PROTOCOL

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

1 PROTOCOL SUMMARY

Title:

STIMPACT: Stimulant Therapy Targeted to Individualized Connectivity Maps to Promote ReACTivation of Consciousness

Précis:

Phase 1 of the STIMPACT trial is an open label, dose-escalation, safety study of intravenous (IV) methylphenidate (MPH) therapy in patients with disorders of consciousness (DoC) caused by severe brain injuries. To be classified as having a DoC, a patient must be in a coma, vegetative state (VS), or minimally conscious state (MCS),[1] as determined by behavioral assessment using the Coma Recovery Scale-Revised (CRS-R).[2] Patients with DoC admitted to the intensive care unit (ICU) will be eligible for the study.

A total of 22 patients with DoC will be enrolled in the Phase 1 study. Patients will receive escalating daily doses of IV MPH starting at 0.5 mg/kg, increasing stepwise to 1.0 mg/kg and 2.0 mg/kg unless an adverse event (AE) necessitates dose de-escalation or a serious adverse event (SAE) necessitates that the patient stop participation in the study. Pharmacokinetics will be evaluated in selected patients with indwelling venous catheters or arterial catheters via serial serum measurements of MPH at each dose. The pharmacodynamic properties of IV MPH at each dose will be assessed by comparison of pre- versus post-dose EEG-based measures. The pharmacodynamic properties of the maximum tolerated dose will also be assessed by comparison of pre- versus post-dose resting state functional MRI (rs-

fMRI) connectivity measures. Finally, we will test the association between structural connectivity of the ventral tegmental area (VTA), a dopaminergic brainstem nucleus that is believed to mediate MPH activation of the cerebral cortex, and EEG and rs-fMRI pharmacodynamic measures.

Objectives:

The primary objectives of the STIMPACT Phase 1 study are:

1) To determine the maximum tolerated dose of IV MPH in patients with DoC caused by severe brain injuries.

2) To define the pharmacokinetics of IV MPH in patients with DoC caused by severe brain injuries.

The secondary objectives of the STIMPACT Phase 1 study are:

1) To explore the effect of IV MPH on an EEG pharmacodynamic biomarker of cerebral cortical connectivity in patients with DoC caused by severe brain injuries.

2) To explore the effect of IV MPH on a rs-fMRI pharmacodynamic biomarker of brain connectivity in patients with DoC caused by severe brain injuries.

3) To explore the relationship between structural VTA connectivity and each pharmacodynamic biomarker in patients with DoC caused by severe brain injuries.

Endpoints:

The outcome variables for the primary outcomes are:

1) The number of AEs and SAEs at each dose.

2) The time to maximal serum concentration (T_{MAX}) and the serum half-life ($T_{1/2}$) of IV MPH at each dose.

The outcome variables for the secondary outcomes are:

1) The effect of each stimulant dose on cerebral cortical connectivity, as measured by EEG.[3]

2) The effect of the maximum tolerated stimulant dose on brain connectivity, as measured by rs-fMRI.[4]

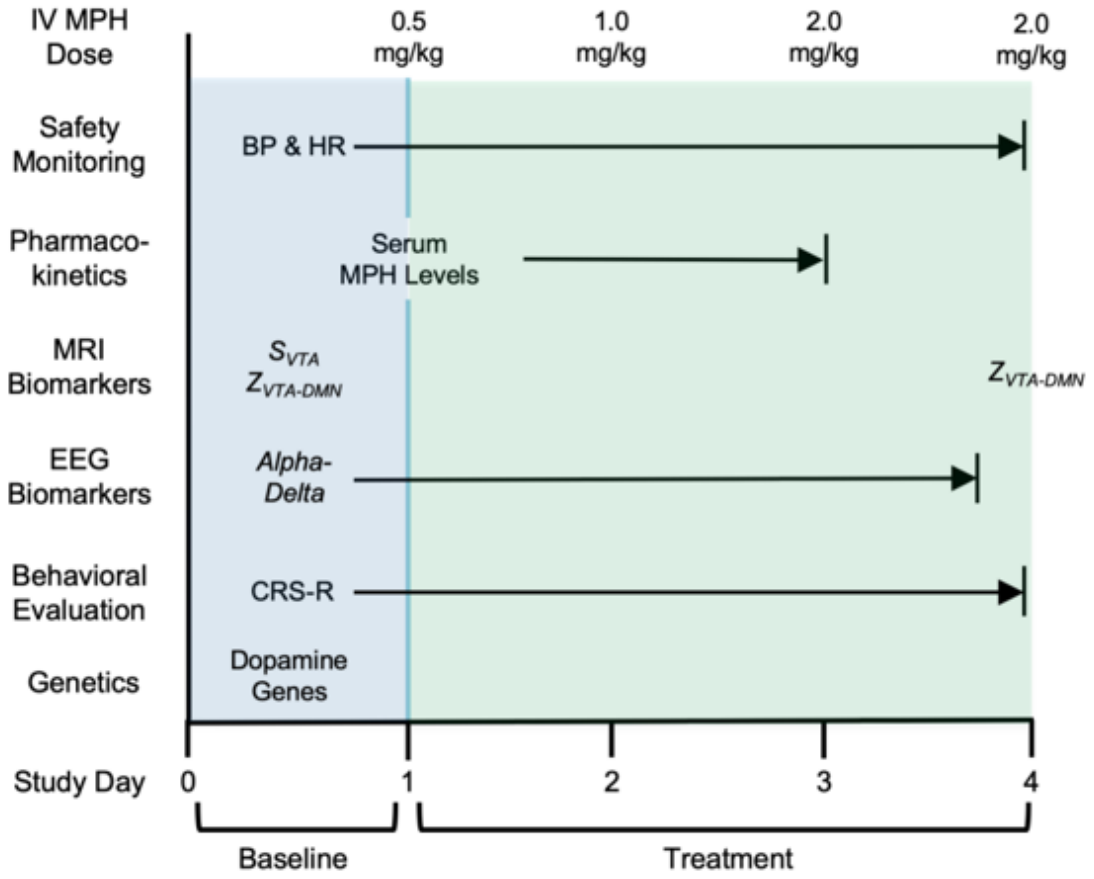
3) The association between VTA connectivity, as measured by high angular resolution diffusion imaging (HARDI),[5] and the pharmacodynamic biomarkers, as measured by EEG and rs-fMRI.

