Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Samuel Snider, MD
Project Title:	REstoring CONsciousness with NEurostimulation of the Central Thalamus: The RECONNECT Study
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1. Background and Significance

It is difficult to overstate the impact of an effective treatment for chronic disorders of consciousness (DoC), which affect an estimated 300,000+ people in the USA.[1] These patients typically spend their days in a skilled nursing facility with severely limited ability to interact with their external environments—for months, years, even decades. Though electrical brain stimulation has been explored as a potential therapy for >50 years,[2-13] there are still no approved treatments. A key factor in this failure is the absence of an empirically derived treatment target—i.e., a brain region to stimulate based on clinical responses in humans.

Patients with chronic DoC have persistent impairments in arousal or awareness resulting from severe central nervous system injuries including intracerebral hemorrhage, ischemic stroke, encephalitis, and hypoxic-ischemic or traumatic brain injuries (TBI)[14, 15]. The severity of DoC ranges from coma (complete absence of arousal or awareness) to unresponsive wakefulness syndrome ([UWS]; open eyes but no behavioral signs of awareness) to minimally conscious state ([MCS]; patients with some isolated behavioral signs of awareness-- including MCS + with intermittent command following). Diagnosis of DoC and its severity can be made using a standardized behavioral scale known as the Coma Recovery Scale-Revised (CRS-R)[16].

The pathophysiology underlying DoC is poorly understood. Outside the brainstem tegmentum, studies attempting to map the location of brain injury in patients with DoC have generally not identified a single responsible brain region. Leading theories include widespread suppression of excitatory neurotransmission,[17] particularly in the "mesocircuit"[18] of the anterior forebrain, which includes the frontal cortex, thalamus, striatum, and brainstem. The resulting process of "dysfacilitation"[19] is characterized slow (<1 Hz) rhythmic oscillations,[20] a state sometimes likened to general anesthesia or sleep in the healthy brain.[21]

There are currently no FDA-approved treatments for patients with DoC. To date, randomized controlled studies of drugs such as zolpidem, and transcranial (non-invasive) brain stimulation approaches, have been negative or yielded short-lived benefits[22-24]. To date, the most promising therapeutic studies, reviewed below, have involved invasive neuromodulation of the central (intralaminar) thalamic nuclei[7, 10]. The intralaminar nuclei, a key component of the mesoocircuit model hypothesized to underlie arousal and awareness[18], consist of the centromedian (CM) and parafasicular (Pf) nuclear complex (CM-Pf) and the central lateral (CL) nucleus (**Figure 1**). Both regions are densely innervated with projections from arousal nuclei in the brainstem tegmentum—the more inferiorly situated CM-Pf complex receives projections via the ventral tegmental tract, and the more superior CL receives projections via the dorsal

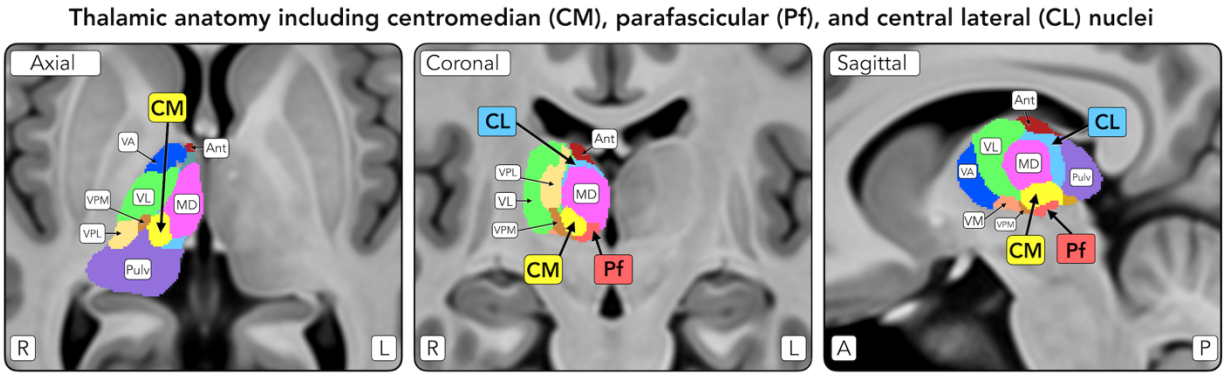


Figure 1: Anatomy of the thalamus. *Axial, coronal, and sagittal MRI views showing the Morel atlas of the thalamus (digitized by Krauth et al. 2010). Positions of the intralaminar nuclei targeted for DBS in DoC are shown, including the centromedian (CM) and parafascicular (Pf) thalamic complex (CM-Pf) and the central lateral (CL) nucleus. Other abbreviations: Ant, anterior; MD, mediodorsal; Pulv, pulvinar; VA, ventral anterior; VL, ventral lateral; VPM, ventral posterior medial; VPL ventral posterior lateral; VM, ventral medial.*

tegmental tract[25-31]. Both have been targeted in human studies of patients with chronic DoC. More patients have been implanted with electrodes targeting CM-Pf, but these studies have all been open-label and uncontrolled[6, 7]. Blinded stimulation targeting CL showed improvement in a patient with chronic DoC[10], but this evidence remains limited to a single subject. As such, significant uncertainty remains about which target is more promising for further development.

This proposal seeks to provide the first-in-human comparison of the safety, feasibility, and efficacy of stimulation delivered to a data-derived target abutting CM-Pf and CL in patients with chronic DoC.

Report of Prior Investigations and Rationale

Invasive electrical stimulation has been explored as a potential therapy for patients with chronic DoC for >50 years. Pioneering work by Hassler in 1969[3] was followed by larger case series of deep brain stimulation (DBS) in the 1990s[4, 32] and beyond[5-7, 9-11, 13, 33, 34]. Various stimulation targets have been tested in small, unblinded trials, including the thalamus,[4-7, 10, 32-34] brainstem,[4, 5] pallidum,[3, 13] and nucleus accumbens,[11] with variable behavioral effects.

The most rigorous experimental results in humans come from stimulation of the intralaminar thalamic nuclei (CM-Pf and CL; **Figure 1**), which are key components of the mesocircuit model hypothesized to underlie impaired arousal and awareness[18]. These nuclei form part of the ascending arousal network, projecting widely to the hypothalamus, forebrain, striatum and frontal cortex[25, 30, 35, 36]. However, there is substantial uncertainty about which nucleus is a more optimal stimulation target for DoC. This uncertainty stems from subtle differences in their neurotransmitter profiles, connectivity, and precise roles in supporting consciousness[37], as well as variable clinical experience in targeting them with DBS.

A landmark case report by Schiff et al. in 2008,[10] which employed double-blinding, a sham condition, and repeated behavioral assessments in single subject with chronic

DoC, found that bilateral DBS to the CL led to sustained behavioral improvement. A recent phase 1, randomized, double-blind clinical trial[38] of DBS to CL and its associated dorsal tegmental tract in six participants with cognitive impairment after TBI reported improvements in executive function, although these participants did not have disorders of consciousness.

A larger number of DoC patients have been treated with DBS targeting CM-Pf in open-label studies[5-7, 32, 39]. This includes a recent open-label cohort study of DBS for DoC conducted in Croatia, the largest of its kind *(n*=40; **Figure 2**)[6, 7]. Though there was no blinding or sham stimulation, a subset of participants (~30%) showed dramatic behavioral improvements in the first year following implantation. Some participants regained volitional language and motor function, a level of improvement that does not typically occur spontaneously in chronic DoC.[40, 41]

Our recent analysis of patient-level data from this cohort found that responders were more likely to have an electrical stimulation field within a specific location in the inferior CM-Pf complex, abutting the ventral tegmental tract in the midbrain **(Figure 3**)[42]**.** This DBS "sweet-spot" is densely innervated by projections from brainstem arousal nuclei via the ventral tegmental tract and is functionally connected to a distributed cortical network—a "DBS improvement network"—anchored in frontal and parietal association cortex (**Figure 3**). Furthermore, by analyzing an *independent* cohort of patients with stroke lesions, we found that post-stroke outcomes were worse when lesions overlapped the DBS improvement network, providing external validity to support its clinical and pathophysiological relevance[42]. In other words,

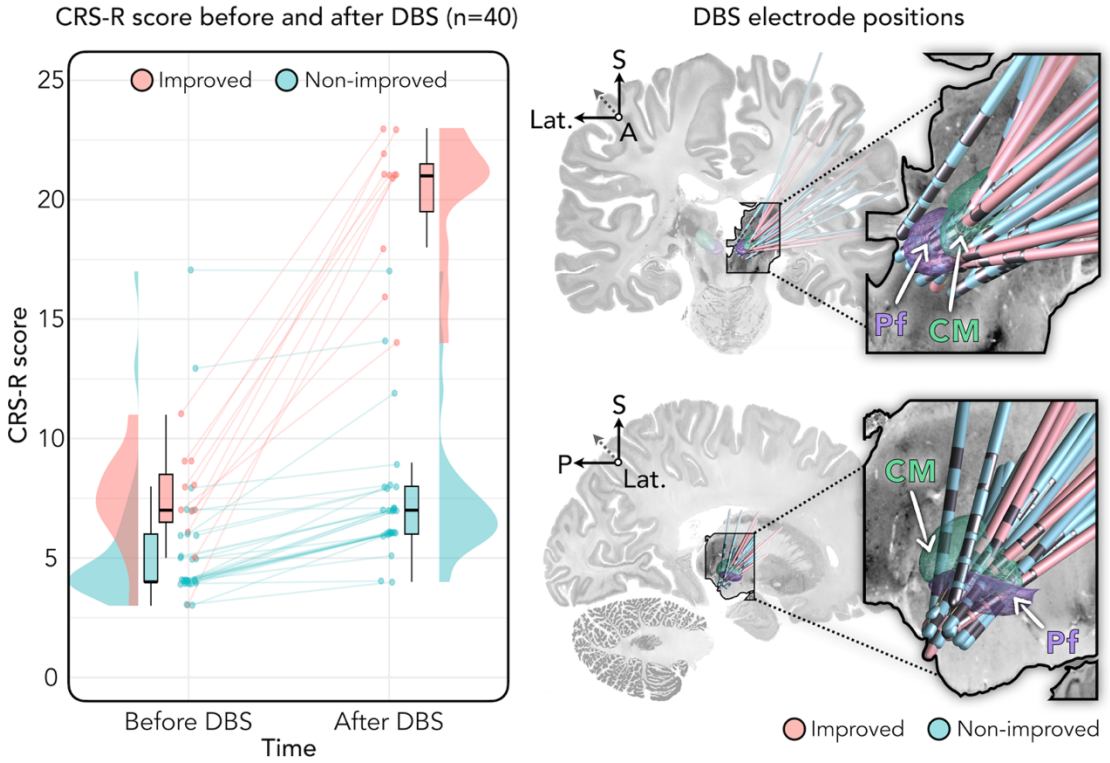


Figure 2: Clinical outcomes and electrode positions in a cohort of patients with DoC undergoing unilateral DBS of the CM-Pf. The plot on the right shows change in coma recovery scale-revised (CRS-R) scores between baseline (pre-DBS) and up to 12 months following DBS delivered to the thalmic CM-Pf in 40 patients. Scores were used to separate patients into an improved group (11/40 patients; defined as those who transitioned from one state of consciousness to another, for example, unresponsive wakefulness syndrome [UWS] to a minimally conscious state [MCS], or from MCS to aware) and a non-improved group (29/40 patients; defined as patients who did not improve to a different consciousness level). The images on the right show DBS electrode positions in the improved and non-improved groups, with respect to the CM-Pf nuclei. Figure from: Warren et al. (pre-print): https://doi.org/10.1101/2024.10.17.24314458

lesions occurring within the network appear to impair consciousness, whereas DBS to the network could improve consciousness.

