effects of deafferentation and impaired cellular function across long-range cortico- cortical connections and modulatory cortico-striato-pallidal-thalamocortical pathways following brain injuries by direct activation of the frontostriatal network. We have further identified a strategic location within the three-dimensional confines of the central thalamus that provides an optimal means for facilitating arousal, attention, executive function and motivation.

Our proposed study aims to support development of CT-DBS as a novel therapeutic avenue for accessing cognitive reserve in patients with acquired brain injuries. In the proposed feasibility study of 6 subjects at a single investigational site, we will test the safety of CT-DBS in the moderate to severe traumatic brain injury (SMTBI) population with GOSE 5-7 level recovery and collect data to establish the translation of preclinical studies into human application of CT-DBS. We estimate a screen failure rate of 3:1 for this study.

This is a single-site feasibility study being conducted by a sponsor-investigator. There have been no changes made to the Medtronic Percept PC for use in this study.

2.1. Traumatic Brain Injury

TBI is a leading cause of death and long-term disability in the United States as well as worldwide (Murray and Lopez 1997 [19]). Significant attention has been given to TBI in recent years, particularly due to significant numbers of military personnel who have suffered TBI in combat since 2000. According to the Defense and Veterans Brain Injury Center, there were 212,742 TBIs between 2000-2011Q1 in all Armed Forces and 2,235 of these were severe TBIs. Additionally, the statistics of TBI are even more concerning in the civilian population. In addition to 50,000 TBI-related deaths in the US civilian population, there are over 1 million Americans treated in emergency departments every year and 235,000 hospital admissions (Corrigan et al. 2010 [4]). It is estimated that 43% of those discharged from hospital admissions (124,000 patients per year) will develop long-term disability due to TBI (Selassie et al. 2008 [27]). Thus, TBI disproportionately affects young and otherwise healthy individuals who could contribute to the work force. The intervention proposed here is aimed at providing functional improvements that may produce social and vocational reentry and improved vocational performance. Successful treatment of individuals in this disability range thus has the potential for tremendous impact, both for the individual and for society.

Deep brain stimulation is a standard FDA approved treatment for advanced movement disorders and holds great promise for other neurologic disorders, including TBI because of its distinct mechanism of action that can produce control of axonal action potential generation. The safety and feasibility of DBS for patients in chronic post- traumatic injury who fulfilled the behavioral criteria for the minimally conscious state (MCS) and emergence from minimally conscious state (MCS and EMCS) has been demonstrated in a previous IDE and we have provided the proof-of-concept that cognitively-mediated functions can be facilitated in chronic brain injury with DBS directed into the central thalamus (Schiff et al. 2007 [22]). The scientific basis for the CT/DBS approach taken here has evolved over a 20-year period of study of the pathophysiology of impaired consciousness in human subjects and the physiological investigations of the role of the central thalamus in forebrain arousal regulation (Purpura and Schiff 1997 [20]; Schiff and Plum 2000 [21]; Shirvalkar et al. 2006 [28]; Schiff et al. 2007 [22]; Smith et al. 2009 [29]; Schiff 2008 [23], 2009 [24], 2010 [25], 2012 [26]). These studies are described in more detail in the section that follows.

Approximately 70% of persons who sustain moderate to severe TBI experience chronic cognitive impairments (TBI Model Systems National Data and Statistical Center [31]) that disrupt vocational, social and emotional functioning. This is due, in part, to diffuse axonal injury which results in widespread disconnection across the cerebrum, leading to secondary neuronal death concentrated in the intralaminar nuclei of the central thalamus. After one year, one-third of these individuals remain unemployed and nearly 40% continue to require supervision (TBI Model Systems National Data and Statistical Center [31]). After five years, more than 30% still require some level of supervised care, and 29% report dissatisfaction with life (Corrigan 2014 [5]). Self-report and neuropsychometric findings suggest that slowing in processing speed, mental fatigue and deficient mental control contribute significantly to residual disability following TBI. We have established that CT-DBS can significantly modulate and facilitate performance across a wide range of executive function tasks in the non-human primate (Baker et al. 2011 [1]; 2012 [2]) and in a pilot human study (Schiff et al. 2007 [22]), including tasks involving sustained

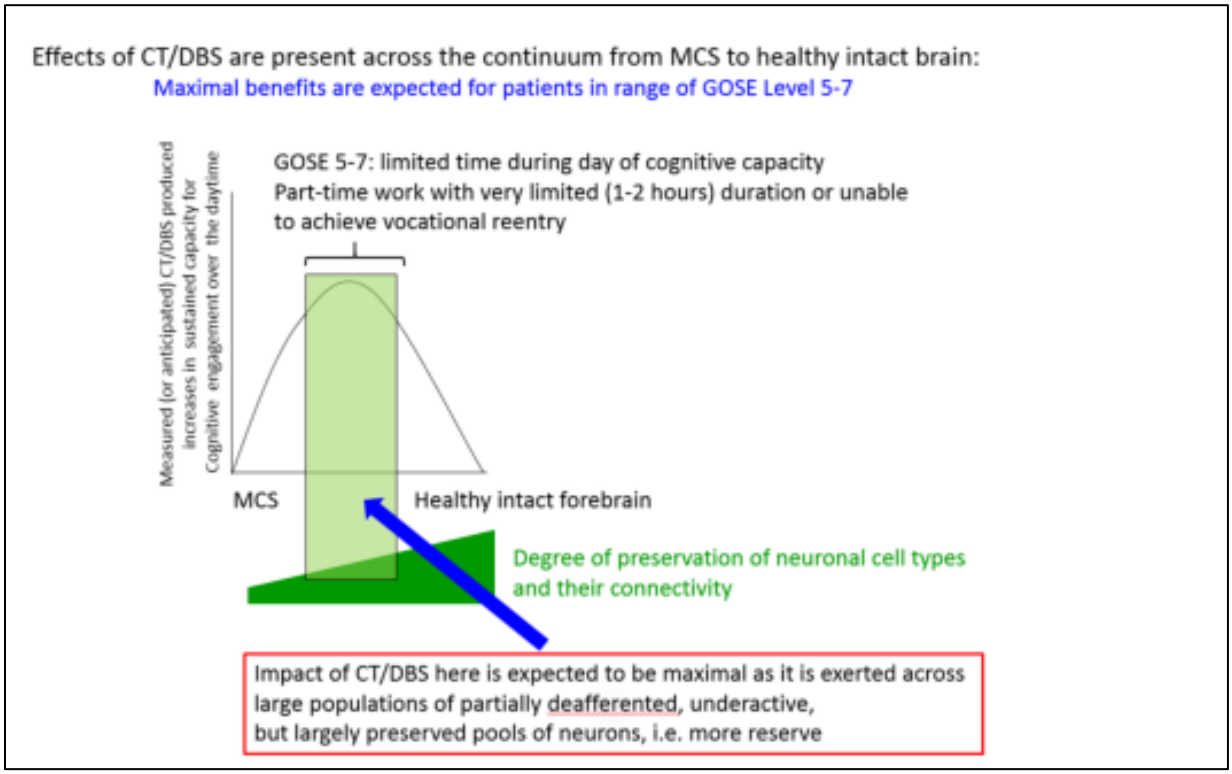
attention, working memory and complex visual pattern recognition. We postulate based on our prior investigation that the effects of CT-DBS are mediated by activation of downregulated frontocentral cortical regions and will produce improvements in processing speed and executive functions as measured by standardized neuropsychometric measures (Trails B, continuous performance tasks) and customized behavioral tasks assaying sustained attention and working memory. We also anticipate that these changes in cognitive efficiency will facilitate improvements in vocational productivity, psychological health and self-reported quality of life.

2.2. Rationale for Proposed Study

In the proposed feasibility study of six subjects, we plan to evaluate the safety and efficacy of CT/DBS in patient subjects who have recovered from a moderate or severe brain injury (initial GCS 12 or lower) to an outcome level ranging from GOSE 5 to the lower half of GOSE 7. As briefly outlined below and based on our pre-clinical studies of CT/DBS in intact non-human primates and rodents with and without TBI, and our clinical experience with CT/DBS in MCS/EMCS subjects, we outline the rationale that this new patient TBI population is optimally matched to obtain clinically meaningful benefits from CT/DBS (see Figure 1). We are targeting a collection of well-defined neuronal populations within the central thalamus that have known anatomical and physiological specializations that both provide a key role in arousal regulation during cognitively- mediated behaviors and are particularly vulnerable to dysfunction in the setting of multi- focal, non-selective brain injuries.

As per Figure 1, an optimal benefit of CT/DBS in patients recovering from moderate to severe traumatic brain injury is proposed for the functional outcomes captured across the GOSE level 5 to 7 range on this scale. The conceptual basis for targeting this population includes evidence that CT/DBS can have a significant behavioral facilitation effect across the range of minimally conscious state (Schiff et al. 2007) to executive function in the intact mammalian forebrain (Baker et al. 2011, 2012, 2013). Patients with initial moderate to severe brain injury (GCS<12) and recovery to GOSE level 5 to lower 7 are anticipated to demonstrate significant cerebral deafferentation leading to a large population of neocortical, striatal and thalamic neurons that do not reach their full potential dynamic range as a result of deafferentation but could under conditions of sufficiently increased background synaptic activity.