Population:	Patients with DoC caused by severe brain injuries.
Phase:	Phase 1
Number of Sites:	1
Description of Study Agent:	IV MPH, administered as a bolus, at escalating doses of 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg
Study Duration:	2 Years (including data analysis)
Participant Duration:	5 days

1.1 DESCRIPTION OF STUDY DESIGN

In this Phase I open label, dose-escalation, safety study, we will test a novel stimulant therapy, IV MPH, which we believe has potential to promote recovery of consciousness in patients with DoC caused by severe brain injuries. The trial will begin with a HARDI MRI scan to generate individualized connectivity maps of the subcortical ascending arousal network (AAN) that is critical to human consciousness.[5] On the day of the MRI (Day 0), patients will also undergo continuous EEG and serial behavioral assessments to determine the patient's baseline variation in the EEG pharmacodynamic biomarker and the level of consciousness, respectively. Starting the next day (Day 1), each patient will receive escalating doses of IV MPH for four days (Days 1-4). Dosing will start at 0.5 mg/kg, and then increase to 1.0 mg/kg and 2.0 mg/kg. Blood pressure (BP) and heart rate (HR) will be monitored continuously, given that elevated BP and HR are the most common side effects associated with IV MPH according to prior human studies. In the case of an AE that is deemed to be possibly related to IV MPH administration, the patient will either 1) be discontinued from the study if the AE occurred at the lowest dose (0.5 mg/kg); or 2) be continued in the study at the previously tolerated dose if the AE occurred at a dose of 1.0 mg/kg or 2.0 mg/kg. If there is an SAE that is deemed to be possibly related to IV MPH administration, the patient will be discontinued from the study. All AE's and SAE's will be reported to the Independent Medical Monitor, Institutional Review Board (IRB), and FDA in compliance with published guidelines. If the patient emerges from DoC during the trial, the patient will be discontinued from the study. Serum levels of IV MPH will be measured at each dose to assess pharmacokinetics. Continuous EEG data will be acquired to assess the EEG pharmacodynamic biomarker. A follow-up MRI will be conducted on the last day of the study (Day 4) to assess the rs-fMRI pharmacodynamic biomarker.

1.2 SCHEMATIC OF STUDY DESIGN



2 BACKGROUND AND SIGNIFICANCE

More than a million civilians worldwide experience an acute DoC caused by a severe brain injury each year.[6-9] In addition, thousands of military personnel have experienced an acute DoC caused by severe brain injury since 2001.[10] These patients typically arrive at the hospital in a coma, unable to open their eyes or respond purposefully to any stimulus. Some civilians and veterans remain in VS or MCS after emergence from coma.[11, 12] Although the precise prevalence is unknown, it is estimated that thousands of people are currently living in the United States and Europe with persistent DoC.[13, 14]

Nevertheless, recovery of consciousness, communication, and functional independence are possible after severe brain injury.[11, 12, 15-18] Indeed, recent evidence suggests that recovery of consciousness is possible even for patients who have persistent DoC in the subacute and chronic stages of severe brain injury.[15, 19, 20] Emerging evidence suggests that specific patterns of brain network connectivity are necessary to enable this recovery.[21-23] Given the profound

implications of recovering consciousness for the individual, the family, and society, it is essential that patients whose brain network connectivity is capable of supporting recovery are identified and that stimulant therapies are developed to promote this recovery.

Currently, no stimulant therapy has been shown to promote recovery of consciousness in patients with DoC in the ICU. The treatments available for patients with subacute and chronic DoC are limited,[24-27] with amantadine hydrochloride being the only therapy to show efficacy in a randomized controlled trial.[25] A key lesson from the amantadine trial and other proof-of-principle studies is that **therapeutic modulation of injured brain networks is feasible and may improve the level of consciousness in selected patients with DoC**. Moreover, since patients with DoC have heterogeneous patterns of brain network disruption, and since not all patients respond to therapy, these studies suggest that specific nodes and/or connections within brain networks must be preserved for stimulant therapies to promote consciousness. Currently, there is a critical gap in knowledge about which brain network connectivity properties enable a response to stimulant therapy.