In this proposal, we now seek to generate preliminary data comparing the safety, feasibility, and efficacy of DBS delivered to two alternative targets within the central thalamus: the data-derived CM-Pf sub-region and the CL.

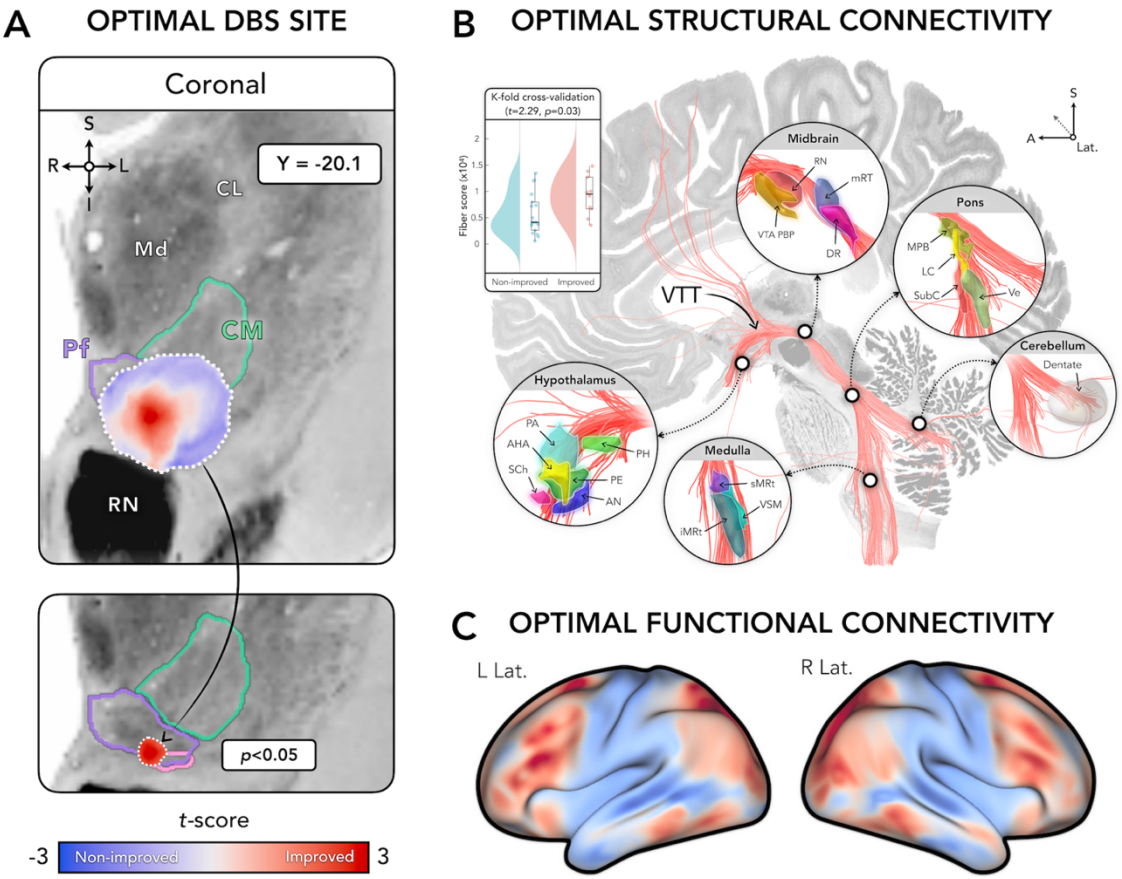


Figure 3: Analysis of optimal stimulation location and connectivity for DBS in patients with DoC. (A) By analyzing variability in electrode locations, we identified a thalamic location where stimulation was linked to clinical improvement. The location was in the inferior part of the centromedian-parafascicular (CM-Pf), near the midbrain ($p<0.05$, K-fold cross-validation). (B, C) Using normative structural (B) and functional (C) connectivity analyses, we saw that the optimal DBS site engaged structural connections including the ventral tegmental tract (VTT) and was functionally connected to a distributed cortical network in frontal and parietal cortex. Figure adapted from Warren et al. (pre-print): https://doi.org/10.1101/2024.10.17.24314458

Overall Strategy:

Our overall goal is to collect pilot data on the safety, feasibility, and comparative behavioral efficacy of DBS to a specific CM-Pf sub-region and CL. We will recruit 2

patients over two years to participate in a single-center, double-blinded, cross-over study.

After consent, we will first confirm the stability of the clinical DoC diagnosis during a 1-month screening period. The purpose of this phase is to ensure that participants are not already on a trajectory of clinical improvement. We will then implant two DBS electrodes (Percept™; Medtronic) into each thalamus, one targeting the thalamic CM-Pf sub-region and the other targeting the CL nucleus. After a one-month recovery period, we will titrate stimulation settings, and participants will then enter a 10-month blinded stimulation phase comprising periods of either continuous daily real (STIM-ON) or sham (STIM-OFF) stimulation delivered separately to each target. One patient will receive CM-Pf stimulation blocks first and CL stimulation blocks second; the other patient will receive the reverse target order (CL then CM-Pf). We will enroll two patients, measuring procedure and device-related adverse and serious adverse events, as well as the feasibility of successfully targeting the CM-Pf sub-region. Finally, we will measure and compare the magnitude of CM-Pf versus CL stimulation induced changes on a standardized behavioral scale for evaluating patients with DoC. Complete details of the approach are provided below.

2. Specific Aims and Objectives

The overall goal of this pilot study is to generate preliminary data on the safety, feasibility, and comparative efficacy of DBS to two alternative thalamic stimulation targets (CM-Pf subregion and CL) in the treatment of patients with chronic DoC.

We have three primary and two secondary objectives.

Primary Objectives

1) **Establish the safety of DBS to a CM-Pf thalamic subregion overlapping the ventral tegmental tract, and to the CL nucleus overlapping the dorsal tegmental tract, in 2 patients with chronic DoC**

2) **Establish feasibility of implanting electrodes into a CM-Pf subregion overlapping the ventral tegmental tract, and to the CL nucleus overlapping the dorsal tegmental tract, in 2 patients with chronic DoC**

3) **Define the time-course and magnitude of behavioral changes induced by blinded bilateral CM-Pf and CL stimulation in 2 patients with chronic DoC.**

Secondary Objective

4) **Determine whether alpha-band power (8-12 Hz) from thalamic local field potential recordings (recorded continuously from the Medtronic Percept™ device) changes with CM-Pf or CL stimulation or correlates with behavioral changes in patients with chronic DoC.**

This research will establish the clinical and research infrastructure necessary to bring novel invasive therapeutics to a patient population for whom none currently exist.

3. General Description of Study Design

Here, we describe an Early Feasibility Study[43] involving 10-months of blinded bilateral thalamic DBS to two alternative targets (CM-Pf and CL thalamus) in two subjects with chronic DoC. The study timeline is shown in **Figure 4**.

The overall design is single-center, assessor- and caregiver-blinded, randomized cross-over study. The study design and schedule of all assessments is in **Figure 4.** Briefly, this will include 4 phases: a 1-month screening/baseline phase, DBS surgery and 1-month post-implantation recovery phase, a 1-2 day DBS parameter titration phase, and a 10-month randomized cross-over stimulation phase. During the study, subjects will serve as their own controls.

To assess safety, we will monitor systematically and continuously for adverse events and serious adverse events and at specific time points post-surgery. The feasibility criteria will be the ability to implant two patients within two years that have

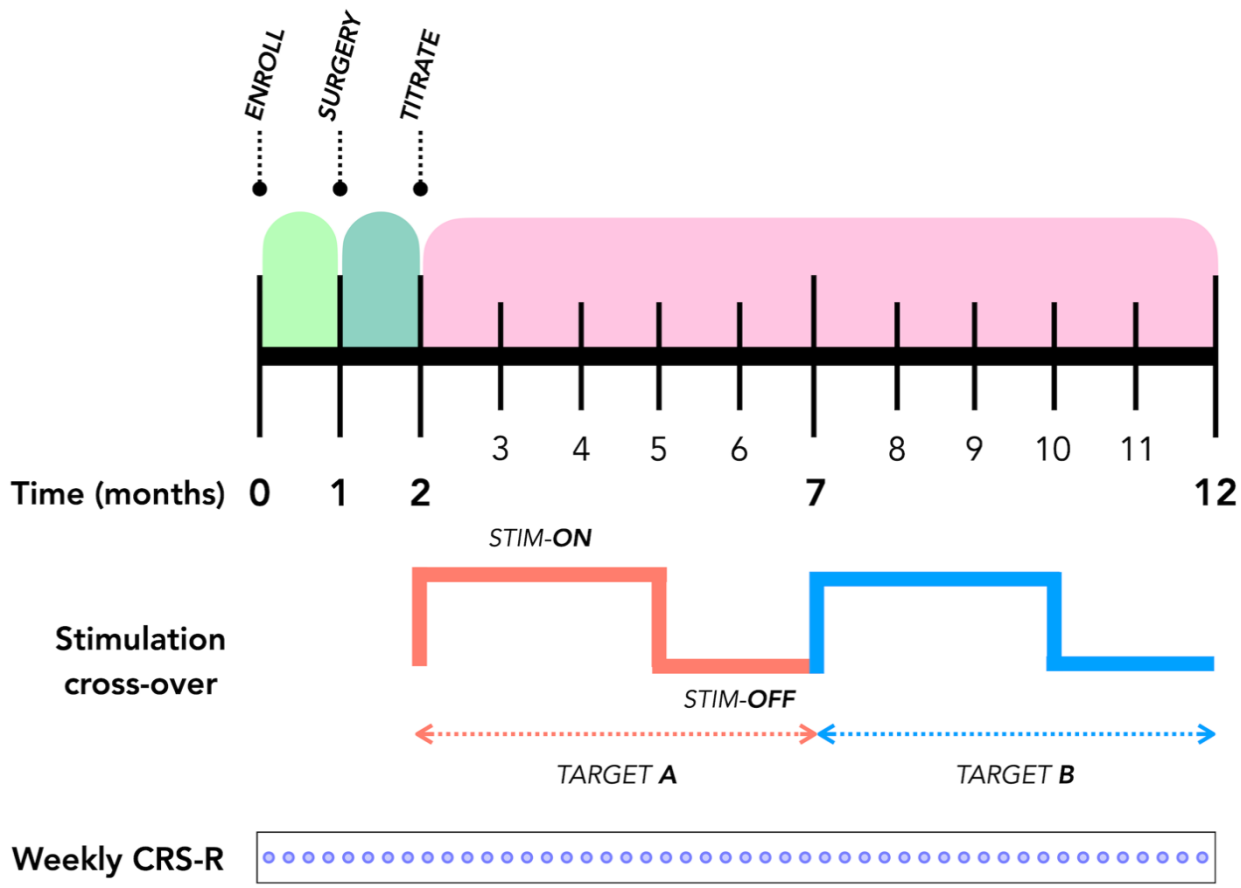


Figure 4: Timeline of study phases. Each patient's participation in the study spans 15 months and includes 5 phases: (i) a 1-month baseline/screening phase with weekly CRS-R assessments to establish a stable level of consciousness; (ii) DBS surgery followed by a 1-month recovery period; (iii) DBS therapy titration; and (iv) a 10-month stimulation crossover phase with alternating blocks of active (STIM-ON; 3 months) and sham (STIM-OFF; 2 months) stimulation. The crossover phase is divided into two 5-month periods: one targeting either the CM-Pf or CL (target A) and the other targeting the remaining nucleus (target B). In one patient, target A will be CM-Pf and target B will be CL; in the second patient, target A will be CL and target B will be CM-Pf. Finally, (v – not shown) will include a 3-month open-label follow-up phase using settings and target at the discretion of the clinicians and surrogate.

overlap between the intended targets and each stimulation contact's modeled electrical field. The primary clinical efficacy outcome will be the estimated change in the behavioral (CRS-R) scale during each target's STIM-ON periods as compared to STIM-OFF periods.