Figure 1: Effects of CT/DBS are Present across the Continuum from MCS to Healthy Intact Brain



2.3. Rationale for CT/DBS

The fundamental rationale for CT/DBS as a therapeutic modality in the SMTBI patient population with recoveries in the range of GOSE 5-7 targeted here is based on several considerations:

- the frequent observation of a specific clustering of neuropsychological impairments in this patient population
- the specific role of frontostriatal systems in establishing these specific neuropsychological functions in the brain
- the functional role of the central thalamus in supporting frontostriatal systems and regulating activity across frontostriatal neuronal populations in response to cognitive demands
- the common pathology of deafferentation of the central thalamus arising across all moderate to severe brain injuries with a maximal predicted preservation of neuronal cell types in the GOSE 5-7 level recovery from STBI patient population
- clinical and pre-clinical studies demonstrating that CT-DBS can facilitate behaviors in humans and rodents with TBI, and that these specific neuropsychological functions affected in the SMTBI patient population can be significantly facilitated by CT-DBS in a human subject with very severe brain injury, as well as in intact non-human primates.

2.4. Neuropsychological impairment following moderate to severe TBI: Target patient population

Diffuse traumatic brain injuries produce a very wide range of neuropsychological deficits that associate with distinct injury patterns but have considerable overlap (Levin et al. 2013). Several studies, however, have characterized common symptom clusters which do show clear consistency across large population cohorts of patients with both moderate to severe and mild traumatic brain injuries (Levin et al. 2013 [14]; Dikmen et al. 2003 [6]). A larger proportion of the STBI patient population targeted here is known to suffer significant ongoing morbidity due to cognitive impairment (Dikmen et al. 2003 [6]). A systematic relationship has been established between the severity of initial deafferentation (as assessed by clinical variables) and neuropsychological measures of working memory, learning, attention, and information processing speed (Dikmen et al. 2003 [6]). Detailed evaluation of a cohort of 500 patients suffering STBI provides additional population data supporting both the uniqueness and the specificity of measures of working memory, attention and processing speed in the STBI patient population that identify the sub-cohort we plan to target in this study (Dikmen, unpublished studies). Specifically, population data show clear separation of performance of the Trails B test (TMT-B) in the group of symptomatic patients with GOSE 5-7 level recovery from those in the Upper Good recovery range (GOSE 8). These population-based data show a marked difference in median completion time on the TMT-B between patients functioning in the Lower or Upper Moderate (UM=76s) to Lower Good (LG=75s) outcome categories of the GOSE, as compared to those functioning in the Upper Good (UG=52s) range. A primacy of these symptoms in the STBI group is further identified in studies of outcomes of mild TBI supporting the biological continuity of the effects of TBI and linkage of the primary neuropsychological functions targeted for support here using CT-DBS. In mild TBI subjects, processing speed deficits are identified as the first principal component of measurable deficits, followed by an index of visual working memory (Levin et al. 2013 [14]). These measurements are consistent with the hypothesis that the anterior forebrain is the area most sensitive to deafferentation injuries associated with TBI of all types (Schiff 2010 [25]).

2.5. Role of frontostriatal systems in supporting sustained attention, working memory and processing speed

Human neuroimaging and studies in non-human primate provide a convergence of evidence that frontostriatal systems organize and support the neurophysiological substrate underpinning a group of psychological capacities collectively described as executive functions (Stuss and Knight 2013 [30]). At the core of this wide-ranging set of capacities are the neuropsychological functions of sustaining attention; holding instructions or briefly presented information in memory; and processing information quickly ahead of executing a variety of motor responses such as gestures and spoken language. Persistent activity in specialized neuronal populations in frontal cortex, striatum and thalamus has been consistently identified as supporting sustained attention, working memory, and processing speed (McCormick et al. 2003 [18]). The loss of dynamic range of activation of frontostriatal systems in response to demands on executive function systems can thus be understood as the result of deafferentation of these neurons resulting from brain injuries and of their main source of activation in the central thalamus (see below). The dominance of psychological effects of STBI by the cluster of impaired sustained attention, working memory, and cognitive processing speed deficits is the direct result of the

graded impact in those patients remaining functionally affected by their injuries of the loss of this general purpose base function of frontostriatal systems (Duncan and Owen 2003 [7]).

2.6. Role of central thalamus in pathophysiology of moderate to severe TBI

The central thalamus is anatomically specialized to provide strong synaptic drive across the frontal and prefrontal cortices and rostral striatum in response to cognitive demands (reviewed in Schiff 2008 [23]; Mair and Hembrook 2012 [16]). Control of the activation of central thalamus in response to these demands emanates from medial frontal cortex and is modulated by the full set of brainstem 'arousal system' inputs from cholinergic, noradrenergic, and other monoamine pathways. Diffuse axonal injury results in widespread disconnection across the cerebrum with secondary neuronal death of these central thalamic neurons arising as a common pathology; the concentration of damage in the central thalamus (intralaminar) and related association nuclei indexes the severity of outcome (Maxwell et al. 2006 [17]). These nuclei show a greater vulnerability to multifocal brain injury because of their widespread projections that lead to their disproportionate deafferentation that is associated with diffuse injuries. Loss of input from these neurons secondary to this deafferentation leads to a failure to maintain sufficient membrane depolarization to produce or sustain action potential firing rates typical of frontocortical and striatal neuronal populations in the wakeful state; in studies of severely brain injured human subjects who remain within the very severely impaired categories of minimally conscious state and confusional state this effect can be measured in differences in regional cerebral metabolic rates (Fridman et al. 2014 [9]); the level of recovery of central thalamic metabolism in these studies grades level of recovered behavioral function. Several circuit- level specializations of the central thalamus underlie dysfunction of the forebrain after STBI and deafferentation of the central thalamus (Schiff 2010 [25]).

3. Study Objectives

This is a feasibility study to inform the safety and efficacy of central thalamic-deep brain stimulation (CT-DBS) in the treatment of chronic cognitive impairment and residual disability caused by traumatic brain injury (TBI).

4. Study Design

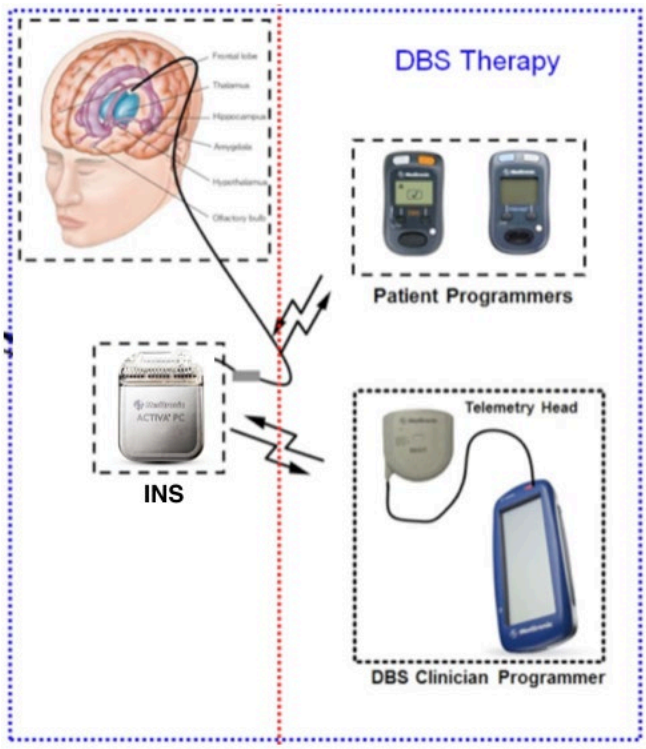
This is a single arm, sponsor-investigator feasibility study to be conducted at a single investigational site.

5. Study Device

This study utilizes the Medtronic Percept PC Deep Brain Stimulation system. The Percept PC has been approved by the FDA for Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication. The device is being provided by the manufacturer, Medtronic, and no changes have been made to the device for use in this study.

The Percept PC system consists of the neurostimulator, leads, extensions and clinician and patient programmers. As shown in Figure 2 below, there are separate programmers for the clinician and the patient.

Figure 2: Percept PC System



6. STUDY PLAN

The research plan is organized around the central aim of acquiring pilot clinical data that will inform the safety and efficacy of central thalamic-deep brain stimulation (CT-DBS) in the treatment of chronic cognitive impairment and residual disability caused by TBI. We intend to recruit 6 adults with a history of moderate to severe TBI (GCS = 3-12) who continue to demonstrate neuropsychological impairment and functional disability at least 24 months post-injury (Glasgow Outcome Scale- Extended = 5-7) {Wilson, 1998, Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use}.

Following study enrollment, participants will be randomly assigned to 1 of 3 baseline conditions lasting 30, 44, or 58 days. Two participants will be assigned per condition. The staggered baseline schedule will enable assessment of CT-DBS effects within individual subjects and across subject pairs. Each participant will also be randomly assigned to a treatment withdrawal or continuation condition. This process is explained in detail in Section 6.3 of this document.