Recent advances in the field of brain imaging now make it possible to map the connectivity of brain networks that mediate consciousness.[4, 5, 28-30] These advanced imaging techniques provide personalized connectivity maps for individual patients,[21] which creates a new opportunity to target therapies to specific brain network connectivity patterns. These brain network mapping tools have recently been applied to the brainstem connections that are the target of IV MPH. Specifically, it is now possible to map the connections of the VTA in the human brain[5, 31] – a key methodological advance that will allow us to assess whether DoC patients with partially preserved VTA connections respond to IV MPH.

2.1 RATIONALE

The pathophysiological basis of altered arousal in patients with DoC is disruption of brainstem monoaminergic, cholinergic, and glutamatergic pathways that project to the thalamus, hypothalamus, basal forebrain, and cerebral cortex.[5, 32] Histopathological studies show that the brainstem is invariably injured in patients with traumatic DoC.[31, 33, 34] For patients with DoC caused by other types of brain injuries (e.g. hypoxic-ischemic injury), the brainstem itself may be spared but its connections with the thalamus, hypothalamus, basal forebrain or cerebral cortex are at least partially disrupted.[35-37] However, regardless of the type of brain injury causing the DoC, not all brainstem arousal nuclei are lesioned and not all axons are disrupted.[37, 38] Rather, histopathological data in trauma patients indicate that the ventral brainstem, where VTA neurons reside, is often spared.[33, 34, 39-46] MRI studies by our group and others similarly reveal that brainstem lesions often spare the ventral brainstem.[47, 48] There is thus a strong scientific rationale for our central hypothesis that preserved dopaminergic VTA neurons are a target for stimulant therapy to promote restoration of consciousness in patients with DoC.

MPH acts by blocking the dopamine transporter protein, thereby enhancing dopaminergic neurotransmission at synapses throughout the brain.[49, 50] There is also evidence that MPH may block reuptake of norepinephrine and histamine as well.[51] Today, oral MPH is widely prescribed to treat attention deficit hyperactivity disorder (ADHD), which has an incidence of 6-9% in

children.[52] Swanson and Volkow reported that MPH levels reach their peak concentration (T_{MAX}) in the brain rapidly after IV administration in healthy humans, as evidenced by ^{11}C-MPH PET scans showing peak levels in the striatum within 8-10 minutes.[53] MPH levels in the striatum remain at approximately 70% of peak concentration one hour after IV administration in healthy humans, indicating that MPH clearance is slow.[53] The half-life ($T_{1/2}$) in the brain, per ^{11}C-MPH PET scans, is approximately 90 minutes. These pharmacokinetic data acquired in healthy human subjects indicate that if IV MPH does promote recovery of consciousness, this effect should be rapid in onset and should be sustained for a period of several hours after administration.

A response to IV MPH could change the course of a patient's recovery in multiple ways. For patients with DoC in the ICU, the emergence of consciousness in response to IV MPH could reduce the likelihood of withdrawal of life-sustaining therapy, enable self-expression and autonomous decision-making, shorten ICU length-of-stay, decrease complications associated with immobility, and increase access to rehabilitative care.

3 SUBJECT RECRUITMENT, SELECTION, AND ENROLLMENT

3.1 SUBJECT RECRUITMENT

This study will take place at Massachusetts General Hospital (MGH) in the ICU at Lunder 6 and Ellison 4. For Phase 1, we will aim to enroll 22 patients aged ≥ 18 years who have sustained a severe brain injury and are in coma, VS, or MCS.

3.2 SUBJECT SELECTION

Only those patients who have a surrogate available to provide consent will be considered for this study.

Inclusion Criteria:
1) Age ≥ 18 years
2) Severe TBI (post- resuscitations Glasgow Coma Scale score ≤ 8) within the past 28 days
3) Disorder of Consciousness (DoC), defined as coma, vegetative state (VS) or minimally conscious state (MCS)

Exclusion Criteria:
1) Metallic foreign body contraindicating a 3T MRI for any participant undergoing a MRI scan
2) Prisoner or ward of the state
3) Neurological
    a. Bilateral dilated unresponsive pupils
    b. Intracranial hypertension (Intracranial Pressure [ICP] > 20 mmHg for > 5 min within past 24 hours with head of-bed at standard clinical angle of 30-45^{o})

    c. Intracranial bolt
    d. Status epilepticus or concern for post-ictal state
4) Cardiovascular
    a. Poorly controlled hypertension (SBP sustained > 200 mmHg or DBP > 120 mmHg for 30 minutes, despite anti-hypertensive therapy, within the past 24 hours)
    b. Coronary artery disease
    c. ST elevation myocardial infarction
    d. Acute coronary syndrome
    e. Hemodynamically significant dysrhythmia
    f. Congestive heart failure
    g. Cardiomyopathy (including Takotsubo cardiomyopathy)
    h. Other severe structural cardiac abnormalities
5) Renal
    a. Renal failure requiring renal replacement therapy (e.g. CVVH or HD)
6) Endocrine
    a. History of or clinical suspicion for thyrotoxicosis
7) Reproductive
    a. Pregnancy
8) Ophthalmologic
    a. History of glaucoma
9) Pharmacologic
    a. Monoamine oxidase inhibitor therapy within past 14 days
10) Other
    a. Any condition or finding that in the judgment of the PI or treating clinical team significantly increases the risk or significantly decreases the likelihood of a response to IV MPH