At the end of this study, we will make a GO/NO-GO decision to proceed with a larger study based on the following three criteria being met:

1) Feasibility criteria are met (defined in Section 9)

2) Either target's estimated stimulation-induced change in CRS-R exceeds the conditional minimum detectable change (defined in Section 9)

3) Members of the independent Study Monitoring Committee (SMC) make a consensus determination that the observed safety events do not preclude proceeding with a larger trial.

4. Subject Selection

Patients with DoC will be recruited from Neurorecovery clinics in Boston and from advertising at rehabilitation facilities, skilled nursing facilities, long-term acute care facilities, and through the Brain Injury Association of Massachusetts (BIAMA). We will post fliers at these facilities and provide the fliers via email to BIAMA. We will additionally share basic information about the study inclusion criteria with clinicians working at these facilities via email.

Because study candidates will be definitionally unable to communicate, all screening and informed consent will occur through a legally authorized representative (LAR). Procedures around informed consent for this vulnerable population are described in detail later. To be screened for the study, the participant must have a LAR, **defined as either a documented health care proxy or court-appointed guardian.**

LARs of potential study candidates will undergo an initial telephone screen with study staff prior to complete eligibility screening. Briefly, the target population is participants with chronic DoC who are unlikely to spontaneously improve and who may benefit from DBS based on previously described clinical, neurophysiological and radiological criteria[6, 7]. The full set of inclusion criteria are listed below.

Inclusion criteria:

<u>Clinical</u>

- Men and women aged 18 to 55 years old

- Central nervous system injury of any etiology (e.g., cardiac arrest, traumatic brain injury, ischemic stroke, cerebral hemorrhage, encephalitis) that occurred at least 3 months prior to the eligibility phone call
- The participant does not exhibit either of the following behaviors every day: meaningful interaction (defined as intelligible speech and ability to follow verbal commands) or functional object use
- A CRS-R based diagnosis of DoC; either Unresponsive Wakefulness Syndrome (UWS) or Minimally Conscious State (MCS- or +).
- The participant must have a documented health care proxy or court-appointed guardian

Radiological

- Neurologist and neurosurgeon consensus review of most recent clinical MRI (if no MRI, then most recent CT) determines there is no bilateral subcortical injury preventing precise placement of electrodes (e.g., major injuries to the bilateral thalami or severe and bilateral subcortical anatomical distortions).

Exclusion Criteria

- Pregnant
- Contraindication to brain MRI
- Due to transportation requirements, participants whose primary residence (Skilled Nursing Facility, Long Term Acute Care, or home) is inaccessible by ambulance from BWH
- Pre-existing psychiatric, neurological or medical condition that makes the patient, in the opinion of the study team, a poor surgical candidate (e.g., neurodegenerative disorder, significant cardiopulmonary disorder, need for chronic anticoagulation)
- Structural abnormality of the chest wall, neck, brain, or skull that makes safe placement of the electrodes, in the opinion of the study team, infeasible or prone to complication

- Neurologist and neurosurgeon consensus review of most recent clinical MRI (if no MRI, then most recent CT) determines there is no bilateral diffuse injury to the basal ganglia
- Medical contraindications to surgery including:
    - Chronic infection
    - Coagulopathy (INR > 1.5, aPTT 45 sec, platelet count < 100 x 10^3 / uL)
    - Poorly controlled blood pressure (> 2 episodes during screening phase of blood pressure > 180/110 sustained on repeated measurements) and evidence of cardiovascular disease
    - Participation in another drug, device or biological trial within 90 days
    - Current implanted stimulation device (e.g., pacemaker, defibrillator, spinal cord stimulator, deep brain stimulator)
    - Anticoagulant or anti-platelet medication that cannot be safely stopped for > 2.5 weeks in the peri-operative period

5. Subject Enrollment

Given that this study is enrolling participants with DoC, participants will not be able to consent for themselves. All consent will therefore occur through a legally authorized representative (LAR), which we define strictly for the purposes of this study as a health care proxy (supported by written documentation) or court-appointed guardian. LAR for the candidate participants will undergo an initial scripted telephone eligibility screen with a study coordinator (Appendix 3). The coordinator will then describe study procedures to the LAR and obtain verbal assent to begin the informed consent process. LARs for the eligible participants will then undergo informed consent with study PIs (Snider/Rolston) via in-person meeting or video conference call on a secure platform (Mass General Brigham approved platform). The LAR will have as much time as necessary to review the written consent form and ask questions. The participant must not have an advanced directive refusing invasive procedures, and the LAR must not have reason to believe that the participant would not have wanted to pursue experimental therapies. Informed consent will be e-signed via a secure Mass General

Brigham REDCap form. We will have informed consent documents in English and Spanish. If language barriers or literacy issues prevent the LAR from reading the full consent form, we will use a short-form consent and a third-party witness not involved with this study (Appendix 5.2). In this case, a third-party witness must sign and attest that the required information was presented orally and understood by the LAR.

A subject will be considered enrolled after their LAR signs informed consent. Each subject whose LAR signs informed consent will be given a unique subject identification number, used to identify the subject on all study-related documents. Any updates to the consent form requiring re-consenting will be done at the next scheduled visit. Updates will be explained in plain language to confirm LAR understanding. These may occur by phone or video call, with documentation in the study binder. Upon signing consent, an initial behavioral assessment with the CRS-R will occur as well as a comprehensive review of available medical and radiological records with study staff.

Notably, this consent process is separate from the consent process for DBS surgery. Written consent for DBS surgery will be obtained separately from the LAR at the appropriate time by neurosurgeon PI (Rolston).

6. STUDY PROCEDURES

PHASE 1: SCREENING

Following signed consent, participants will enter a 1-month screening/baseline assessment period, where they will undergo four (weekly) behavioral assessments with the CRS-R at their place of residence. To remain eligible for DBS, participants must have:

(1) CRS-R based DoC (UWS or MCS–/+) diagnosis,

(2) the CRS-R scores must not change by more than the recently-described conditional minimum detectable change (cMDC) during this screening period[44](**Table 1),** and

(3) the participant must have 2 consecutive CRS-R measurements that are not increasing.

The cMDC maps the 95% confidence interval for measurement error based on initial CRS-R score. If a participant's CRS-R increases by more than the cMDC during this phase, or if the last two CRS-R measurements are increasing, the screening phase will continue with consecutive weekly assessments. To enter the next phase of the study, participants must have 4 consecutive weekly CRS-R assessments without a change exceeding cMDC, 2 consecutive assessments without an increase, and must remain with a CRS-R based diagnosis of DoC.

The rationale for this requirement is to ensure that any subsequent behavioral improvement observed after DBS is less likely due to spontaneous recovery or measurement variability. In other words, this stability criterion is essential for establishing a reliable baseline from which to interpret treatment effects.