Following a 30 to 60-day presurgical baseline phase to ensure surgical readiness and establish current level of function across multiple domains, participants will undergo implantation of a deep brain stimulator in the central lateral nucleus of the thalamus. Implantation of the stimulator will be followed by a staggered post-surgical baseline that will increase progressively for each pair of participants. After a 14-day stimulation titration phase, CT-DBS will be

administered for 90 consecutive days. Following the unblinded stimulation phase, participants will enter a 21-day double-blinded treatment withdrawal phase. The study will formally conclude at the end of the withdrawal phase. Participants will be given the option to continue to use the device following study termination, if they are receiving benefit.

The study design includes 3 unique features that were incorporated to detect treatment effects, reduce sources of bias and estimate generalizability:

- Subject pairs will be randomized to one of 3 progressively-increasing baseline observation periods. Should treatment be effective, improvements in performance on the outcome measures will occur in temporal contiguity to the onset of CT-DBS. This design element will help differentiate the effects of CT-DBS from random fluctuations in function.
- Treatment will be withdrawn in a double-blinded manner- neither the investigators nor the subjects will have knowledge of when CT-DBS is discontinued. This feature will minimize the influence of examiner and subject bias on the outcomes of interest.
- Outcome assessment across multiple subjects following establishment of a stable baseline will enable identification of a significant treatment effect and permit inferences to be drawn concerning generalizability of results (Schiff, 2007 [22], Behavioral improvements with thalamic stimulation after severe traumatic brain injury).

Study Operations: This is a single site study. All procedures, assessments and follow-up care will be take place at Stanford University under the leadership of Jaimie Henderson, MD. The study co-investigators from Weill-Cornell, Spaulding Rehabilitation/Harvard, Cleveland Clinic and University of Utah will travel to Stanford for procedures. Two additional Weill-Cornell faculty members will travel to Stanford to do EEG testing and other data collection. Dr. Nicholas Schiff at Weill-Cornell will lead the data analysis.

The members of the team have had successful remote collaborations for over a decade. The project has adequate funding for remote collaboration tools for conference calling and document sharing, travel for in-person meetings and a project manager.

6.1. Study Population

6.1.1. Inclusion Criteria

- History of moderate to severe TBI based on worst GCS score within first 48 hours of injury (acceptable GCS range = 3-12)
- Age 22-60
- At least 24 months from date of onset
- Fluent in English and able to independently provide consent
- Retains decision-making capacity and is able to function independently (i.e., unsupervised) in the home setting
- Multiple unsuccessful attempts to sustain competitive employment or complete an academic degree-granting program of study

- Either receives no CNS stimulants or other medications known to affect cognitive function, or on stable doses of these medications for the last three months (see additional information regarding concomitant medications below)

6.1.2. Exclusion Criteria

- History of major developmental, neurologic, psychiatric or substance use disorder with evidence of disability prior to onset of TBI
- Major medical co-morbidities including: end stage renal failure, severe heart failure, severe congestive heart disease, coagulopathy severe respiratory problems, severe liver failure, uncontrolled hypertension or other significant medical co morbidities
- Have had a documented seizure within 3 months of study screening (subjects may re-screen if seizure free after initial screen failure
- Malignancy with < 5 years life expectancy
- Untreated / uncontrolled (severe at the time of enrollment) depression or other psychiatric disorder
- Women of childbearing age who do not regularly use an accepted contraceptive method
- Inability to stop anticoagulation or platelet anti-aggregation therapy before, during and after surgery
- Previous DBS or other brain implants
- Previous ablative intracranial surgery
- Implantable hardware not compatible with MRI
- Condition requiring diathermy after DBS implantation
- Hardware, lesions or other factors limiting placement of electrodes in optimal target location in the judgment of the operating surgeon
- Concurrent enrollment in any other clinical trial
- Any condition or finding that, in the judgment of the PI, significantly increases risk or significantly reduces the likelihood of benefit from DBS

6.1.3. Concomitant Medications

Subjects who are on centrally-acting medications will remain eligible for enrollment as long as the dose of the medication has been stable for at least three months prior to the date of enrollment. All concomitant medication and concurrent therapies will be documented during the Baseline Visit, and at every subsequent study visit. At each study visit, the Study Coordinator will review and print the list of concomitant medications that were completed at the participant's prior visit in order to accurately review and document changes in the participant's concomitant medications or concurrent therapies. The generic name of the drug, presence/absence of the drug at the time of randomization, date started, dose, route, unit frequency of administration (i.e., schedule) and the date stopped or changed will be recorded. We will also record whether the medication was prescribed to treat an AE (and, if so, the date of the AE form) or a new clinical

problem that arose after enrollment. The same information will be recorded for non-pharmacologic therapies, with the exception of dose and route of administration.

If there are any changes in a centrally-acting medication, or if a new centrally-acting medication is added following randomization, the Study Coordinator will apprise the Sponsor and a protocol violation will be recorded. The Sponsor will evaluate the potential influence of the new medication on the study treatment and will make a disposition regarding continued participation in the trial. Any disposition recommending withdrawal from the trial will be reviewed by the Clinical Oversight Committee (see Section 10 below) before any action is taken.

6.2. Informed Consent

If no exclusion criteria are identified during the pre-screening interview, the investigator/coordinator will provide the informed consent form ahead of time to potential candidates. Candidates will be asked to review and mark the document with questions. Study investigators will be available for questions in person or over the phone or teleconference. The coordinator will then arrange for a consent meeting with the sponsor to: (a) review the informed consent form; (b) clearly explain all study procedures, risks, potential benefits, alternative therapies (if available); and (c) answer any questions the participant may have regarding the study. The sponsor will be present for the entire informed consent meeting. A consent for release of medical records will be obtained during the consent meeting to acquire additional information and medical records related to study eligibility. The participant will be reminded that study eligibility will not be finalized until all screening and pre-operative tests and procedures have been completed.

After the study has been fully explained to the potential subject and all questions have been addressed, written informed consent will be obtained prior to the performance of any study-specific procedures. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirements, including local IRB requirements.

6.3. Randomization to Multiple Baseline Condition and Treatment Withdrawal

Following study enrollment, participants will be randomly assigned to 1 of 3 baseline conditions lasting 30, 44, or 58 days. Two participants will be assigned per condition. The staggered baseline schedule will enable assessment of CT-DBS effects within individual subjects and across subject pairs. Each participant will also be randomly assigned to a treatment withdrawal or continuation condition. Neither the investigator nor the participant will have knowledge or be apprised as to whether DBS is on or off during this period. For participants assigned to the treatment withdrawal condition, DBS will be switched off for 21 days (on days 170, 184, and 198 for cohorts 1-3, respectively) immediately after completing the 90-day unblinded treatment phase. Participants randomized to the continuation condition will continue to receive stimulation 12 hours per day over the same 21-day period. Upon conclusion of the 21-day treatment withdrawal phase, participants will undergo a final re- assessment on the multi-dimensional outcome assessment battery and on the electrophysiologic measures (on day 191, 205, or 219, depending on cohort). Currently there are no known safety issues related to withdrawing stimulation. The purpose of this follow-up visit is to determine if there is evidence of loss of effect in those assigned to the treatment withdrawal condition, and to evaluate the influence of

intervening factors on the effectiveness of DBS. The trial will be considered complete at the end of the treatment withdrawal phase.

6.4. Screening Imaging

Following study enrollment but before the screening visit, participants will undergo volumetric MRI imaging including diffusion tensor imaging for surgical planning and to assess the degree of structural damage, which could preclude successful targeting of the DBS leads. Feasibility of successful targeting of the CT will be determined by the investigative team. If targeting is determined to be infeasible the subject will be withdrawn from the study.

6.5. Screening and Preoperative Baseline Evaluation

One to two months before DBS implant surgery (with 1 month defined as 30 days ± 3 days), participants will complete physical and neurological screening examinations and complete laboratory studies to ensure study eligibility and suitability for surgery. A screen failure is defined as a potential participant who has been consented for screening but is not enrolled for randomization and implantation. A screen failure does not meet all inclusion criteria and/or has answered or tested affirmatively to any exclusion criteria. A potential participant may also fail screening if they are deemed unsuitable for participation based on the clinical judgment of the sponsor investigator. We estimate the screen failure rate to be 3:1, which is based on efficiently pre-screening interested participants, and extensive team review of each case prior to screening.

Participants will also undergo pre-operative multi- dimensional baseline assessment using a battery of cognitive (e.g., attention, memory, information processing speed, executive functions), psychological health (e.g., depression, anxiety) functional status (e.g., employment level) and quality of life (e.g., satisfaction with life) measures (see *Description of Outcome Asssessments* below). A structured interview will also be conducted to obtain additional background information and determine pre-injury levels of academic, vocational and social function. These evaluations can be done either on a single day or on multiple days.