3.3 SUBJECT ENROLLMENT

If a patient is deemed eligible for the study, study staff will approach the surrogate to explain the study and answer any questions. A consent form will be presented for review and each section of the consent form explained. Surrogates will have as much time as needed to review the consent form and make a decision regarding participation. This will allow adequate time for the surrogate to review the consent form in detail, have any questions answered and consider enrollment.

If the surrogate chooses to enroll the patient in the study, the surrogate and study investigator will sign the consent form. We will make clear to the surrogate that he/she may withdraw from the study at any time prior to the start of the study or once the study has begun and that participation and/or withdrawal will not affect the patient's clinical care.

<u>Remote Consent:</u>

We will attempt to obtain informed consent for study participation from a surrogate in person. However, if the surrogate (LAR) is not available to meet with the research team in person (e.g.,

due to being out of town, COVID restrictions, etc.), a remote (phone) consent will be obtained from their LAR according to the remote consent policy and guidelines defined by PHS (Partners HealthCare System) Human Research Affairs Department. In such a situation, a member of the research team will call the surrogate and send them the consent form electronically through the FDA COVID MyStudies App, REDcap or via email or facsimile; if by email, the email will be sent securely per Partners IS guidelines. The surrogate will review the consent form, discuss participation in the study with the physician investigator, sign and date (including time) the consent form agreeing to the patient's participation in the research and return the signed (handwritten or digital) and dated consent form electronically (via email, facsimile or the FDA COVID MyStudies App). The consent discussion that takes place by phone will include a healthcare worker (physician, patient's nurse or other floor nursing staff) not associated with the study as a witness to the consent process. The investigator and the witness will sign and date (including time) the consent form to indicate that phone consent has been granted by the LAR.

Additionally, if the surrogate/LAR resides within two hours of drive of the Study site (MGH), then remote, off-site, in-person consent may be obtained. A meeting will be held with the Investigator and the patient's legal representative/surrogate that is authorized to sign for the patient. Additionally, during this meeting, an impartial third-party witness will also be present (in-person or virtually by phone/videocall).

4. STUDY PROCEDURE

4.1 PROTOCOL DETAILS

As this is a Phase I study, all eligible subjects will be enrolled without randomization to study arms.

Subjects enrolled in this study will undergo behavioral, EEG, and MRI assessments on Study Day 0 before receiving IV MPH. The goals of these Day 0 assessments are 1) to establish a baseline diagnosis regarding the patient's level of consciousness; 2) establish the baseline variance in EEG measures of cortical connectivity that will subsequently be used as pharmacodynamic biomarkers; and 3) acquire the structural HARDI MRI data needed to generate the VTA connectivity biomarker. Subjects will also undergo hemodynamic monitoring on Day 0 to assess BP and HR. The cerebral perfusion pressure (CPP) will also be monitored if ICP is being measured via an external ventricular drain (EVD). The purpose of these Day 0 hemodynamic assessments is to determine if there is a baseline correspondence between any hemodynamic parameter (BP, HR, or CPP) and any behavioral assessment (e.g. CRS-R score) or EEG biomarker (e.g. cortical connectivity). These Day 0 assessments will thus allow us to subsequently account for the possibility that IV MPH may affect behavioral and/or EEG measures because of a hemodynamic change related to IV MPH rather than because of a change in dopaminergic neurotransmission.

Throughout the 5-day study (from Day 0 to Day 4), each subject will be monitored for hemodynamic and behavioral changes. IV MPH is known to increase BP and HR, but these

predictable changes should be easily manageable in the ICU environment, where subjects will be appropriately monitored and a full armamentarium of vasoactive drugs will be immediately available.

On Day 1, each subject will receive an IV bolus of 0.5 mg/kg MPH, using the actual body weight to calculate the dose. Serum levels of MPH will be measured in subjects with indwelling catheters (e.g. central venous catheter or arterial catheter) at baseline immediately pre-dose and post dose at 5 min, 15 min, 30 min, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, 12 hours, and 16 hours after each dose. Serum collection for pharmacokinetic analysis will continue from Day 1 to Day 4 as per Table 1 below, where 1mL serum samples will be collected at each time point. Patients without these indwelling catheters will not undergo the pharmacokinetic part of the study, given the potential discomfort associated with multiple needle sticks. Any patient whose hematocrit is <21 g/dl, who is actively bleeding, or whose clinical team does not approve the blood draws will not undergo the pharmacokinetic part of the study. Serum creatinine and liver function tests will be assessed on each study day to assess daily renal and liver function. All participants will have a single baseline blood draw (~ 3 mL) collected for genetic analysis of dopamine transmission genes such as DAT1 and SLC6A3. No other genetic testing is part of this protocol. The results of the blood assays and genotyping will be used for research purposes only and will not be entered into the medical record.