CRS-R Time 2

CRS-R Time 1	Raw Points	Rasch Measure	SE	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
				0	11	19	24	29	34	38	42	45	47	49	51	53	55	57	60	63	66	69	73	77	82	89	100
				15	9	7	6	6	6	6	5	5	4	4	4	4	4	4	5	5	5	5	6	6	7	9	15
0	0	15		33.8	31.0	30.1	29.7	29.5	29.1	28.4	27.7	27.1	26.8	26.6	26.6	26.8	27.2	27.7	28.1	28.4	28.6	29.0	29.5	30.6	33.4	42.2
1	11	9	33.8		22.4	21.4	21.1	20.9	20.4	19.7	19.0	18.5	18.1	18.0	18.0	18.2	18.6	19.1	19.5	19.8	20.0	20.3	20.9	22.0	24.8	33.6
2	19	7	31.0	22.4		18.7	18.3	18.1	17.7	17.0	16.3	15.7	15.4	15.2	15.2	15.4	15.8	16.3	16.7	17.0	17.3	17.6	18.2	19.2	22.0	30.8
3	24	6	30.1	21.4	18.7		17.4	17.2	16.7	16.0	15.3	14.8	14.4	14.3	14.3	14.5	14.9	15.4	15.8	16.1	16.3	16.6	17.2	18.3	21.1	29.9
4	29	6	29.7	21.1	18.3	17.4		16.8	16.4	15.6	14.9	14.4	14.1	13.9	13.9	14.1	14.5	15.0	15.4	15.7	15.9	16.3	16.8	17.9	20.7	29.5
5	34	6	29.5	20.9	18.1	17.2	16.8		16.1	15.4	14.7	14.2	13.9	13.7	13.7	13.9	14.3	14.8	15.2	15.5	15.7	16.0	16.6	17.7	20.5	29.3
6	38	6	29.1	20.4	17.7	16.7	16.4	16.1		15.0	14.3	13.8	13.4	13.3	13.3	13.5	13.9	14.3	14.8	15.1	15.3	15.6	16.2	17.3	20.1	28.8
7	42	5	28.4	19.7	17.0	16.0	15.6	15.4	15.0		13.6	13.1	12.7	12.6	12.6	12.8	13.2	13.6	14.1	14.3	14.6	14.9	15.5	16.5	19.4	28.1
8	45	5	27.7	19.0	16.3	15.3	14.9	14.7	14.3	13.6		12.4	12.0	11.8	11.9	12.1	12.4	12.9	13.4	13.6	13.9	14.2	14.8	15.8	18.7	27.4
9	47	4	27.1	18.5	15.7	14.8	14.4	14.2	13.8	13.1	12.4		11.5	11.3	11.3	11.5	11.9	12.4	12.8	13.1	13.3	13.7	14.2	15.3	18.1	26.9
10	49	4	26.8	18.1	15.4	14.4	14.1	13.9	13.4	12.7	12.0	11.5		11.0	11.0	11.2	11.6	12.1	12.5	12.8	13.0	13.3	13.9	15.0	17.8	26.6
11	51	4	26.6	18.0	15.2	14.3	13.9	13.7	13.3	12.6	11.8	11.3	11.0		10.8	11.0	11.4	11.9	12.3	12.6	12.8	13.2	13.7	14.8	17.6	26.4
12	53	4	26.6	18.0	15.2	14.3	13.9	13.7	13.3	12.6	11.9	11.3	11.0	10.8		11.0	11.4	11.9	12.3	12.6	12.8	13.2	13.7	14.8	17.6	26.4
13	55	4	26.8	18.2	15.4	14.5	14.1	13.9	13.5	12.8	12.1	11.5	11.2	11.0	11.0		11.6	12.1	12.5	12.8	13.0	13.4	13.9	15.0	17.8	26.6
14	57	4	27.2	18.6	15.8	14.9	14.5	14.3	13.9	13.2	12.4	11.9	11.6	11.4	11.4	11.6		12.5	12.9	13.2	13.4	13.8	14.3	15.4	18.2	27.0
15	60	5	27.7	19.1	16.3	15.4	15.0	14.8	14.3	13.6	12.9	12.4	12.1	11.9	11.9	12.1	12.5		13.4	13.7	13.9	14.2	14.8	15.9	18.7	27.5
16	63	5	28.1	19.5	16.7	15.8	15.4	15.2	14.8	14.1	13.4	12.8	12.5	12.3	12.3	12.5	12.9	13.4		14.1	14.3	14.7	15.2	16.3	19.1	27.9
17	66	5	28.4	19.8	17.0	16.1	15.7	15.5	15.1	14.3	13.6	13.1	12.8	12.6	12.6	12.8	13.2	13.7	14.1		14.6	15.0	15.5	16.6	19.4	28.2
18	69	5	28.6	20.0	17.3	16.3	15.9	15.7	15.3	14.6	13.9	13.3	13.0	12.8	12.8	13.0	13.4	13.9	14.3	14.6		15.2	15.8	16.8	19.6	28.4
19	73	6	29.0	20.3	17.6	16.6	16.3	16.0	15.6	14.9	14.2	13.7	13.3	13.2	13.2	13.4	13.8	14.2	14.7	15.0	15.2		16.1	17.2	20.0	28.7
20	77	6	29.5	20.9	18.2	17.2	16.8	16.6	16.2	15.5	14.8	14.2	13.9	13.7	13.7	13.9	14.3	14.8	15.2	15.5	15.8	16.1		17.7	20.5	29.3
21	82	7	30.6	22.0	19.2	18.3	17.9	17.7	17.3	16.5	15.8	15.3	15.0	14.8	14.8	15.0	15.4	15.9	16.3	16.6	16.8	17.2	17.7		21.6	30.4
22	89	9	33.4	24.8	22.0	21.1	20.7	20.5	20.1	19.4	18.7	18.1	17.8	17.6	17.6	17.8	18.2	18.7	19.1	19.4	19.6	20.0	20.5	21.6		33.2
23	100	15	42.2	33.6	30.8	29.9	29.5	29.3	28.8	28.1	27.4	26.9	26.6	26.4	26.4	26.6	27.0	27.5	27.9	28.2	28.4	28.7	29.3	30.4	33.2	

Table 1: The conditional minimum detectable change (cMDC) for the CRS-R score (from Weaver et al. *J Neurotrauma* 2024): Between each pair of CRS-R measures (row: measure 1, columns: measure 2). The values highlighted in gray reflect pairs of CRS-R measures that are within the cMDC. Values in each row on either side of the grey boxes reflect changes to the CRS-R that exceed the cMDC.

PHASE 2: DBS SURGERY AND RECOVERY

After informed consent, prior to proceeding with additional study activities, a member of the study team will first confirm that all required elements of the consent are signed and securely saved.

Participants remaining eligible after the screening phase will be admitted to Brigham and Women's Hospital (BWH) and undergo a standard pre-surgical 3T MRI. This scan will include all sequences we typically use for DBS planning at BWH including a gadolinium contrast-enhanced T1-weighted magnetization-prepared rapid acquisition gradient echoes (MPRAGE) scan (for visualization of blood vessels), a white-matter nulled MPRAGE scan (**Figure 5;** for direct visualization of thalamic subregions and use of the Thalamus Optimized Multi Atlas Segmentation (THOMAS) thalamic segmentation software)[45, 46], and a multi-direction (60 gradient directions; b=3000) diffusion MRI scan (for reconstruction of major white matter tracts for safe surgical neuronavigation), and a resting-state functional MRI scan (10 mins; this will be used for exploratory research analyses investigating associations between DBS target connectivity and behavioral outcomes). Total scan time will be approximately 1 hour.

Unilateral versus bilateral implantation will be decided based on the study team's confidence in their ability to accurately target the intended regions in each hemisphere, accounting for any structural distortions present.

For CM-Pf targeting, we will used an approach modeled after our current approach to clinically target the CM-Pf in patients with generalized epilepsy[47, 48]. We will plan the electrode trajectory using Brainlab software, which is FDA cleared for this purpose. The intended target will be identified using three criteria. First, we will directly visualize the

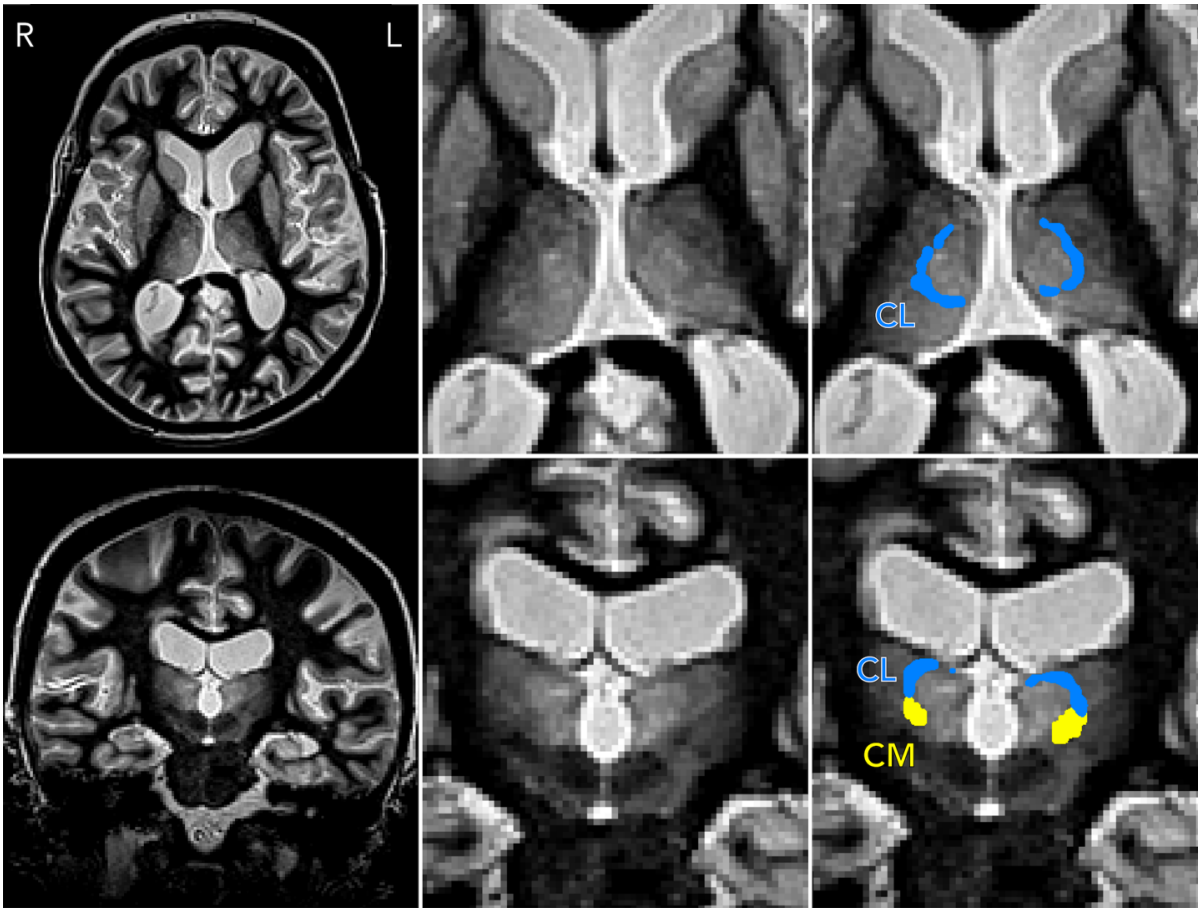


Figure 5: Thalamic visualization and segmentation for DBS targeting. Patients undergo a pre-surgical white matter-nulled (WMn) magnetization-prepared rapid acquisition gradient echoes (MPRAGE) scan, allowing direct visualization of the intralaminar thalamus. To aid visualization, the WMn image is also segmented using Thalamus Optimized Multi Atlas Segmentation (THOMAS) software, which uses the observed signal intensity within the patient's thalamus, along with a set of anatomical priors, to segment thalamic nuclei including the central lateral (CL) and centromedian (CM) nuclei, among others.

CM-Pf on the patient's white-matter nulled MPRAGE MRI scan (**Figure 5**). Second, we will identify the relevant CM-Pf subregion by non-linearly registering the binarized "optimal stimulation site" from the Croatian cohort in Montreal Neurological Institute space (**Figure 3**) onto the participants' brain using Lead-DBS software[49]. Accuracy of the registration will be manually reviewed by the study team, who have extensive experience registering atrophied/distorted anatomical brain scans.[48, 50]. Third, the

ventral tegmental tract[30] will be reconstructed from the participant's diffusion MRI (**Figure 6**), seeding from the midbrain reticular formation with a hypothalamus termination mask[30]. The ultimate target for surgical implantation will be the union of these three regions (one per hemisphere) visualized in Brainlab. In the event of qualitatively inaccurate co-registrations or white-matter tract reconstructions (potentially due to anatomical distortions), the final target will be defined anatomically based on the white-matter nulled image only.

For CL targeting, we will use the approach modeled in Schiff 2023[38] in their study of CL stimulation for cognitive impairment after TBI. This approach based on direct visualization of the CL (from the white-matter nulled MPRAGE MRI scan) in combination with two supporting approaches to confirm localization accuracy. The first supporting approach involves an automated segmentation of the patient's thalamus (THOMAS software; **Figure 5**). The THOMAS software uses anatomical priors (based on expert labelling of individual thalamic nuclei from high-resolution MRI scans in a healthy control group) to segment the same nuclei in the participant's thalamus, and was used in the previous clinical study of CL DBS[38]. The result of this includes a binary mask of the CL that can be used to confirm the visual impression of the CL observed directly on the patient's white-matter nulled MPRAGE scan (**Figure 5**). The second supporting approach involves localization of the dorsal tegmental tracts using the participant's diffusion-weighted MRI scan, based on the published method in the previous clinical study of CL DBS[38]. This involves defining a seed region in the midbrain reticular formation of the brainstem from which white matter tracts are extracted, using MRTrix3 software[51] **(Figure 6**). The location within the CL showing the greatest density of tract terminations will be identified and used as a reference point for positioning the bilateral CL DBS leads. Despite being widely in clinical settings (including a study of CL targeting in awake patients after TBI[38]), THOMAS software is not FDA cleared. However, it will not be used in isolation to target electrode placement. In situations where the clinical team lacks confidence in the qualitative accuracy of the THOMAS segmentation or the tract reconstructions, the white-matter nulled image will be used in isolation.