6.6. Inpatient Hospital Stay

Following completion of the preoperative baseline evaluation, participants will be admitted for surgical implantation of the DBS system. All patients will receive one DBS lead in each side of the diencephalon. Both leads will be connected to a single pulse generator that may be implanted on the right or left side of the chest. The procedures may be performed on the same day or staged. The surgical procedures are discussed in more detail below.

6.6.1. Stage I: Bilateral DBS Lead Implantation

Patients will undergo implantation in a fashion similar to that routinely performed by the investigators for movement disorders (Bronte-Stewart, Louie, Batya, & Henderson, 2010 [3]; Machado et al., 2006 [15]). We anticipate that targeting will be simpler in the present study than in our prior experience (Schiff et al., 2007 [22]) because patients in the present population are expected to have less post- traumatic gross anatomical deformities of the cerebrum and diencephalon (see Figure 3). Surgical planning will be performed prior to surgery based on preoperative volumetric MR images acquired with and without contrast, unless there is a clinical contraindication to the use of contrast (Figure 4 below).

Figure 3: **Bilateral DBS, targeting the central thalamic region. In this example, the DBS lead has 1.5 mm height contacts, separated by 1.5 mm gaps. The ventral-most contact was targeted at the central lateral nucleus of the thalamus.**

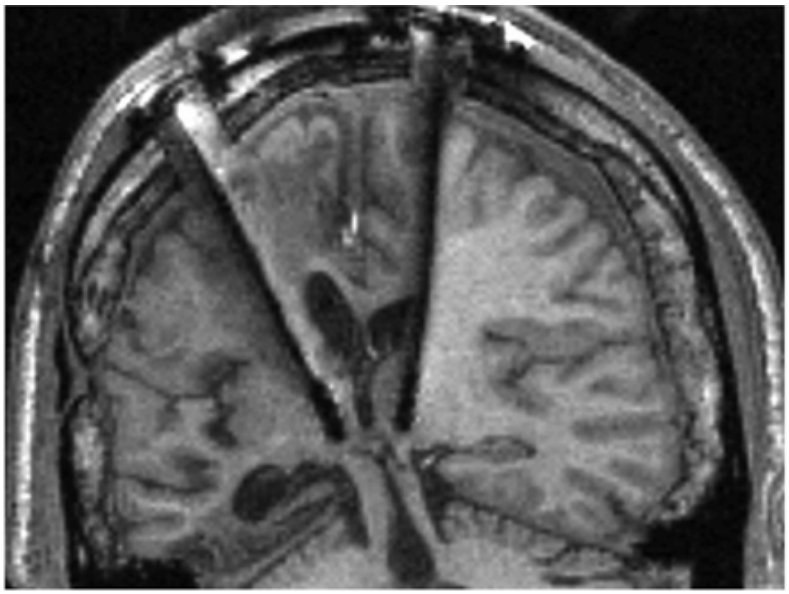
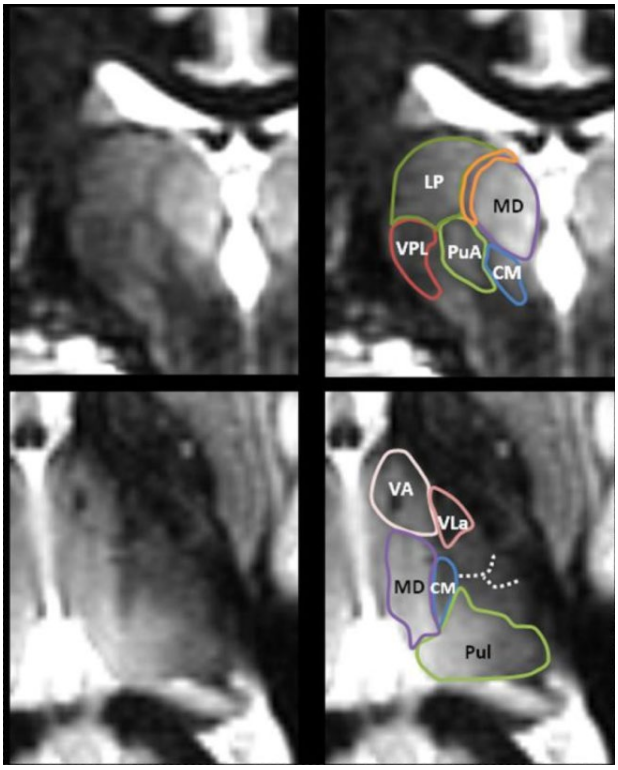
R  L

Figure 4: **Thalamic nuclei visualized at 7T (left), with corresponding segmentations (right) based on the Morel thalamic atlas (Tourdias, Saranathan, Levesque, Su, & Rutt, 2013 [32])). The central lateral nucleus is highlighted in orange.**



One or more days prior to surgery, five stainless steel fiducial markers will be implanted in the skull through small stab incisions under local anesthesia in the neurosurgery outpatient clinic

(Holloway et al. 2005 [12]). A high-resolution volumetric CT scan will be obtained and these images will be imported into the surgical planning station and fused with the previously obtained MRI images, and the final target location determined. On the day of surgery, the patient will be positioned in a custom head cradle. The patient's anatomy will be registered to the neuronavigational system by touching each fiducial marker with a passive planar registration probe equipped with reflective spheres, which can be tracked by the cameras of the surgical navigation unit. Entry points will be marked on the scalp and the patient will be prepared and draped in a sterile fashion. After burr-hole placement, high-impact plastic towers will be attached to the skull bilaterally with 3 titanium bone screws. A sterile reference arc will be fastened to the base of the platform to allow real-time tracking for maximum accuracy. Each fiducial marker will be touched through the drape to perform registration again. Alignment of the trajectory will be accomplished by adjusting the frameless device platform to orient the trajectory to the planned target, using the guidance view of the target provided by the planning software.

Implantation will be guided either by intraoperative imaging (O-arm or MRI) or by microelectrode recording and intraoperative macrostimulation via the DBS leads. Image-guided procedures will be performed under general anesthesia. Microelectrode-guided procedures will be performed under conscious sedation, titrated according to the judgement of the anesthesiology team. In either case, routine procedures for DBS placement will be used. In a recent meta-analysis, no significant difference was found between the two techniques with regard to targeting accuracy and symptom reduction (Ho et al. Mov Disord 2017). Based on the results from the first 5 patients in this study, there does not appear to be a unique neurophysiological signal associated with the CL nucleus. In addition, intraoperative stimulation has not caused side effects that proved informative with relation to the eventual postoperative lead location. Therefore, the final patient in the study will be implanted using image guidance, which we believe will result in equivalent or improved accuracy.

Once the final location for the DBS lead is selected, it will be anchored to the skull in the routine fashion and the surgical sites closed under sedation. The procedure will then be repeated on the opposite side. Following surgery, the patient will be admitted for observation under routine neurosurgical care for intracranial surgery. The investigators will attempt to implant both sides in the same surgical procedure. However, if the patient is tired or, if in the opinion of the investigators there is added risk to completing the implantation of the second side in the same day, the investigator can make the decision to stop the surgery and implant the second side in a separate date, no more than 60 days after implantation of the first side. Because this is routinely done in surgery for movement disorders we will not consider staging of the DBS lead implants to be a deviation of the protocol. At least one CT scan will be done postoperatively during the hospital admission to verify lead location and rule out intracranial hemorrhage.

6.6.2. Stage II

Implantable pulse generator (IPG) implantation and connection to the DBS leads. This is a routine procedure that will be performed under general anesthesia on the same day, following bilateral DBS lead implant. The pulse generator (Model 37601 PC, Medtronic, Inc., Minneapolis, MN) will be implanted on the right or left chest and connected to the DBS leads. Under general anesthesia and with standard surgical technique for DBS, the skin over the distal tip of the leads (protected by a temporary connector) will be opened and the connector externalized and discarded. An approximately 7-10 cm incision will be made in the

infraclavicular region and a pocket fashioned for the pulse generator. A tunneling tool will be used to create a subcutaneous tunnel connecting the infraclavicular subcutaneous pocket to the scalp incision where the lead is externalized. The extension wires will be passed with the tunneling tool. The extension wires will then be connected to the DBS leads and to the pulse generator. Medical adhesive may be used to insure a tight seal and improve signal quality. The incisions will then be approximated with standard surgical technique.

6.7. Post-Surgical Washout Phase

Participants will enter the washout phase following hospital discharge. The length of the baseline will be staggered for each participant pair. The purpose of this phase is twofold: (1) to provide a 30-day surgical washout for resolution of any transient physiological or behavioral effects of surgery and (2) to detect the temporal onset of the stimulation effects for each subject, should these occur at the time of stimulation titration onset. At the end of the surgical washout period, the multidimensional outcome assessment battery that was administered during the pre-surgical baseline phase will be repeated to assess for any changes in function before CT-DBS is switched on (see *Description of Outcome Assessments* below). A CT scan will be performed on day 65 to assess the final lead location, after any post-surgical changes have been allowed to resolve.