Table 1. Serum Specimen Collection Schedule and Intended Analyses

Study Days / **Timepoint**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Intended Analysis**
Baseline	X	-	-	-	-	Dopamine Genes
Pre-Dose	-	X	X	X	X	Pk[3] and Genetic[4]
Post- Dose[1]	-	X	X	X	X[2]	Pk

1. Post-Dose Serum samples will be collected as follows: 5 mins (+/- 5 mins) , 15 mins (+/- 5mins) , 30 mins (+/- 15 min), 1 hour (+/- 15 min), 1.5 hours (+/- 15 min), 2 hours (+/- 15 min), 4 hours (+/- 15 min), 8 hours (+/- 15 min), 12 hours (+/- 15 min) and 16 hours (+/- 15 min) post infusion.
2. Day 4 post infusion blood draw at 5 mins, 15 mins, 30 mins may not always be possible as the participant will be in the scanner
3. Pk = Pharmacokinetic analysis; serum concentration assays performed at Worldwide Clinical Trials (WCT), data analysis performed at MGH
4. Genetic analysis for presence of dopamine transmission genes conducted at MGH Center for Genomic Medicine

Serum samples collected for genetic analysis will be processed and stored at MGH in the lab of Dr. W. Taylor Kimberly. Plasma samples will be stored at -80°C and analysed for MPH enantiomers (ng/mL) and for total ritalinic acid (metabolite, ng/mL) concentrations using an achiral LC-MS/MS assay. Sample analysis will be performed at Worldwide Clinical Trials (Austin, TX).

In compliance with the Partners Healthcare Blood Sampling Guidelines, the total amount of blood drawn for research will not exceed the lesser of 50 ml or 3 ml/kg in 8 weeks (https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb/Documents/IRB%20Clinical%20Research%20Documents/BLOOD_SAMPLING_GUIDELINES.pdf).

EEG will be performed continuously from Day 0 to Day 4, and the EEG pharmacodynamic biomarker will be assessed from one hour before to one hour after the bolus is administered on Days 1-4. MRI will be performed on Day 0 and Day 4. The rs-fMRI connectivity biomarker will be assessed on Day 4 over a 40-minute continuous scanning period beginning 10 minutes before and ending 30 minutes after administration of the IV MPH bolus.

If the 0.5 mg/kg dose of IV MPH does not cause an AE or SAE on Day 1, then the next day (Day 2) the subject will receive 1.0 mg/kg IV MPH. If there is no AE or SAE at this dose, the subject will receive 2.0 mg/kg IV MPH on Day 3. The maximum tolerated dose, as defined below, will then be administered on Day 4 while the subject is in the MRI scanner.

Participating in this research study will in no way change the standard care or clinical protocols that guide the management of patients with severe brain injuries at MGH.

Changes in HR and BP are common in patients with severe brain injuries, and increases in both are more likely in the patients who receive MPH.[54, 55] Therefore, MPH will not be administered if the patient's systolic BP is greater than 180 mmHg, if the diastolic BP is greater than 100 mmHg, or HR is greater than 120 bpm. A study protocol checklist will be used by the study team to ensure that the patient's BP and HR do not surpass these prespecified thresholds.

If a patient experiences a significant neurologic or cardiovascular AE, the patient will be treated immediately, and continuous hemodynamic monitoring will continue per ICU protocols. Any patient with a life-threatening myocardial infarction or cardiac dysrhythmia will be treated according to Advanced Cardiac Life Support protocols, and a cardiologist will be promptly consulted for management recommendations. Acute hemodynamic changes that are not life-threatening will be managed at the discretion of the clinical care team assigned to the patient, not the study staff. We expect that all patients in this study will be under the care of a neurologist, but if that is not the case and a neurologic adverse event occurs, then a neurologist will be promptly consulted to guide further management.

It is possible that a subject may emerge from DoC during the 5-day study period, as defined by the behavioral criteria for emergence from MCS on the CRS-R assessment (i.e. functional object use or functionally accurate communication). If this occurs, then the subject will remain in the study to undergo the behavioral, EEG, and rs-fMRI assessments on the remaining study days, but the subject will not receive another dose of IV MPH. The reason that another dose of IV MPH will not be administered is that the purpose of the study drug is to promote recovery of consciousness, and once a subject emerges from MCS to a higher level of consciousness, the potential benefits of the therapy may no longer outweigh the risks.

If a subject emerges from DoC, a board-certified neurologist on the study staff will assess the subject's decision-making capacity to determine if the subject is capable of providing assent or consent. If the subject is deemed to have capacity to provide assent or consent, the study investigator will ask the subject is he/she wishes to remain in the study to undergo additional study procedures. The additional procedures would include safety assessments (e.g. BP and HR monitoring), serum measurements of IV MPH (if the subject emerged from DoC within hours of receiving a dose of IV MPH while the pharmacokinetic measurements were still being performed), behavioral assessments, EEG and MRI. The subject will be informed about the risks and benefits of the study, will be given the opportunity to ask questions (if capable of doing so), and will be notified that he/she may withdraw participation from the study at any time. The subject will be asked to provide written or verbal assent or consent, according to his/her capacity to do so.