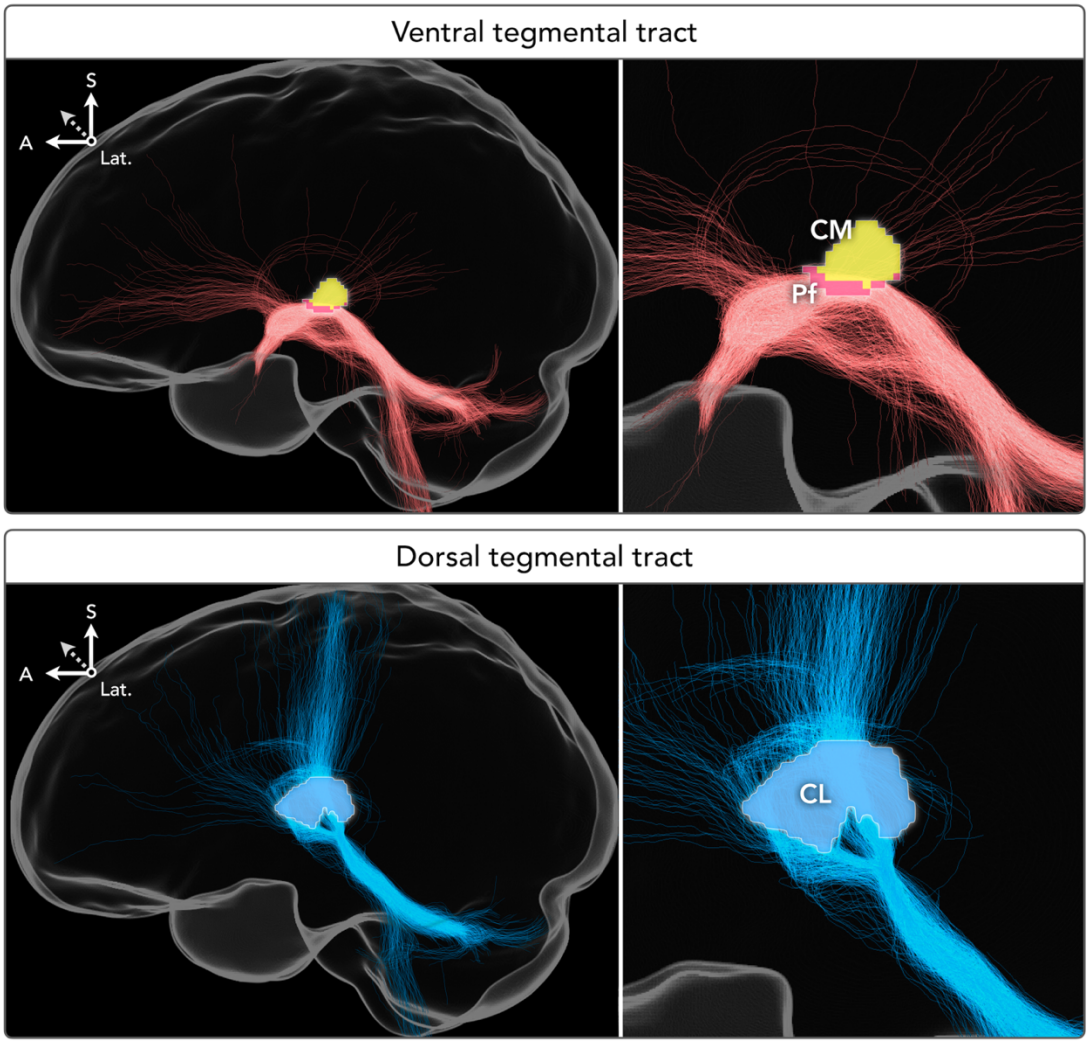


Figure 6: Diffusion MRI tractography to define ventral and dorsal tegmental tracts. Patients undergo a pre-surgical diffusion-weighted MRI scan for visualization of white matter fiber pathways. Using the previously described approach by Schiff et al. (*Nature Medicine* 2023*)* in a pilot trial of DBS for traumatic brain injury, a seed is placed in the midbrain reticular formation of the brainstem. Tractography is then performed to visualize the ventral tegmental tract (VTT), which abuts the centromedian-parafascicular (CM-Pf) thalamic nuclei and our previously identified optimal stimulation target for DoC (**Figure 3**). Separately, tractography is performed to visualize the dorsal tegmental tract (DTT) which connects the midbrain to the central lateral nucleus (CL).

Surgery: The default plan will be to implant the CM-Pf subregion and the CL bilaterally. In the event of anatomical distortions in either hemisphere preventing accurate electrode placement, we will perform a unilateral implantation in the preserved hemisphere. After finalizing the surgical targeting plan (unilateral versus bilateral), LARs will then undergo an additional surgical consent for the participant to undergo DBS surgery. This will be the standard DBS surgical consent in clinical use at Brigham and Women's Hospital for the robot-assisted clinical technique. Following this additional

signed consent, DBS implantations will follow our published, robot-assisted technique.[47] A stereotactic frame is affixed to the patient's head, then to the arm of a Robotic Stereotactic Assistance (ROSA) system.[47]

Up to one day post-operatively, a high-resolution CT scan (<0.5 mm slices) is acquired and co-registered to the pre-operative MRI to confirm electrode positioning.

Patients will be implanted with the Medtronic Percept™, a rechargeable system with battery life of 15+ years, currently FDA-approved (PMA: P960009) for use in Parkinson's Disease, epilepsy, essential tremor, and dystonia[47, 52]. The Percept system can be connected to a maximum of two DBS leads. Assuming a bilateral implantation, two devices will be implanted per patient, each connected to two leads: one device will have leads implanted bilaterally into the CM-Pf and the other device will have leads implanted bilaterally into the CL. The requirement for two devices/four leads (as opposed to one device/two leads) is based on the dimensions of the thalamus which make single-lead targeting of both the CM-Pf subregion and the CL infeasible using this DBS hardware. Multi-target DBS (using four or more leads) is an emerging practice in DBS[53-55], and the Vercise™ (Boston Scientific) device is FDA approved for this purpose. Even in the absence of multi-target DBS, many centers still use two pulse generators when performing bi-hemispheric implantations for Parkinson's Disease. In the event of a single hemisphere implantation, only one device/two leads will be implanted.

A twist drill approach will be used for electrode placement, as described in our prior work, offering a minimally invasive alternative to traditional burr hole craniotomy[47]. This technique involves creating a small cranial perforation using a twist drill, 3.2mm in diameter, allowing for precise trajectory planning and electrode insertion while minimizing soft tissue disruption. Avoiding the use of extra hardware involved in traditional burr hole covers reducing the presence of foreign bodies in the patient, likely lowering the risk of infection, and resulting in a more cosmetic entry point (no bulge from the burr hole cover underneath the skin). Intraoperative validation of electrode placement is achieved using a Medtronic O-arm, which provides real-time, high-

resolution cone-beam CT imaging. This imaging allows for immediate confirmation of lead trajectory and depth relative to preoperative planning, increasing placement accuracy and reducing the need for repositioning. Once proper electrode positioning is confirmed, the system is anchored using a titanium dog bone fixation plate, which is secured to the skull with screws and designed to firmly stabilize the lead at the site of the twist drill opening. This method maintains lead integrity and minimizes migration risk, offering a streamlined and efficient workflow for central thalamic DBS implantation.

To determine the success of anatomical targeting, we will measure the volumetric overlap (for each implanted hemisphere) between the CM-Pf sub-region and the modeled electrical field of the contact with the shortest Euclidian distance to the sub-region's center of mass. For the CL target, we mean volumetric overlap (for each implanted hemisphere) between the target and the closest electrode's modeled electrical field.

Once deemed clinically stable by the admitting team, the participant will be discharged from the hospital on post-operative day 1 or 2 and will return to clinic for a routine post-operative surgical site check within 2 weeks of hospital discharge. To allow recovery from implantation, there will be no stimulation for 1 month. The participant will undergo weekly behavioral assessments during this period.

PHASE 3: DBS TITRATION

At one month-post implantation, the participant will return to clinic for device programming. The goal will be to identify the contacts and stimulation settings that will be used during the blinded stimulation phase. We will start with the contacts closest to the CM-Pf and CL targets, as described above. For each target, we will start with previously used stimulation settings but will systematically screen a variety of similar settings to identify those which induce the strongest behavioral arousal responses. Acute arousal responses that have been identified with central thalamic stimulation in

patients with DoC include eye opening, head turning, facial expressions, mydriasis, and elevation in heart rate or blood pressure[6, 7].

Given multiple prior studies using different stimulation frequencies to each of these targets, for each target, we will screen frequencies of 40, 100, and 150 Hz at a starting current amplitude of 2 mA, with a pulse with of 210 s. If no arousal responses are observed at any frequency, we will increase the current amplitude in steps of 1 mA to a max of 5.5 mA. If no responses are seen, we will switch to the second-closest contact and the screening process of frequencies/amplitude repeated. For the next phase of the study, we will use the settings that elicit the strongest arousal response (the largest number of the possible physiological and behavioral changes listed above). If there are no discernable differences in the arousal response between settings, we will use the stimulation settings for which there is a precedent in more recent human data (40 Hz for CM-Pf stimulation and 150 Hz for CL stimulation). If no arousal responses are observed, we will use the maximum (5.5 mA) current amplitude.

At the final selected frequency and amplitude, during STIM-ON blocks, stimulation will occur continuously to one of the two targets during the day (8AM-6PM), and turned off at night (6PM-8AM), with the goal of promoting sleep-wake cycles, as in other DBS studies for DoC.[4, 6, 7, 39]

During this titration, we will record heart rate and blood pressure using standard GE devices in Brigham and Women's Hospital clinic rooms. We will additionally collect scalp EEG data and DBS-evoked cortical potentials during the titration visit. Scalp EEG and DBS-evoked cortical potentials will be repeated monthly during each treatment block to explore changes in response to chronic stimulation.

PHASE 4: STIMULATION CROSS OVER

Following the titration visit, participants will then enter a 10-month stimulation cross-over phase (**Figure 4**), consisting of two 5-month blocks. In participant 1, the first 5-month block will target the CM-Pf, and the second block will target the CL. In participant 2, this

order will be reversed. Within each block, patients will receive 3-months (12 weeks) of STIM-ON followed by 2 months (8 weeks) of STIM-OFF (Figure 4). Because the stimulation paradigm used here is continuous, 3-months of STIM-ON is equivalent to 12 months of stimulation under a previous paradigm (where stimulation was administered for 30 minutes every two hours due to battery limitations of older devices)[7].