6.8. DBS Stimulation Titration/Optimization

On completion of the postsurgical washout phase (beginning day 66, 80, or 94, depending on cohort), DBS will be turned on for the first time to initiate the stimulation titration phase. During this phase, which will last 14 days for all participants, an array of stimulation parameters will be assessed to optimize the settings that will be used during the treatment phase. See Appendix 1 to this protocol for the device programming SOP.

6.9. Unblinded Treatment Phase

After DBS titration/optimization is complete, participants will enter the unblinded 90-day treatment phase during which DBS will remain on for 12 hours per day. At the end of the 90-day treatment phase, participants will undergo re-assessment on the multi-dimensional outcome assessment battery. Electrophysiologic measures will also be sampled on day 139 (± 3 days), 153 (± 3 days), or 167 (± 3 days), respectively, to compare performance before and after treatment.

6.10. DBS Stimulation Long-term Continuation

If ongoing benefits for the subject are determined by the patient and the team, the patient will continue long-term DBS. Decisions about the presence of benefit are expected to be guided by evidence of causal influence of DBS on changes in neuropsychological functions that covary with clinically meaningful outcomes on performance measures or quality of life indices. After the initial battery expires, a rechargeable replacement will be available for individuals who will continue with stimulation.

6.11. Six Month Open Label Follow-Up Period

There will be a 6-month follow-up period at the end of the unblinded treatment phase. There will be two visits during this period with the visits occurring at months three and six. The month three follow up visit will be to assess general health, quality of life and to monitor battery supply

of the device. The six month follow up visit will be to assess general health, quality of life, neuropsychological status and to monitor battery supply of the device.

6.12. Unscheduled Visits:

Participants may have visits in between their regularly scheduled study visits if the sponsor-investigator deems necessary.

7. DESCRIPTION OF OUTCOME ASSESSMENTS

7.1. Measures of Cognition

- ***Trail Making Test (Primary Outcome Measure) {Army Individual Test Battery, 1944, Manual of directions and scoring}***. The TMT is a measure of attention, speed, and mental flexibility. It also tests spatial organization, visual pursuits, recall, and recognition. Part A requires the individual to draw lines to connect 25 encircled numbers distributed on a page. Part A tests visual scanning, numeric sequencing, and visuomotor speed. Part B is similar except the person must alternate between numbers and letters and is believed to be more difficult and takes longer to complete. Part B tests cognitive demands including visual motor and visual spatial abilities and mental flexibility. Both sections are timed and the score represents the amount of time required to complete the task.
- ***Ruff 2 & 7* (Ruff, 1992, The Ruff 2 and 7 Selective Attention Test: a neuropsychological application).** The Ruff 2 & 7 Test was developed to measure two aspects of visual attention: sustained attention (ability to maintain consistent performance level over time) and selective attention (ability to select relevant stimuli while ignoring distractors). The test consists of a series of 20 trials of a visual search and cancellation task. The respondent detects and marks through all occurrences of the two target digits: "2″ and "7." In the 10 Automatic Detection trials, the target digits are embedded among alphabetical letters that serve as distractors. In the 10 Controlled Search trials, the target digits are embedded among other numbers that serve as distractors. Correct hits and errors are counted for each trial and serve as the basis for scoring the test. Speed scores reflect the total number of correctly identified targets (hits). Accuracy scores evaluate the number of targets identified in relation to the number of possible targets.

7.2. Physical Symptoms (self-report)

- ***Rivermead Post-Concussion Symptom Questionnaire (RPQ)* {King, 1995, The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability}**. The Rivermead PCS Questionnaire (RPQ) was originally developed as a measure of severity of symptoms following mild TBI. It consists of 16 post-concussion symptoms including headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed/tearful, feeling frustrated/ impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision and restlessness. In the original version of the RPQ, participants are asked to rate the

degree (on a scale of 0 to 4) to which a particular symptom has been absent or a mild, moderate or severe problem over the previous 24 hours compared with premorbid levels.

7.3. Psychological Health (self-report)

- ***Patient Health Questionnaire-9 (PHQ-9) {Kroenke, 2001, The PHQ-9}***. The Participant Health Questionnaire 9 is a standardized assessment instrument designed to screen, diagnose, monitor, and measure the severity of depression.
- ***Columbia Suicide Severity Rating Scale (C-SSRS)* {Posner, 2011, The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults}**. The C-SSRS is a standardized assessment instrument designed to assess the presence and severity of suicidal ideation and behavior, identify those at risk, and track response to treatment. It has three main sections that evaluate suicidal ideation, the intensity of ideation and suicidal behavior. The first section, suicidal ideation, assesses risk ranging from a death wish or unspecific suicidal thoughts to active ideation with specific plans. In the second section the severity of ideation is evaluated and takes into account the frequency, duration and controllability of suicidal thoughts as well as environmental and cultural deterrents and reasons for suicidal ideation. The third section evaluates actual suicidal behavior and asks if there was an actual attempt, interrupted attempt, aborted attempt or preparatory acts of behavior. It also asks whether there was active suicidal behavior at the time of assessment and, finally, if suicide was completed. A fourth section is only answered in case there was / were suicidal attempts and measures the lethality and potential lethality of each suicidal attempt and respective dates. The CCSRS is a widely-used instrument and is currently being utilized in other first-in-man DBS clinical trials. The C-SSRS will be administered during the pre-surgery baseline assessment and then at any follow-up visit **only if the participant screens positive for suicidal ideation/behavior on the PHQ-9** (i.e. score ≥ 1 on question 9).

7.4. Quality of Life (self-report)

- **Traumatic Brain Injury Quality of Life (TBI-QOL) {Tulsky, 2015, TBI-QOL: Development and Calibration of Item Banks to Measure Patient Reported Outcomes Following Traumatic Brain Injury}**. The TBI-QOL was developed as a comprehensive patient-reported outcomes (PRO) measurement system specifically for individuals with TBI. It consists of 20 independent calibrated item banks and 2 uncalibrated scales that measure physical, emotional, cognitive, and social aspects of health-related quality of life. We will administer the short form (6-10 questions each) of the TBI-QOL Fatigue, Attention/Concentration, and Executive Function subscales.

7.5. Global Functional Outcome Measure

- **Glasgow Outcome Scale – Extended (GOSE) {Wilson, 1998, Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use}**. The Glasgow Outcome Scale Extended (GOSE) is a measure of disability and handicap intended for use following head injury. The

GOSE subdivides the upper three categories of the original Glasgow Outcome Scale (GOS), severe disability, moderate disability and good recovery, into an eight-category scale: dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery to provide more detailed assessment of the functional effects of the injury. A structured interview has been developed to standardize assignment of an outcome category (Wilson et al. 1998).

7.6. Participant Interview

- A structured interview will be administered to obtain information about preinjury medical and social history, and level of social, educational and vocational function.

7.7. Exploratory Measures

7.7.1. Electrophysiological

Each enrolled participant will have electroencephalogram (EEG) studies obtained several times during the course of the study following DBS implantation. The initial EEG recording will be made on the day of admission for surgery. EEG recordings will be obtained using an EGI system (129 scalp sites using the Geodesic EEG Net Station (EGI, Eugene, OR) with the 129-channel Geodesic Sensor Net (Tucker 1993 [33]). For each recording session 5 minutes of resting baseline will be obtained at the beginning and end of the session. In addition, subjects will perform the Attention Network Test paradigm, a standard measure for assessment of attention that has been normed in the study population (Fan et al. 2002 [8]). The ANT will be presented using Eprime (Psychology Software Tools) on a standard flat screen monitor and the total duration of each ANT experimental session will be approximately 25 min. Local thalamic recordings will be recorded using the Percept PC system during the performance of the Attention Network Task.

To measure local population dynamics within the central thalamus during stimulation conditions in clinic we will record a differential signal on pairs of open channels adjacent to the channel used for stimulation using the Percept PC system. We will record up to 6 channels during OFF stimulation periods and 2 channels during stimulation. We will use a sampling rate of 250Hz (to optimize recording against known noise characteristics of the device) and filtered (4Hz to 100Hz) in compressed format. To characterize the EEG activation profiles we will use monopolar and bipolar stimulation through each contact individually and pairs of contacts in ON/OFF blocks of 5-10 second stimulation periods interleaved to obtain a minimum of 100 seconds of recording per condition with matched adjacent resting periods.

A similar approach will be used to collect behavioral, EEG and local thalamic recording data during performance of the Attention Network Task (Fan et al. 2002). EEG and local thalamic recordings will be synchronized using brief 1-2 second 20Hz pulses at the start and end of recording sessions. We will compare behavioral and EEG effects during interleaved blocks of 10 minutes of continuous ANT performance. Monopolar review for side effects will be completed prior to behavioral testing with the ANT.

We will use the sensing recording capabilities of the Percept PC to obtain longitudinal samples of brain activity during sleep-wake cycles in between outpatient office visits. Recordings with the device will occur as described above and as follows. Uniformly sampled and bandpassed

power will be obtained from one channel per electrode every ten minutes over 2 months. These data are stored on the device and will be downloaded at patient visits during the trial. We will evaluate the time domain recordings with spectral analysis.