If a subject emerges from DoC during the study, but then has a subsequent decline in level of consciousness such that the subject returns to a DoC (e.g. a subject could emerge from MCS but then go back into MCS), the subject will resume dosing of IV MPH according to the study protocol.

Video recording of participants will be obtained pre-dose, during dose administration and post dose using an Apple iPhone 12 set upon a gorilla stand. The recording apparatus will not have direct contact to the participant and will be set up out of the way of clinical care. Further functionalities of the recording device (Apple iPhone 12) will be disabled such as voice recognition through Siri and calling services. The iPhone will be encrypted using the Partners research computing security system: mobileiron. The recording will allow us to detect discreet changes in level of consciousness (if any) in response to IV Methylphenidate and may be correlated to the CRSR-R exam. Data will be recorded to the iPhone's memory and uploaded to Partner's Dropbox. The iPhone will be assigned an ID number and labeled with the PI name and IRB number. We will ensure data is linked to its respective participant by linking the data with each subject identification number (SID). The iPhone will be disinfected and stored, all participant data will be copied from the device and erased from iPhone storage to allow sufficient memory and the device to be reused for other participants.

At the time of study consent, participants will be notified that video recordings will take place before, during and after drug administration.

4.2 DOSING CONSIDERATIONS

There is extensive literature on the use of oral MPH.

There is also literature on the use of IV MPH, which has been shown to be safe at doses ranging from 0.5 mg/kg to 0.88 mg/kg in healthy human subjects (see Section 7, Previous Human Experience). Thus, our proposed starting dose of 0.5 mg/kg of IV MPH has, in effect, already been shown to be safe for administration to humans. Notably, doses far higher than our maximum dose of 2.0 mg/kg have also been shown to be tolerated in human patients, albeit in a smaller number of studies. Specifically, one study of 11 patients who had overdosed on barbiturates found that these patients tolerated IV MPH doses of 30 mg to 1400 mg without harmful side effects

(representing an estimated ~0.5 mg/kg to ~20 mg/kg, although exact patient weights were not reported in this study).[54] Another study of 26 patients with barbiturate intoxication found that patients tolerated IV MPH doses of 60 mg to 1100 mg without harmful side effects (representing an estimated ~0.9 mg/kg to ~15.7 mg/kg, although exact patient weights were not reported in this study either).[56] All doses of IV MPH that we propose in the STIMPACT trial – 0.5 mg/kg, 1.0 mg/kg and 2.0 mg/kg – have thus been shown to be safe for administration to humans.

In Section 7 (Previous Human Experience) we provide a comprehensive literature review on previous experience with IV MPH in human subjects. In it we cite numerous papers that reported an MPH dose of 0.5 mg/kg IV or greater in healthy human subjects, with no serious adverse reactions. We also cite several papers that detail the use of IV MPH in humans receiving sedation, which are relevant to our proposed study of patients with DoC, because both types of patients have depressed levels of consciousness that may have similar underlying neurobiological mechanisms.

After carefully reviewing the literature, we concluded that 0.5 mg/kg IV MPH is a safe starting dose for this patient population in the ICU setting. We believe that stepwise escalation of the dose to 1.0 mg/kg and 2.0 mg/kg on subsequent days is also likely to be safe, based upon the absence of SAEs at doses up to approximately 20 mg/kg in humans,[54] as described above. As in previous studies, MPH will be administered as an IV bolus. All of the previous human studies cited in our IND application administered MPH as an IV bolus, indicating that this is safe.

We selected a maximum dose of 2.0 mg/kg for our population of patients with DoC caused by severe brain injuries. In doing so, we carefully considered the possibility that this dose of IV MPH, or even the 0.5 mg/kg or 1.0 mg/kg doses, could cause AEs in patients with brain injuries who may have hyperactivity of the sympathetic nervous system and elevated levels of serum catecholamines.[57] Indeed, it is possible that serum catecholamine levels may be higher in the brain-injured population than in the populations of healthy human controls or patients with barbiturate overdoses who have been studies previously. Nevertheless, we believe that dose escalation to a maximum of 2.0 mg/kg is clinically and ethically appropriate for the following reasons:

1) Patients with severe brain injuries are likely to have at least partial disruptions to their VTA dopaminergic pathways, with consequent decreased production of dopamine. Thus, a larger dose of IV MPH may be needed to generate adequate dopaminergic activity in VTA synapses to restore consciousness.

2) If we proceed to Phase 2 and Phase 3 without establishing the maximum tolerated dose of IV MPH in the population of patients with DoC caused by severe brain injuries, we run the risk of an ethically unjustifiable enrollment of future patients in trials whose study design has not been optimized because the maximum tolerated dose was never appropriately identified in Phase 1.