Study investigators involved in monitoring safety and study oversight will be aware of block assignment; however, the assessors performing the CRS-R measurements and participants' caregivers will be blinded to both block assignment and block duration. All clinical assessments will be conducted at the patient's residential location, either by a physiatrist, physical therapist, occupational therapist, or speech language pathologist trained to administer the CRS-R scale, blinded to the design of the crossover phase. If the patient no longer resides at a long-term acute care hospital or skilled nursing facility in the Greater Boston Metropolitan area, assessments will occur with the patient's primary caregiver using the recently validated CRS-R telephone interview using a standard procedure[56]. If CRS-R telephone assessments will be used, at least two will occur concurrently with in-person assessments to confirm alignment. During this 10-month phase, the participant will undergo weekly CRS-R evaluations, for a total of 40 post-surgical assessments. The subject will then enter a final 3-month open-label follow-up period, with stimulation settings to be determined based on study team and caregiver preference, with once monthly CRS-R assessments, until the of the study period.

During this time, we will also perform prospective and systematic safety monitoring. A research coordinator will conduct weekly prospective and systematic adverse event monitoring with participant's caregivers (facility nursing staff, LAR, and involved family). Study investigators will review these forms weekly. The Study Monitoring Committee (SMC) will meet regularly to review safety monitoring data. Pre-specified adverse events of interest will include cardiac arrhythmia, hypertension (requiring new medication), seizure, intracranial hemorrhage, ischemic stroke, central nervous system infection, surgical site infection, myocardial infarction, and bloodstream infection.

It is possible that non-serious adverse events may emerge during chronic stimulation, without having been present during titration. If, during an active stimulation block, a non-serious adverse event is detected that by the judgement of study investigators is potentially related to stimulation, then the stimulation current amplitude will be reduced by 25%, with serial monitoring of the symptom to resolution. Further reductions (each time: at least 25% of initial current amplitude) will be instituted if the symptom is persistent. If, at any point, a caregiver or LAR request that that stimulation be stopped for any reason, stimulation will be stopped immediately.

Alternate outcome measures

Clinical Outcomes

To assess whether CRS-R evaluations are associated with outcomes that are detectable by caregivers, we will pair each CRS-R evaluation with a Social and Family Evaluation (SAFE) scale completed by the participant's caregiver[57]. The SAFE scale is a standardized tool that caregivers can autonomously use to collect their impressions about the level of consciousness in patients with DoC, based on the behaviors manifested by the patient over a pre-defined time interval[57]. The SAFE scale includes YES/NO questions about whether the patient manifested a particular behavior at any point during the observation period (here: 1 week, to align with CRS-R assessments). A study in 22 patients with DoC and their caregivers found that the SAFE scale has high internal consistency ($\alpha = 0.91$), high criterion validity when correlated to clinically performed CRS-R total scores (Spearman's rho=0.7), and high test-retest reliability (Spearman's rho=1.0). Due to the high degree of similarity between the SAFE and CRS-R phone assessments, if CRS-R phone assessments are used, we will not additionally collect SAFE scores.

We will also collect the Disability Rating Scale (DRS)[58] at each assessment time point. This is a scale previously used as the primary outcome measure in a longitudinal study of participants with DoC after TBI[23]. It has a broad dynamic range, able to quantify the degree of dependency in patients who are comatose to those re-integrating into independent life in the community[58]. The primary purpose of the DRS will be to quantify

the participants' overall level of dependency over time. Its broader dynamic range will be particularly useful in patients who may emerge from the minimally conscious state, reaching maximum or near-maximum CRS-R values.

Physiological Outcomes

Because recent evidence from invasive recordings suggests that thalamic alpha frequency (8-12 Hz) power is correlated with severity of impairment in patients with DoC[59], we will include thalamic alpha power as a secondary physiological outcome measure. Using the chronic sensing/recording capabilities of the Medtronic Percept™ device, we will record alpha power from local field potentials in the thalamus. The Percept™ records frequency power in 10-minute intervals. This will be measured continuously following DBS implantation and used to perform exploratory correlations with behavioral changes before and during stimulation.

Because studies have demonstrated that stronger circadian rhythmicity across a number of physiological measures may be predictive of outcome in brain-injured patients with DoC[60, 61]. Secondary physiological outcome measures will therefore also include intermittent measurements of skin temperature and physical movement from wrist-worn actigraphy devices.

PHASE 5: OPEN-LABEL FOLLOW-UP

From months 12-15, all participants will enter an open-label follow-up period. Stimulation settings (including absence of stimulation) during this time will be at the discretion of the caregiver and treatment team. Monthly standardized assessments using the previously described measures will occur during this time frame.

At the end of the study period, the device will remain implanted unless explantation is deemed medically necessary by any physician on the participant's care team, or the participant's LAR (health care proxy or legal guardian) requests explantation. Though removing DBS intracranial leads do not commonly result in neurological deficit, there is a risk of asymptomatic intracerebral hemorrhage. In one case series, no hemorrhages

were observed in nearly 80 explantations[62]. However, because this risk theoretically exists, we will not plan to explant the devices unless requested by the LAR or it is deemed medically necessary.

Follow-up at the end of all study activities will be determined on a case-by-case basis. DBS management will be guaranteed by our team for at least the 18 months following the end of all study activities, should the LAR wish to continue stimulation. Beyond that time-frame, the participant will be referred for ongoing follow-up in a DBS clinic within our Mass General Brigham hospital system. The implanted pulse generator will last 15 years per Medtronic's labeling, though may last longer in real-world use; participants will not need replacement surgery for that duration. If replacements are required in the future, we will handle each case based on the clinical standards regarding commercial approval and availability of DBS therapy for DoC at that time. We will encourage participants to enroll in long-term follow-up studies to monitor the continued safety of this system.

End of Study

End of Trial is defined as all enrolled participants have completed the cross-over phase or have been early-terminated from the study.

7. Risks and Discomforts

Here, we detail potential risks to the human subject participants in this study. Informed consent will highlight the most comment potential adverse events, the most serious potential adverse events.

Risks of Implantation Surgery

Intracranial hemorrhage (2.9%)[63]

Perioperative seizures (3.4%)[64]

Skin erosion or infection (6.6%)[64]

Implanted stimulator malfunction (0.9%)[64]

Lead migration or malposition (1.3%)[64]

Risks of multi-lead DBS configurations appear similar to standard implantations[53-55]

Risks of general anesthesia associated with neurosurgical procedures
The risks of general anesthesia (required for device implantation) will be discussed in detail by the anesthesiologist before the procedure. In general, these include temporary risks (behavioral worsening, nausea, constipation, urinary retention, infection, and others). Less common but more serious risks include blood clots in the legs or lungs that could cause respiratory compromise, lung collapse or infection, and medication-induced hypotension, cardiac arrhythmias, or even death.

Risks of electrical stimulation
The side effects of CM-Pf stimulation, derived from studies of patients with epilepsy, have included paresthesias and fatigue[65]. The side effect profile of CL stimulation in awake patients with subjective cognitive impairment included dysarthria, abnormal facial sensation, akathisia, anxiety, and increased verbal output/perseveration[38]. None of these reported side-effects will be readily assessable in the population we propose to study.

Risks associated with brain MRI
The safety of brain MRI is well established in the medical literature. For the pre-operative brain MRI, subjects will be screened for the presence of implanted metallic objects in a standard fashion using an institution specific protocol. Any subject with ferromagnetic metal in their body precluding MRI will not be allowed to participate in the study.

The risks related to undergoing MRI are temporary disequilibrium, dizziness or nausea. Participants may also be bothered by loud clicking noises, which will be mitigated through the provision of ear plugs. Subjects with claustrophobia may

also be disturbed by time within the small-bore MRI. However, this is not likely relevant here, as study participants will not be interactive with their environment.

Risks associated with assessment administration

There are no substantial risks associated with administering the behavioral assessments, which occur at similar frequency in some long-term acute care facilities even in the absence of study procedures.

Risks associated with CT scans

This study will utilize traditional CT scans in the post-operative setting (2 scans per subject). These scans involve radiation exposure of 2mSv or roughly 4% of the annual allowable limits, based on EPA guidelines[66]. CT scans are contraindicated and pregnancy, and no pregnant patients will be enrolled into this study.

Risks of DBS system removal

The risk of removing a DBS system is low[62]. Apart from the risks of general anesthesia previously discussed, these risks include hemorrhage in the brain and infection.

Risks associated with secondary and exploratory endpoint measures

There is a small risk associated with discomfort from the EEG cap during the neuroelectric assessment, this discomfort has been reported as being minor. Cleaning and sterilization of the EEG is consonant with manufacturer's recommendations and will be done prior to and after each assessment.

Additionally, participants may experience red skin or discomfort from wearing the actigraphy device around the wrist too tight or for an extended period of time. Study staff will ensure that the watch is fitted correctly and participants' skin will be

monitored for redness and discomfort. The device can be removed at any time if any signs of discomfort appear.

Inability to undergo MRI after device implantation

This implanted lead configuration has not been evaluated for MRI safety. Once the device has been implanted, the participant will not be able to undergo an MRI scan, even if recommended for an unrelated medical condition. This will be explicitly discussed in the informed consent.

Risk Mitigation

Procedures to mitigate risk of DBS implantation surgery

Compared to other neurosurgical procedures, DBS implantation surgery is a relatively lower risk procedure. To reduce the risk of surgical complication, we will institute the following measures:

- Strict exclusion of higher-risk patients (uncontrolled medical conditions, need for anticoagulation).
- Use of robot assisted stereotaxy. This technique has been shown to have high reliability (sub-millimetric accuracy) and is our standard technique for CM DBS[47, 67].
- Intensive post-operative care, including immediate post-op CT to rule out a clinically occult intracranial complication.
- Use of peri-operative antibiotics. Cefazolin will be administered one hour prior to incision and continued for 24 hours post-operatively.

Procedures to mitigate the risk of DBS

Side effects associated with neuromodulation are typically reversible with stimulation setting adjustment. To reduce the risk of side-effects, we will perform the following procedures:

- limit charge density to 30 c/cm^2

- Participants will be monitored for 30 minutes after the last change to stimulation settings during the titration phase, to monitor for acute changes
- Caregivers will be provided with an information sheet describing potential adverse effects and emergency 24-hour contact information of key study staff.
- Participants will be monitored by study staff for symptoms and safety events weekly. However, if unforeseen effects or symptoms emerge that are distressing to caregivers or LARs and are adjudicated by the SMC to be potentially related to stimulation, we will make intensity modifications.

Serial enrollment strategy

We will leave a minimum window of four months after implanting the first participant before enrolling a second participant. The SMC will perform an interim safety review and make a consensus recommendation on whether to proceed or halt enrollment based on the safety events observed in the first three months.