8. EARLY WITHDRAWAL OR TERMINATION

Subjects will be informed that they may withdraw or be discontinued (early termination) from this study at any time. Further, they will be informed that the Investigator may withdraw them if they fail to comply with the study requirements or if the investigator feels it is in the best interest of the subject to discontinue their participation. The reason(s) for withdrawal or early termination will be documented on the appropriate page of the CRF. No further study assessments will be performed after the subject has withdrawn.

Subjects who consent to participate but do not receive the DBS device will not count towards the 6 patients limit for this study and new patients will be screened. No attempt will be made to replace subjects who are withdrawn or prematurely discontinue their study participation after the device has been implanted.

9. ADVERSE EVENTS

9.1. Adverse Event Identification and Assessment

An adverse event is any undesirable clinical occurrence in a participant during the clinical investigation, having been absent at baseline (or, if present at baseline, appears to worsen), whether or not it is considered to be related to the device or to stimulation. The investigator will not be required to record transient stimulation-induced neurological effects (e.g., paresthesias) or findings within normal expected postoperative outcomes. For example, postoperative pain that is not outside expected levels will not be recorded as an adverse event. Postoperative events that involve a clinically significant severity of symptoms, duration of symptoms, or that require deviation from usual postoperative clinical interventions (e.g., pain lasting longer than expected and requiring long-term opioid use) will be recorded as adverse events. The testing of DBS in MCS subjects did not identify any adverse events that are specific to brain injured subjects.

9.2. Adverse Device Effect

An adverse device effect is a device related adverse event. During this clinical investigation an event should be considered related to the device when it is the result of:

- The implanted components (lead, extension, neurostimulator)
- The implant procedure
- Programming
- Stimulation

A non-related event is one that results from:

- A patient related condition
- Concomitant medication

- Other (specify)

The relationship or association of the AE to the study product will be characterized by the Investigator as one of the following in Table 2.

Table 2: AE Relationship to Device

Relationship	Definition
Not related	There is no temporal relationship between the study product/treatment and the event, which makes a causal relationship clearly and incontrovertibly due to extraneous causes, i.e. not related to the study product.
Unlikely	Other factors, such as concurrent illness, progression or expression of a disease, or a reaction to a concomitant medication are more likely the cause of the event. It is improbable that the study product/treatment caused the AE.
Possibly	The AE cannot be fully explained by other causes, and it is possible that the study product/treatment caused the event.
Probably	A reasonable temporal association exists between the AE and the study product/treatment, and, based upon the investigator's clinical experience, the association of the AE with the study product/treatment seems probable.
Definitely	A definite or certain temporal association exists between the AE and the study product/treatment, and, based upon the investigator's clinical experience, the association of the AE with the study product/treatment seems definite or certain.

9.3. Serious Adverse Events (SAEs)

A serious adverse event is one that meets any of the following criteria (ICH Good Clinical Practice Guideline, April 1996, Section 1.50):

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Events that do not meet these criteria are considered non-serious

A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

9.4. Anticipated & Unanticipated (UADEs) Adverse Device Effects

9.4.1. Anticipated Adverse Events

Those **known** adverse events and surgical interventions related to the device or procedure are extrapolated from a population of 299 patients who underwent DBS for movement disorders (Medtronic® DBS™ Therapy for Parkinson's Disease and Essential Tremor CLINICAL SUMMARY, 2013):

- Abnormal behavior
- Abnormal dreams
- Activities of daily living impaired
- Adverse drug reaction
- Agitation
- Akinesia
- Anemia
- Anxiety
- Aortic stenosis
- Appendicitis perforated
- Arteriosclerosis
- Arthralgia
- Arthritis
- Asthenia
- Asthma
- Back pain
- Balance disorder
- Benign prostatic hyperplasia
- Biopsy bone
- Bladder catheter removal
- Blood pressure increased
- Bone Fractures
- Bone graft
- Bradykinesia
- Breast cancer
- Bronchitis
- Burns third degree
- Cardiac pacemaker insertion
- Cartilage injury
- Cellulitis
- Cerebral haematoma
- Cerebral haemorrhage
- Cerebrovascular accident
- Chest discomfort
- Chest pain
- Cholelithiasis
- Clostridium difficile colitis
- Clostridium difficile sepsis
- Cognitive disorder
- Complication of device removal
- Confusional state
- Constipation
- Convulsion
- Cough
- Debridement
- Decubitis ulcer
- Deep vein thrombosis
- Deep vein thrombosis postoperative
- Dehydration
- Delirium
- Delusion
- Delusional disorder, persecutory type
- Depression
- Depression suicidal
- Device electrical finding
- Device failure
- Device migration
- Diabetic ketoacidosis
- Diverticulitis
- Dizziness
- Drooling
- Drug hypersensitivity
- Drug toxicity
- Dysgraphia
- Dyskinesia
- Dysphagia
- Dyspnoea
- Dystonia
- Dysuria
- Erectile dysfunction
- Fall
- Fatigue
- Freezing phenomenon
- Gait disturbance
- Gastric polyps
- Gastroduodenitis
- Gastrointestinal disorder
- Gastrooesophageal reflux disease
- Glioma
- Grand mal convulsion
- Haematoma
- Haemoglobin decreased
- Haemorrhage intracranial
- Hallucination
- Head injury
- Headache
- Hiatus hernia
- Hip arthroplasty
- Homelessness
- Hyperhidrosis
- Hyperkalaemia
- Hypertension
- Hypoaesthesia
- Hypotension
- Hypovolaemia
- Hypoxia
- Implant site erosion
- Implant site infection
- Implant site reaction
- Incision site complication
- Incision site pain
- Inguinal hernia
- Insomnia
- Intestinal obstruction
- Intestinal perforation
- Intraventricular haemorrhage
- Labile blood pressure
- Labile hypertension
- Lethargy
- Localized infection
- Lumbar spinal stenosis
- Lung neoplasm malignant
- Major depression
- Malnutrition
- Mechanical complication of implant
- Mediastinal haemorrhage
- Medical device complication
- Medical device discomfort
- Medical observation
- Memory impairment
- Meniscus lesion
- Mental status changes

- Mental status changes postoperative
- Metabolic encephalopathy
- Mobility decreased
- Motor dysfunction
- Muscle rigidity
- Muscle spasms
- Musculo-skeletal pain
- Musculo-skeletal stiffness
- Musculoskeletal chest pain
- Nausea
- Neck pain
- Neuropathy peripheral
- Oedema peripheral
- Oesophageal spasm
- Oesophagitis
- Orchitis
- Orthostatic hypotension
- Osteoarthritis
- Pain
- Pain in extremity
- Paraesthesia
- Parkinson's disease
- Perseveration
- Pleuritic pain
- Pneumocephalus
- Pneumonia
- Pneumonia aspiration
- Pollakiuria
- Poor quality sleep
- Post-traumatic stress disorder
- Procedural complication
- Procedural pain
- Prostate cancer
- Prostate cancer metastatic
- Psychotic disorder
- Pyelonephritis
- Pyrexia
- Rapid eye movements sleep abnormal
- Rash
- Rectal haemorrhage
- Rectocele
- Restless legs syndrome
- Retinal detachment
- Reversible ischaemic neurological deficit
- Road traffic accident
- Rotator cuff repair
- Rotator cuff syndrome
- Scar pain
- Self-medication
- Sepsis
- Sexual dysfunction
- Sialoadenitis
- Small intestinal obstruction
- Somnolence
- Speech disorder
- Subdural haematoma
- Suicidal ideation
- Suicide attempt
- Syncope
- Syncope vasovagal
- Tooth abscess
- Transient ischaemic attack
- Treatment noncompliance
- Tremor
- Upper respiratory tract infection
- Urethral injury
- Urethral stenosis
- Urinary incontinence
- Urinary tract infection
- Urosepsis
- Viral infection
- Visual disturbance
- Vomiting
- Weight decreased
- Weight increased
- Wound dehiscence

The known or expected adverse effects that are attributable to stimulation are the following:

- Paresthesia
- Diplopia
- Dysarthria
- Dysequilibrium
- Paresis
- Dystonia
- Gait disorder
- Electrical shocking or jolting
- Headaches
- Pain, discomfort or local stress
- Attention deficit
- Dysphasia
- Insufficient therapeutic effect
- Ataxia
- Dyskinesia
- Sensory deficits
- Suicidal ideation
- Mania or hypomania
- Facial weakness
- Fatigue
- Loss of energy
- Numbness
- Other speech deficits
- Rebound symptom worsening with discontinuation of stimulation
- Transient heaviness in arm

- Changes in blood pressure or heart rate
- Nausea or vomiting
- Rapid or shallow breathing
- Anxiety
- Apathy
- Agitation
- Aggression
- Asthenia
- Balance disorder
- Akinesia
- Bradykinesia
- Chest discomfort
- Seizures
- Weight gain or weight loss
- Somnolence
- Tremor
- Undesired change in libido

9.4.2. Unanticipated adverse device effects (UADEs)

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

9.5. Adverse Event Reporting

Since we do not know in advance what, if any, adverse effects deep brain stimulation may have in this patient population, we will record and code any adverse clinical event on the Adverse Event form, whether it is mild or severe, and regardless of whether it is likely to be stimulation related or not. The AE forms will subsequently be analyzed to empirically determine which AEs are likely to be due to or exacerbated by the stimulation. We have developed specific procedures for coding AEs and have developed guidelines for breaking the blind should this be viewed as necessary by the treating physician. These procedures and guidelines are described below:

Two types of AE's be recorded:

- A new onset AE refers to the onset of an abnormality in a patient previously determined to have normal function in that area. This would include such things as the onset of spasticity in a patient who had normal tone previously, or the development of a tremor in someone who had active movement without a tremor before.
- A worsening AE involves either an increase in severity of some symptom or some deterioration of function or ability. This would include such things as worsening hypertonia in someone who already had hypertonia. This category should be used once an adverse event has already been recorded, to indicate subsequent worsening of that adverse event.