Given the need to establish the maximum tolerated dose, we considered the possibility of administering IV MPH at a dose higher than 2.0 mg/kg, especially since doses up to approximately

20 mg/kg were well tolerated, with non-harmful increases in HR and BP, in the 11-patient barbiturate overdose study.[54] However, after carefully balancing the potential clinical benefits of higher doses of IV MPH with the potential risks, our judgment is that a dose of 2.0 mg/kg is the maximum dose at which the potential benefits continue to outweigh the potential risks. Although doses far higher than 2.0 mg/kg were tolerated in the barbiturate overdose study, these patients likely were not experiencing the higher levels of catecholamines that may be present in patients with acute brain injuries caused by trauma, hypoxic-ischemic injury, or other mechanisms. Thus, we believe that a maximum dose of 2.0 mg/kg minimizes the potential risk of a harmful increase in HR or BP, while still optimizing the chances that a subject will have an increase in level of consciousness due to IV MPH-mediated stimulation of partially preserved dopaminergic VTA neurons.

4.2.1 ROUTE OF ADMINISTRATION

Intravenous.

4.2.2 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Day 0: no study drug administered

Day 1: 0.5 mg/kg

Day 2: 1.0 mg/kg

Day 3: 2.0 mg/kg

Day 4: 2.0 mg/kg

4.2.3 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

If the subject experiences an AE at the lowest dose, then the subject will stop participation in the study. If there is an AE at a higher dose, then the subject will receive the previously tolerated dose on subsequent days. If there is an SAE at any dose, the subject will be withdrawn from the study.

Prior to each administration of the study drug, the clinical team will be asked to approve administration of the drug. If the clinical team states that the next dose should not be administered because of a clinical concern about the risk of IV MPH administration, then the dose will not be administered and the patient's surrogate will be informed of the reason provided by the clinical team. The subject would remain in the study to complete the observational components of the study (e.g. EEG, behavioral assessments, and rs-fMRI). If this were to occur before the last day of the study, then the subject would have the opportunity to receive the drug on the next day if the clinical team approves of the next dose. Importantly, the patient would not

skip a dose in the escalation protocol. For example, if the patient has received the 0.5 mg/kg dose on Day 1 and the clinical team states that the 1.0 mg/kg dose should not be administered on Day 2 but can be administered on Day 3, then the subject would receive the 1.0 mg/kg dose on Day 3 and Day 4 and would not receive the 2.0 mg/kg dose.

4.2.4 DURATION OF THERAPY

4 days (Days 1-4). No IV MPH is administered on Day 0.

4.2.5 TRACKING OF DOSE

Not applicable, given that each dose will be administered as an IV bolus in the ICU, directly observed by study staff.

4.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

4.3.2 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

4.4 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Monoamine oxidase inhibitors are contraindicated during the study.

4.5 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

		HR (bpm)	
		< 120	≥ 120
SBP * (mmHg)	< 180	None	5-10 mg IV metoprolol
	≥ 180	5-20 mg IV hydralazine	5-50 mg IV labetalol

Prior to administration of each dose of IV MPH, the SBP must be < 180 mmHg and HR must be < 120 bpm. If these goals are not met, prophylactic medications should be administered, as detailed in the table above. The clinical team may decide to administer a different medication, or a different dose, per its clinical judgment, to meet these hemodynamic goals.

* SBP > 180 mmHg is an exclusion criteria for enrollment in STIMPACT. However, a subject's SBP could rise above 180 mmHg *after* enrollment, *prior* to administration of IV MPH. The prophylactic medication plan for SBP > 180 mmHg pertains to this type of subject.

4.6 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

		HR (bpm)	
		< 120	≥ 120
SBP (mmHg)	< 180	None	5-10 mg IV metoprolol
	≥ 180	5-20 mg IV hydralazine	5-50 mg IV labetalol

After administration of each dose of IV MPH, the SBP goal is < 180 mmHg and HR goal is < 120 bpm. If these goals are not met, rescue medications should be administered, as detailed in the above table. The clinical team may decide to administer a different medication, or a different dose, per its clinical judgment, to meet these hemodynamic goals.

4.7 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request of their surrogate. Given that participants will only be enrolled if they have a DoC, no participant will have the decision-making capacity to withdraw himself/herself at the beginning of the study. However, a participant may emerge from DoC and regain the capacity for assent or consent during the 5-day study (as detailed above), in which case the participant will be notified that he/she is free to withdraw from participation at any time.

An investigator may terminate participation in the study if:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

4.8 BIOSTATISTICAL ANALYSIS

Sample Size Calculation

22 subjects will be enrolled in this Phase 1, open label, dose-escalation, safety trial.

Safety Analysis

The incidence of AEs and SAEs will be calculated as the ratio of the number of events divided by the number of administrations of IV MPH at each dose. The percentage of subjects experiencing each documented AE and SAE will be reported for each dose.

Pharmacokinetic Analysis

The $T_{1/2}$ and T_{Max} of IV MPH will be determined by analyzing the concentration of serum-level MPH over a time frame of 5 minutes to 16 hours.

As pharmacokinetic and pharmacodynamic potency may differ between MPH enantiomers [73], serum samples will also be analyzed for d-threo-MPH and l-threo-MPH enantiomer concentrations (ng/mL). Non-compartmental analysis will be used to calculate pharmacokinetic parameters using Pheonix WinNonLin (Version 8.1; Certara, L.P; Princeton, NJ) to determine time to maximum concentration (T_{max}) and elimination half-life ($T_{½}$), as well as maximum concentration (C_{max}) and area under the concentration-time curve (AUC_{inf}). Pharmacokinetic data will be summarized using descriptive statistics.