8. Benefits

There are multiple clear justifications for enrolling participants into this study who cannot themselves consent. First, DBS to each thalamic target has been previously performed safely in this patient population[6, 7, 10]. Second, comparative analyses of the two targets have been previously performed in primates[26, 68]. Third, the patient population we propose to enroll in this study is known to have extremely poor outcomes[69, 70]. It would be extraordinarily rare for any patient with DoC for more than 3 months (a requirement for inclusion in the current study) to regain functional independence[70]. Fourth, the devices and thalamic targets selected in this study have been tested[38, 71] or are in current therapeutic use[72-75] in patient populations with significantly less functional disability than the population we proposed to study, suggesting that the overall risk profile is commensurate for the target population in this study. Finally, patients with chronic DoC cannot communicate—so there would be no feasible way to obtain consent from them.

Assuming results are consistent with those observed in prior studies[7, 10], there is the possibility of direct therapeutic benefit to the enrolled patients. Furthermore, the risk of the interventions being offered here is low relative to all standard neurosurgical procedures. We separate the risks below into the risks of the surgical procedure, device-related risks, and target-related risks.

Bilateral DBS surgery has been performed in the US for more than 30 years and has a risk of infection, hemorrhage, and lead migration of <5%, <3%, and <2%, respectively[76-78]. Medtronic DBS electrodes have now been on the market for 30 years, with rates of device malfunctions, lead fractures, and lead migrations each <5% in general use[76, 77]. The intralaminar thalamic nuclei (CM/Pf and CL) are near the FDA-approved target of DBS for focal epilepsy. As discussed above, human data suggests that DBS targeting the CM-Pf and the CL region is safe in patients with and without chronic DoC.

The central thalamic nuclei (both CM-Pf and CL) have been used as DBS targets in studies of patients who function independently[38, 73, 79], who would be substantially more risk-averse than the population we plan to enroll. It stands to reason that targeting these thalamic regions in a different patient population would have a similar safety profile, and would have an acceptable risk/benefit ratio, given the unfavorable natural history of the disease. Published experience of CM-Pf[7] and CL[10] DBS for DoC suggests that the rates of serious adverse events (e.g., cerebral infection or death) are similar to the rates seen with this procedure in other patient populations(epilepsy, TBI).

Finally, multi-target DBS (using four or more leads) is an emerging practice in DBS[53-55], and the Vercise™ (Boston Scientific) device is FDA approved for this purpose. Invasive epilepsy monitoring studies frequently include more than four implanted stereo-EEG electrodes in an awake patient population. Implanting two pulse generators (one in each pectoral pocket) is routinely done clinically in bi-hemispheric implantations for Parkinson's Disease. In this case, both thalamic targets have a

body of pre-clinical and clinical data supporting their use. There is substantial uncertainty about which target (if any) should be used. Given the significant heterogeneity in the population under study, the proposed cross-over design directly comparing stimulation of each target is the most scientifically efficient way to discern target effects. This is consistent with the FDA's EFS guidance that encourages maximizing data yield from few subjects.

9. Statistical Analysis

Primary Objectives

Objective 1 will be analyzed using descriptive statistics. While early phase trials often have a pre-specified criteria such as "absence of unanticipated SAE", we will not have such a cut-point given the severely unfavorable natural history of chronic disorders of consciousness.

Objective 2 will also be analyzed using descriptive statistics. To proceed to a larger study, both feasibility criteria must be met: both participants must be implanted within 2 years of study launch, and each patient must have leads with modeled E-fields at least partially overlapping the CM-Pf sub-region and the CL.

Objective 3: The primary and secondary outcomes for objective 3 will be the CRS-R score and the SAFE and DRS scores (administered to caregiver), respectively. The goal of this objective will be to estimate the stimulation-dependent effects on the primary outcome. Because we are enrolling only two participants, there will insufficient data to fit an informative model.

To proceed to a larger study, the preliminary data must *suggest* a stimulation-dependent effect on participant CRS-R scores at least as large as the conditional minimum clinically detectable difference (cMDC). **One** participant must meet **one** of the following two criteria:

- The difference between values (1) and (2)—defined below—must be at least as large as the cMDC*
    - (1) the greater of:
        - median STIM-ON [CM-Pf or CL] CRS-R
        - average of the last two STIM-ON [CM-Pf or CL] CRS-R scores
    - (2) median STIM-OFF (same block) CRS-R

- The difference between the median STIM-ON (CM-Pf or CL) CRS-R and the median pre-stimulation CRS-R (the higher of the median screening phase or post-op recovery phase) is larger than the cMDC*

  **cMDC defined based on median pre-surgical CRS-R*

We will use the same approach to model the effect of stimulation condition on caregiver SAFE scale score and DRS score.

The primary analysis will be a per-protocol analysis, including individuals who finished at least one 5-month block from the cross-over phase. Missing observations will be replaced with the previous observation carried forward.

Secondary Objectives

Objective 4: During the study, each Percept™ electrode can record (between one pair of contacts) average spectral power within a frequency band of interest every 10 minutes. We will record alpha band (8 to 12 Hz) power continuously during the study period. We will fit a linear model for each participant using the alpha band power as the dependent variable. Independent variables will be time (days) and condition (CM-Pf ON vs CL-ON vs OFF). The primary goal of this analysis will be to model the effect of time and stimulation on thalamic alpha power in chronic disorders of consciousness. The secondary goal of this objective will be to determine if thalamic alpha power is correlated (linear model) with CRS-R in either participant.

Exploratory Objectives:

We will conduct a series of exploratory analyses using the thalamic spectral data, scalp EEG data acquired during titration and monthly during stimulation cross-over, and using

physiological data acquired during titration and monthly during stimulation cross-over. Exploratory analyses will seek to identify associations between stimulation, behavioral changes (CRS-R) and electrophysiological (thalamic and/or scalp alpha power, DBS-evoked cortical potentials) or physiological properties (heart rate variability, circadian changes in skin temperature, or spontaneous motor activity).

Justification for Sample Size (N=2).
Given the uncommon incidence of the condition under study and the mandated minimum four-month delay between implantations, 2 is the maximum number of patients that can reasonably be implanted and followed at a single site in one year. The rigorous cross-over design of this study will enable the collection of pilot data comparing the stimulation-dependent behavioral effects of these two intralaminar thalamic targets that will inform the design of a definitive trial. The small number of participants is justified by the EFS nature of the study, and is motivated by a desire to limit participation to the minimum number needed to meet the developmental objectives in the face of many significant unknowns.

10. Monitoring and Quality Assurance

Study investigators will perform prospective and systematic safety monitoring. A research coordinator will conduct weekly prospective and systematic adverse event monitoring, via case report forms (Appendix 2) administered to the participant's caregivers (facility nursing staff, LAR, and involved family). These will be reviewed by study investigators weekly. The Study Monitoring Committee (SMC) will meet regularly to review safety monitoring data. Pre-specified adverse events of interest will include cardiac arrhythmia, hypertension (requiring new medication), seizure, intracranial hemorrhage, ischemic stroke, central nervous system infection, surgical site infection, myocardial infarction, and bloodstream infection.

The principal investigators are responsible for the detection, documentation, and follow-up of safety events meeting the below criteria:

Safety Event

A safety event is defined as any unexpected medical occurrence, unintended disease or injury, or untoward clinical sign (including laboratory finding) in participants, regardless of whether or not it is related to the investigational device or study procedures.

Not Device or Procedure Related - Adverse Event (AE)

These are safety events not related to the surgical procedure or investigational device.

Device or Procedure Related - Adverse Device Effect (ADE)

These are safety events related to the implantation or operation of the investigational device. These include events resulting from insufficiencies or inadequacies in the Instructions For Use, surgical complications, stimulation, or device malfunction, including a use error or intentional misuse.

Serious Safety Events:

A safety event is serious if:

- Leads to death
- Leads to serious deterioration in health that:
    - Resulted in life-threatening illness or injury
    - Resulted in injury or permanent impairment of body structure or body function
    - Required hospitalization or prolongation of existing hospitalization
    - Resulted in medical or surgical intervention to prevent life-threatening illness
- This includes deficiencies that may have led to a serious safety event if:
    - Suitable action was not taken
    - Intervention was not made

- A planned hospitalization for pre-existing condition, or procedure required by protocol, without serious deterioration in health, is not considered a serious safety event

Not device or Procedure Related - Serious Adverse Event (SAE)
These are safety events that result in the consequences of a serious safety event but are not related to the procedure or the investigational device.

Device or Procedure Related – Serious Adverse Device Effect (SADE)
Safety events resulting in consequences of a serious safety event that is related to the procedure or investigational device and is an event by its nature, incidence, severity, or outcome that is identified in the study protocol or consent form.

Unanticipated – Unanticipated Adverse Device Effect (UADE)
This is a serious adverse event caused by or associated with the investigational device, which was not previously identified in nature, severity, or degree of incidence in the protocol, consent form, IDE application or supplement *or* any other unanticipated serious problem associated with the investigational device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)
These include events that may or may not meet criteria for unanticipated adverse device events, including (but not limited to):

- Unanticipated drug or unexpected device adverse reactions attributable to the intervention and that place participants at increased risk of harm
- Events that occur more frequently than expected or that represent a more severe instance of the event than has previously occurred
- Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop)
- Medication, procedural or laboratory error (e.g., errors in drug administration or dosing, surgical or other procedure, or testing of samples or test results) regardless of whether participants experienced any harm

- Interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding that indicates that there are new or increased risks to participants or others or that participants are less likely to receive any direct benefits from the research
- Change in FDA labeling (e.g., black box warning), withdrawal from market, manufacturer alert from the sponsor, or recall of an FDA-approved drug, device, or biologic used in the research
- Incarceration of a research participant during participation in research that is not approved for involvement of prisoners as participants
- Suspension or termination of the research by an entity other than the IRB, in whole or in part, based on information that indicates that the research places participants at an increased risk of harm than previously known or recognized (e.g., FDA clinical hold)
- Premature suspension, termination or hold of the research by the sponsor
- Suspension or disqualification of an investigator by FDA, sponsor, or others
- Scientific misconduct

Safety Event Assessments

Continuous monitoring for safety events will occur during the entire study period via a case report form. AEs will be assessed and handled in real time as they occur. During the study period, AE monitoring will occur daily in the hospital immediately post-operatively, at the post-operative 1-2 week visit, at the end of the titration visit (1-month post-surgery) and then weekly for the duration of the study period, all via case report form. Participant's caregivers and their care team at the facility will be given 24-hour contact information for study staff to report and/or discuss concerns at any time. AEs reported during these conversations will be recorded and reported.

All AEs will be reported to the IRB and FDA as described below. We will submit annual reports to the IRB and the FDA via the IDE Progress Report. Unanticipated events will be collected, assessed, and reported (Appendix 2). The sponsor (IDE

holder) will be responsible for reporting all reportable unanticipated events to the appropriate regulatory agencies as per each agency's reporting requirements and within the agency's time frame.

Assessment of Causality

The Investigators will assess the relationship between each safety event and the device/procedure using definitions listed below. A safety event can be related to the device, the procedure, or both. The Investigators will assess causality of each event to the device independent from the procedure and to the procedure independent from the device.