Note that many AEs are, by their nature, chronic events with waxing and waning courses (e.g., behavioral dyscontrol) while others are discrete single events (e.g., development of a DVT). Chronic patterns will be reported as AEs only if their pattern of occurrence changes (i.e., the episodes become more frequent or severe), and will be considered resolved when the pattern returns to the pre-treatment baseline. New onset AEs which may become chronic patterns (i.e., a first episode of aggression) will be identified as starting at the time of the first event. AEs which

have no clear date of resolution but require long-term treatment will be considered ongoing until that treatment is completed (e.g., DVT with anticoagulant prophylaxis, osteomyelitis with prolonged antibiotic treatment).

In addition to recording descriptive information about the AE on the form, AEs will be characterized as anticipated or unanticipated (based on the previously-established side effect profile), a severity rating (reflecting seriousness and impact on clinical status) will be assigned, and the probability that the AE was related to the study treatment will be estimated (based on the plausibility to the known clinical effects of neurostimulation, and knowledge of other clinical risk factors for the AE). We will also indicate whether treatment of the AE was required, whether the study treatment was changed as the result of the AE, the date the AE resolved and the outcome of the AE.

9.5.1. Reporting Serious Adverse Events

The Sponsor-Investigator will direct all study personnel to inform him as soon as possible (within 24 hours) of any serious adverse event. If necessary, study personnel may communicate by telephone or e-mail, and follow-up later with completed case report forms. The Sponsor-Investigator will conduct an evaluation of the event and if it is determined to be a UADE, it will be reported as described in the following section.

9.5.2. Reporting UADEs

If an event is determined by the Sponsor-Investigator to be a UADE, he will report the event to the FDA and the IRB within the required timeframe of 5 business days if death or life threatening, and 10 business days if other serious criteria are met.

9.5.3. Stopping Rules

If two of the six study participants experience either a serious UADE or an adverse device effect that the Sponsor-Investigator determines would present an unreasonable risk to other participants enrolled in the trial, the Sponsor-Investigator must terminate the clinical trial 5 days after making that determination and not later than 15 days after the Sponsor-Investigator first receive notice of the effect.

9.5.4. Reporting Deaths and Suicides

For any death that occurs during the course of the study, the sponsor will notify the IRB within an expedited timeframe according to the following guidelines:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

The sponsor will notify the FDA within 5 business days as noted above.

10. CLINICAL OVERSIGHT COMMITTEE

It is the responsibility of the Sponsor-Investigator to oversee the safety of the study participants. This includes careful assessment and appropriate reporting of adverse events as noted above.

In addition, a Clinical Oversight Committee (COC) has been appointed to conduct ongoing reviews of the safety of the Study and make recommendations regarding changes to the risk/benefit of the Study, including recommendations to discontinue new patient enrollments or discontinue the Study. The COC will review all SAEs as they occur and will conduct routine reviews at least quarterly throughout the study.

10.1. Medical Monitor

An Independent Medical Monitor has been designated for this study to regularly assess reports of unanticipated study-related events. Once per quarter the Medical Monitor will review reports of any study-related unanticipated adverse events. The Clinical Oversight Committee will convene an ad hoc meeting to review any report of an unanticipated adverse event that is both study-related and serious.

11. STATISTICAL PLAN

This is a feasibility study to inform the safety and efficacy of central thalamic-deep brain stimulation (CT-DBS) in the treatment of chronic cognitive impairment and residual disability caused by traumatic brain injury (TBI). The primary outcome measure used will be the Trail Making test and secondary outcome measures include measures of cognition (Ruff 2 & 7), physical symptoms (Rivermead Post-Concussion Symptom Questionnaire (RPQ)), psychological health (Patient Health Questionnaire-9 and Columbia Suicide Severity Rating Scale (C-SSRS), quality of life (Traumatic Brain Injury Quality of Life (TBI-QoL subscales)), and measure of global function (Glasgow Outcome Scale-Extended (GOSE)). For the present study all baseline, procedural, and safety and effectiveness follow-up data will be summarized with appropriate descriptive statistics. For continuous variables we will summarize data by the mean, median, standard deviation, minimum and maximum. For non-continuous variables we will summarize by percentages and frequency distributions. We will tabulate data for all enrolled patients. Our statistical analysis will be limited due to the small sample size.

Exploratory statistical analyses of primary and secondary endpoints will be performed to identify potential relationships between the treatment and the outcome variables.

Adverse event data will also be reported and tabulated.

12. RISK ASSESSMENT AND MITIGATION

12.1. Known and Anticipated Surgical Risks

The Sponsor-Investigator (who will also be the implanting surgeon in this study) is an experienced functional neurosurgeon with nearly 20 years' experience with deep brain stimulation. He was one of the original investigators in the first trial of DBS for movement disorders in the US ("Clinical Investigation of Deep Brain Stimulation for Treatment of Tremor Using the Medtronic Model 3382 DBS," 1996-1999). He will perform the surgical procedures in this study using his standard technique, developed in over 600 successful implants.

12.2. Device-Related and Therapy-Related Risks

Co-Investigators Nicholas Schiff, Joseph Giacino, and Andre Machado were all involved in the original trial of CT-DBS for the treatment of the minimally conscious state (MCS). Drs. Giacino and Schiff are world experts in traumatic brain injury. They will direct parameter selection for DBS programming and will consult on targeting of the CT along with Drs. Machado and Butson, both of whom have extensive experience in targeting this region.

The inclusion/exclusion criteria have been developed to exclude participants with concurrent illnesses that could increase the risk of DBS placement, as well as major developmental, neurologic, psychiatric or substance use disorders that may confound interpretation of results. Participants for whom DBS implants are contraindicated are excluded from study participation (e.g., a medical condition requiring MRI, and/or exposure to diathermy).

Participants will be counseled that they are not to undergo an MRI examination or shortwave diathermy as long as the DBS system is implanted.

12.3. Protocol for Managing Suicidal Ideation and Intent

All study personnel will be provided with the following protocol for managing suicidal ideation and intent. Participants will be closely monitored for any suicidal thoughts or plans during all study interactions, including telephone calls and in-person visits.

If the participant endorses an item suggesting suicidal ideation on any self-report questionnaire, or reports suicidal ideation at any time during participation in the study, immediately administer questions 1 and 2 from the Columbia Suicide Severity Rating Scale (CSSRS). Proceed with administering items as needed according to the instructions for that scale. Based on the participant's responses, follow one of the following procedures.

1. **Scenario 1: Participant responds "no" to question 2 on C-SSRS ("Have you actually had any thoughts of killing yourself?")**

   Empathize with how hard things have been for them and let them know that it is not unusual for people to have these thoughts when they have experienced TBI. Encourage them to talk to a family member or friend when they feel this way. Also provide them with a crisis line number and encourage them to phone if they ever start thinking about actually killing themselves. Proceed with the study protocol.

2. **Scenario 2: Participant responds "yes" to question 2 on C-SSRS ("Have you actually had any thoughts of killing yourself?") AND answers "no" to question 3 ("Have you been thinking about how you might kill yourself?")**

   Empathize with how hard things have been for them and let them know that it is not unusual for people to have these thoughts when they have experienced TBI. Encourage them to talk to a family member or friend when they feel this way. Also provide them with a crisis line number and encourage them to phone if they ever start thinking about actually killing themselves. Proceed with the study protocol.

3. **Scenario 3: Participant responds "yes" to question 3 on C-SSRS ("Have you been thinking about how you might kill yourself?") AND answers "no" to question 4 ("Have you had these thoughts and had some intention of acting on them?").**

   Discuss a safety plan with the participant. If you are meeting with the participant in person, have them complete the safety plan themselves, providing guidance as necessary.

Then have the participant sign it and ask the study physician or a licensed psychologist on the team to review the plan with them. Provide them with the crisis line information by writing it on the safety plan. If you are talking with the person by phone, go over the safety plan, asking them to generate responses to the items, while providing guidance as necessary. Record their responses and then ask the study physician or a licensed psychologist on the team to review the plan with them. Send them a copy by mail, provide the contact information for the crisis line verbally over the phone and write it on the safety plan before mailing.