Investigational Device

Related: The safety event has a reasonable temporal relationship to the device. The safety event could have been due to another equally likely cause

Unrelated: The subject did not receive the device, OR the safety event has no temporal relationship to the device, OR the safety event has a more likely alternate explanation, OR the safety event is due to an underlying or concurrent illness or effect of another drug.

Procedure

Related: The safety event has a reasonable temporal relationship to the procedure. The safety event could have been due to another equally likely cause.

Unrelated: The subject did not have the procedure, OR the safety event has no temporal relationship to the procedure, OR the safety event has a more likely alternate explanation, OR the safety event is due to an underlying or concurrent illness or effect of another drug. The Investigators will always assess causality for every event, even in the presence of incomplete information. The Investigator may change their opinion of causality in light of follow-up information and amend the report accordingly.

Serious Safety Event Reporting Requirements

Once the Investigator determines that a safety event meets criteria of Serious (SAE or SADE), the Sponsor-Investigator must provide an assessment within 5 days of becoming aware of the event.

UPIRTSO Reporting Requirements

If the investigator determines a safety event meet criteria for UPIRTSO, the Investigator or their designee must notify the IRB and FDA within 5 working days (7 calendar days) of becoming aware of the event.

The report will include:

1. a detailed description of the event (including how and when the PI/study team learned of the event);
2. the basis for determining that the event is unexpected in nature, severity, or frequency;
3. the basis for determining that the event is related or possibly related to the research procedures;
4. the basis for determining that the research places participants at an increased risk of harm; and
5. whether any changes to the research or other corrective actions are warranted.

A UPIRTSO evaluation will immediately be conducted, and results of the evaluations will be reported to the FDA, relevant Regulatory/Competent Authorities, reviewing IRB, the SMC and participating Investigators in accordance with applicable national and local regulations.

Unanticipated Safety Event Reporting Requirements

If the investigator determines a safety event meet criteria for UADE, the Investigator or their designee must notify the IRB and FDA within 5 days of becoming aware of the event. A UADE evaluation will immediately be conducted, and results of the evaluations will be reported to the FDA, relevant Regulatory/Competent Authorities,

reviewing IRB, the SMC and participating Investigators in accordance with applicable national and local regulations.

Follow-up of Safety Events

SAE/SADE/UADEs will be followed until the event resolves, condition stabilizes, the event is otherwise explained, the subject is lost to follow-up, or death occurs. New or updated information will be recorded on an SAE Report.

Regulatory Reporting Requirements for Unanticipated Adverse Device Effects:

The Sponsor-Investigator has a legal responsibility to notify the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. An Investigator letter will be prepared for all UADEs according to institutional policy and forwarded to all study investigators. The purpose of this letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product being assessed.

Stopping Rules

Stopping rules for the participant

Subject participant in the study will be halted for the following indications:

(1) LAR withdraws consent

(2) Patient regains ability to communicate* and does not assent to continue study procedures

   a. *ability to communicate will be defined as ability to accurately respond (with verbal response or an indicative physical gesture) to a series of 3 yes/no biographical questions

(3) Participant unable to be assessed on 16 consecutive scheduled assessments during cross-over phase

(4) Compromise of participant safety and welfare, based on

   a. Adverse event anticipated or unanticipated AND
   b. Investigator determination that continued participation places participant at foreseeable risk of further ham

(5) Device explantation (for any reason)
(6) Death

Stopping rules for the study

The study will be halted until the Study Monitoring Committee and FDA have reviewed the following events

(1) One participant has intraparenchymal hemorrhage or acute subdural hematoma
(2) One participant has a new focal neurological deficit or a decline in CRS-R from lowest pre-surgical measurement by more than the cMDC on two consecutive assessments
(3) One participant has infection that required re-hospitalization or extends the post-operative period by more than one week
(4) One participant develops post-operative seizures, without a preoperative diagnosis of seizure disorder, which require more than one anti-epileptic drug to control

One participant death attributable to study procedures

Study Monitoring

Source Data

The Investigators will permit study-related monitoring, audits, and IRB access including permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

Monitoring Audits and Inspections

The Investigators will assure that local study staff cooperate with monitoring and audits. The Investigator agrees to allow auditing and inspection of all essential clinical study documents by the FDA or other appropriate regulatory authorities. Auditing visits will be scheduled with the appropriate staff at mutually agreeable times as applicable. Monitoring will be conducted following the ICH Good Clinical Practice E6(R2), and applicable federal, sponsor, and institutional guidelines.

Monitoring procedures and monitor name/address

The sponsor will implement a *risk-based monitoring program* that includes:

• **Site Qualification & Initiation** – Remote pre-study assessment followed by an on-site (or virtual) initiation visit before first enrollment.

• **Interim Monitoring** – On-site visits after the first subject is implanted, then at ~25 %, 50 %, and 75 % of enrollment, with additional visits triggered by any Serious Adverse Device Effect (SADE) or major protocol deviation. Remote data review will occur **monthly** via the EDC system.

• **Close-out Visit** – Within 30 days of last subject's final follow-up.

• **Scope of Verification** – 100 % informed-consent review; 100 % source-data verification (SDV) for primary safety and effectiveness endpoints; ≥10 % SDV for non-critical data; complete device accountability and traceability checks.

• **Reporting & CAPA** – Written monitoring reports issued to the sponsor within 10 business days; deviations graded (major/minor) with timelines for corrective and preventive action (CAPA); unresolved issues escalated to the sponsor within 5 days.

• **Training & Communication** – The monitor will document site personnel training, maintain a monitoring log, and confirm timely submission of required FDA, IRB, and sponsor reports.

Monitor:
Rupali Ranade, MBBS
Clinical Research Monitor, MGB Office of Clinical Research
185 Cambridge Street, Boston, MA 02114
Phone:781-266-6025 • Email: rranade1@mgb.org

Data-Safety Monitoring

A Study Monitoring Committee (SMC) will ensure the safety of the participants and the validity and integrity of the data collected. This group may also be called a data safety monitoring board (DSMB). The SMC will include Dr. Barbara Changizi (neurologist, Mass General Brigham, Dr. Daniel Rubin (neurologist, Mass General Brigham), Dr. Rees Cosgrove (neurosurgeon, Mass General Brigham). The SMC will monitor, among other things, recruitment procedures, protocol deviations, and adverse events.

The SMC will be notified within 5 days of any SAE in this study. Meetings will be held annually, with additional meetings convened within 48 hours of an unexpected SAE, and at four-months after the first participant has been implanted. Official interim monitoring results of the study will be presented for review. As discussed above, the SMC for this trial is composed of an independent group of clinicians that includes a neurologist with expertise in DBS, a neurosurgeon with expertise in DBS, and a neurologist with expertise in disorders of consciousness. Meetings will be assembled in person or via secure teleconference, as determined by the chair of the SMC. The SMC will ensure that all SAEs have been followed to resolution, and the appropriate regulatory agencies (FDA and IRB) have been informed. Data and safety monitoring will additionally be conducted by co-PIs and co-investigators, who will meet regularly to review new information from clinical ratings, assessments, medical records, and clinical survey data. Study-related adverse events or threats to patient confidentiality will be monitored and any needed safety changes will be addressed.

Assessment of adverse events, including grading of severity and attribution to procedures/devices will be conducted at the schedule previously indicated and noted on the rating coversheet. The PIs will report all unanticipated serious adverse events, both verbally and in writing, to the full SMC within 48 hours. A full report will be provided to the IRB and FDA within 5 working days (7 calendar days) The Scientific Steering Group (Drs. Snider and Rolston) will evaluate all adverse events and determine whether the event affects the risk/benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or to the consent form (at Risks and Inconveniences) are required.

11. Data and Research Material Sharing

The investigators are response for complying with the requirements for all assessments and data collection as stipulated in the protocol for each subject in the study. In the case of a subject awakening and withdrawing assent, or the LAR withdrawing consent to complete all protocol related assessments, the investigators or study staff can search publicly available records (where permitted) to ascertain survival status. This ensures that the data produced will be complete and as comprehensive as possible.

The following data types will be collected as part of this study:

- Brain imaging data
- Thalamic LFP data from Percept™
- Titration related behavioral and ERP EEG data
- Scalp EEG and physiological (skin temperature, heart rate, actigraphy) data
- Behavioral data
- Caregiver Survey data
- Event report forms
- LAR informed consent documents

Subject Tracking

Subject identification log (to be retained only be Investigators; with link to the LAR), subject screen failure log, and a subject enrollment log will be used to track subject participation.

Recording of data

Clinical information required for study eligibility and medical clearance for surgical procedures will be maintained in HIPAA-compliant electronic systems. Data obtained for research purposes will be de-identified, encrypted, and password protected. Study data will be recorded in paper and digital format without specific subject identifiers. The Investigators will certify on a regular basis that the data entered CRFs is complete and accurate. Subject identifiers will be stored in a codebook in a

locked cabinet in Dr. Snider's (co-PI) office while study data will be stored in a different locked cabinet in Dr. Snider's office area. The database will be stored in an MGB REDCap database, which includes approved back-up procedures and is protected by user specific password accessible only to study investigators. Clinical data will be stored in the electronic medical record. Hard copies of relevant clinical data will be stored in the locked file cabinet. A clean file procedure will be adopted. Only coded and data considered clean will be made available for analysis. After completing the analysis and writing of final signed report, the data will be de-identified and archived on an encrypted server.

Records Retention

Health Insurance Portability and Accountability Act of 1996 - The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act.

Storage

Investigational devices must be received by a designated person at the study locations, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access to. Upon receipt, all devices will be stored in a locked and secured location. The investigator or designated staff must maintain an accurate record of the shipment and use of the research system in an accountability ledger. Monitoring of the study accountability will be performed periodically and at the completion of the trial.
Medical records of research study participants will be stored for at least 6 years per legal requirements.

A) Sending Data/Materials to Research Collaborators outside Mass General Brigham

We will transfer de-identified EEG and physiological monitoring data to co-investigator Dr. Morris (Northeastern University) for analyses. These data will be transferred via encrypted hard drive.

B) Receiving Data/Materials from Research Collaborators outside Mass General Brigham

There will be no material transferred to MGB from outside institutions.

12. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting.
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected.
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol.
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies.
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research.
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens.
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research.
- ☐ Additional privacy and/or confidentiality protections

ENTER TEXT HERE

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required* if this Appendix has been completed and approved by the IRB.

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
As discussed above, the SMC for this trial is composed of an independent group of clinicians that includes a neurologist with expertise in DBS, a neurosurgeon with expertise in DBS, and a neurologist with expertise in disorders of consciousness
3 Members:

- Dr. Barbara Changizi (neurologist, Mass General Brigham,
- Dr. Daniel Rubin (neurologist, Mass General Brigham)

- Dr. Rees Cosgrove (neurosurgeon, Mass General Brigham)

☒ Describe planned frequency of meetings:
The SMC will be notified within 5 days of any SAE in this study. Meetings will be held annually, with additional meetings convened within 48 hours of an unexpected SAE, and at four-months after the first participant has been implanted

☒ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.