4. **Scenario 4: Participant responds "yes" to question 3 on C-SSRS ("Have you been thinking about how you might kill yourself?") AND either answers "yes" to question 4 ("Have you had these thoughts and had some intention of acting on them?") or is equivocal regarding whether they intend to act on their thoughts.**

   Ensure that they are safe at the moment. This means that they are not in imminent danger of harming themselves and do not have guns, knives or other weapons available to use. If you cannot deem that they are safe, ask their permission to speak with a family member who is with them. Tell the family member that they should stay with the patient and should make sure that they are safe, provide them with the crisis line number, advise them to take the person to an emergency room if possible, and advise them to call 911 if they fear that they cannot stop the person from hurting themselves and cannot talk them into going to the emergency room. If there is no family member present, or they refuse to have you speak with one, and you cannot deem that they are safe, maintain them on the line and ask the study physician, another research team member or an administrative assistant to call 911 and ask that the police visit the participant at their current location. Meanwhile, ask the participants' permission to connect them to a crisis line so that they can talk with someone who is trained to help them through the crisis. If they agree, connect them to the crisis line.

NOTE: Occasionally, someone may withhold permission for you to transfer them to a crisis line. If this refusal appears to be due to fear, uncertainty, or embarrassment, then talk them through the reasons for the crisis line and ask their permission again. If they still refuse, or if they appear to simply want to stay on the line talking with you, tell them that for their own safety, you need to connect them to the crisis line. Ask them to stay on hold while you dial the crisis line. Make sure that they have your telephone number so that they can call you back in case you are disconnected. You may call them back if you are disconnected. If you are unable to reach them, and you deem that they are in imminent danger of harming themselves, then call 911 and ask the police to visit the person at their current location.

NOTE: The same protocol can be applied to a person who endorses suicidal ideation and intent during an on-site assessment. Simply have them call the crisis line from a nearby office.

REMEMBER TO DOCUMENT EACH STEP THAT YOU PERFORM, HAVE THE SPONSOR-INVESTIGATOR OR HIS DESIGNEE (EG, STUDY PHYSICIAN, PSYCHOLOGIST) REVIEW THE SAFETY PLAN AND PLACE IT IN THE PARTICIPANTS' RESEARCH FILE.

The process for connecting on-line telephone participant to crisis line:

While on the phone with the participant, ask them to hold while you connect them to the crisis line (or use the conference-calling feature, if available):

Crisis Line #: 1-800-273-TALK (8255) National Suicide Prevention Lifeline
1-888-628-9454 (Spanish)

Be sure that they have been connected to a crisis counselor before hanging up.

13. Administrative Requirements, including Investigator Responsibilities

13.1. Good Clinical Practice (GCP)

The study will be conducted in accordance with, but not limited to, 21CFR parts 812, 11, 50, 54, 56 and ICH - GCP. The Investigator will be thoroughly familiar with the appropriate use of the study product as described in the protocol and Directions for Use. Essential study documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Trial Master Files will be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations and SOPs.

13.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. IRBs will be provided all relevant study documents in order to safeguard the rights, safety, and well-being of the subjects per their mandate. This study will be implemented only at sites where IRB approval has been obtained. The protocol, Product Literature, informed consent, written information given to the subjects, safety updates, and any revisions to these documents will be provided to the IRB by the Investigator.

13.3. Subject Information and Informed Consent

After the study has been fully explained to the potential subject, written informed consent will be obtained prior to the performance of any study-related procedures. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirements, including local IRB requirements.

It is understood that Informed Consent is a process and not an event. The Investigator is responsible for maintaining an ongoing, open dialog with the subject in regards to their continued participation in the study.

13.4. Subject Confidentiality

In order to maintain subject privacy, CRFs, study product accountability records, study reports and communications will identify the subject by initials and the assigned subject number only. The Investigator will grant monitor(s) and/or auditor(s) from regulatory authorities' access to the subject's original medical records for verification of data recorded in the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and no Protected Health Information will be disclosed, other than that which is described in the Informed Consent Form.

13.5. Protocol Compliance

Strict adherence to the protocol is expected. However, there are times when this is not possible. Any failure to follow the protocol (i.e. a deviation) must be identified and recorded. Deviations from the protocol which: (1) increase subject risk or (2) impact on study endpoints, will be

considered protocol violations. Protocol deviations and violations will be tabularized in the data listings.

Substantive changes to the protocol will require written FDA and IRB approval prior to implementation, except when such departures are necessary to eliminate an immediate hazard(s) to subjects. The IRB may provide expedited review and approval for minor change(s) in ongoing studies that have the approval of the IRB.

13.6. Maintenance of Study Records

The Investigator is responsible for maintaining adequate and accurate study records. These may include, but are not limited to: Screening, Consent and Enrollment Logs, staff training records, licenses & certifications, correspondence between Investigator and Sponsor and/or IRB, financial disclosures, investigator agreement, Product Accountability Logs, Protocol Signature Pages, authorization forms and other study related documents.

13.7. Study Monitoring

The Sponsor/Investigator will oversee and monitor the progress of the Clinical Study to assure that it is conducted, recorded, and reported in accordance with the Clinical Protocol, written procedures, agreements, and applicable regulations. This will be accomplished by:

- Ensuring proper informed consent and the protection of the rights and well-being of study subjects
- Assessing data integrity
- Identifying and addressing non-compliance issues
- Identifying research misconduct or fraud
- Reviewing essential documents and approvals
- Assessing overall site capabilities
- Ensuring device accountability is maintained

13.8. On-Site Audits

Regulatory authorities or the IRB, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

13.9. Case Report Form Completion

Case Report Forms will be completed for each subject enrolled in the study. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the eCRF data must indicate the subject's participation in the study and document the dates and details of study assessments, inter-current procedures, and adverse events.

The Investigator will be provided a copy of all completed CRF pages.

13.10. Study Product Accountability

Accountability for the study product and other clinical study supplies at each site participating in this study is the responsibility of the Investigator and appropriate records of receipt of product will be maintained. The Investigator will ensure that the study product is used only in accordance with this protocol and is maintained under appropriate IDE (21CFR 812) conditions.

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APPENDIX 1. DEVICE PROGRAMMING SOP

Programming of the device will utilize standard DBS techniques for assessing effects and side effects during a cathode survey of the DBS leads. Programming will be conducted under the direct supervision of Dr. Henderson or under the direct supervision of personnel trained by Dr. Henderson. Dr. Henderson will review and sign all forms summarizing adverse events observed during stimulation programming.

The primary purpose of DBS programming is to select the optimal chronic stimulation parameters to use during stimulation titration and chronic stimulation. Dr. Henderson may consult with other investigators to select the best stimulation parameters but will be responsible for the final decision based on effects and adverse effects. Given the nature of this study, the selection of initial stimulation parameters for testing will be partially based on available animal data from Dr. Schiff's laboratory as well as the group's prior experience in deep brain stimulation in patients with traumatic brain injury. Based on this combined experience, it is expected that stimulation frequency will be set in the range of 130-185 Hz. Final selection of chronic frequency, active contacts, pulse widths and amplitudes will be based on the titration testing using a systematic cathode survey as outlined below.

A cathodal survey will be performed by activating, in a systematic fashion, each of the four contacts in each DBS lead as the cathode. All patients will have bilateral deep brain stimulation and the investigators will first test the effects of stimulation on the left side lead and then test the right side separately. Bilateral stimulation will only be attempted after each side has been tested individually. All stimulation testing will be conducted below the safe change density limit of 30 $\mu C/cm^2$/phase.

Each contact on each lead will be tested as the cathode (with the IPG set as the anode). Amplitude will be tested with stepwise increments in amplitude from 0 to a maximum of 10 V. Amplitudes will be increased until acute effects are noted or reported by the patient or the charge density limit is reached. Pulse widths will be initially set at 60 microseconds and will not exceed 120 microseconds. The investigators will look for and ask about the following acute effects but will also ask the patient to report any subjective changes:

- Paresthesias or pain
- Motor changes such as twitches, dystonia, changes in posture
- Verbal Fluency
- Speech changes
- Mood and anxiety
- Alertness or energy level
- Occulomotor changes or diplopia
- Behavioral changes

While mild or transient sensory changes such as mild paresthesias may allow stimulation titration to continue, unpleasant effects such as pain, motor effects or occulomotor effects will prompt the investigators to no longer increase stimulation amplitude, at which time it will be recorded that the Threshold for side effect was identified with that given electrical contact as the cathode. Likewise, positive effects such as improvements in energy or alertness will be recorded

and the lowest amplitude that produces desirable effects will be recorded as the Threshold for positive effects. Once the cathode survey is completed, the investigators will select the electrical contacts that produce the most robust positive effects at the lowest amplitudes and negative effects at the highest amplitudes (i.e. therapeutic index) for chronic stimulation. It is relevant to notice that the initial cathode survey will only provide the initial guidance for stimulation adjustment. Because the cathode survey is typically conducted over a session of 2-3 hours, it does not account for temporal summation of effects. If adverse effects are reported over days or hours, further programming will be needed in order to identify the parameters that produce the intended benefits with limited adverse effects.