MRI Predictive Biomarker Analysis

An MRI scan will be performed at the beginning of the study to measure the structural connectivity of the VTA using HARDI. We will focus on VTA connectivity because the VTA is a dopaminergic arousal nucleus upon which IV MPH acts. Graph theoretical analysis will be used to measure the connectivity of the VTA within the AAN.[58] We hypothesize that higher VTA connectivity is associated with larger stimulant-based improvements in the EEG and rs-fMRI pharmacodynamic biomarkers.

EEG Pharmacodynamic Biomarker Analysis

Patients will be monitored with continuous EEG throughout the study. Functional connections between cortical regions will be measured for each pair of EEG electrodes.[3] EEG-based functional connections will be quantified for the hour prior to and following the intervention. We will measure the pre- vs. post-dose change in EEG connectivity. We hypothesize that stimulant therapy is associated with an increase in EEG-based connectivity.

Pharmacodynamic rs-fMRI Analysis

On the last day of the study, all patients will receive IV MPH during an MRI scan. A rs-fMRI sequence will be performed to measure brain network connectivity.[4] The rs-fMRI sequence will be continuously acquired from 10 minutes before to 30 minutes after IV MPH administration. We will measure the pre- vs. post-dose change in brain network connectivity. We hypothesize that stimulant therapy is associated with an increase in brain network connections.

5 RISK AND DISCOMFORT

5.1 KNOWN POTENTIAL RISKS

Overall, MPH has a long history of safe use in patients over the age of 6. The FDA product description for oral MPH[59] includes a comprehensive discussion of its side effects.

Because it is a stimulant medication, MPH carries the risk of sudden death in certain high-risk patients with pre-existing cardiac disease. It may also lower the seizure threshold in certain susceptible patients. Cardiac disease and status epilepticus or post-ictal state are thus

exclusion criteria for our study. Because MPH is a pregnancy Category C drug, expectant mothers will also be excluded from our study. There are also some concerns regarding carcinogenicity, as well as reproductive and developmental toxicities of MPH, but these are related to long-term use and therefore are less of a concern for our study. A recently completed, unpublished study (Clinical Trials Identifier: NCT02051452), in which IV MPH was administered to patients undergoing general anesthesia, showed there were no SAEs over n=10 Phase I and n=32 Phase II patients (42 patients total).

The risks of MPH fall in two categories: cardiovascular and non-cardiovascular.

Cardiovascular Risks:
The expected cardiovascular side effects of IV MPH are increases in HR, systolic BP, and diastolic BP.[55, 60] Because the cardiovascular side effects occur within 4 to 10 minutes of the drug's administration, and because these cardiovascular parameters will be continuously monitored in our study subjects, the ICU care team can readily treat these side effects with standard agents as soon as they appear. Medications to treat these side effects will be prepared in advance and will be ready to administer prior to administering MPH. Because of general concerns that the FDA has recently expressed regarding the effects of brain stimulants on the cardiovascular system and possible increased risk of sudden death and stroke,[61] we will exclude any potential subjects with known structural cardiac abnormalities, cardiomyopathies, serious dysrhythmias, coronary artery disease, or other serious cardiac problems.

Non-Cardiovascular Risks:
In a subset of patients nausea, anxiety, euphoria or insomnia may occur.[59] We will treat nausea/emesis, if necessary, by administering an anti-nausea/anti-emetic agent. Anxiety, euphoria and insomnia are potential side effects in healthy subjects that we do not expect to observe in patients with DoC.

Neurological Risks:
According to the FDA product description of oral MPH, there is some clinical evidence that stimulants may lower the seizure threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures.[59] If seizures occur, they will be treated by the clinical team with anti-seizure therapy, per routine ICU care. If seizures occur and the PI or Independent Medical Monitor believe that the seizure is related to IV MPH, then this will be considered a drug-related SAE and the subject will stop participation in the study.

EEG Risk
EEG is a well-established and safe clinical diagnostic tool. Using standard EEG equipment poses no significant risks to subjects and this component of the study will not interfere with other standard tests and procedures. Minor discomfort such as irritation of the scalp may occur. If a subject has an external ventricular drain in place during the study, the EEG leads will be placed in a way that does not interfere with the functioning or safety of the external ventricular drain, as has been previously reported.[62]

MRI Risk

MRI is a well-established and safe clinical diagnostic tool. Using standard MRI equipment poses no significant risks to subjects and this component of the study will not interfere with other standard ICU tests and procedures. Some people become nervous or restless while in the MRI scanner or feel claustrophobic. Should this occur, the scan can be terminated. The MRI scanner emits loud sounds during image acquisition. Hearing protection is provided to all subjects via headphones or earbuds. If the clinical team states that it is not safe for a subject to lie supine for an MRI scan due to concerns for increased ICP, then the subject will not undergo MRI.

5.2 POTENTIAL BENEFITS

Early recovery of consciousness would benefit patients by decreasing the risk of withdrawal of life-sustaining therapy, facilitating self-expression, enabling autonomous decision-making, decreasing ICU complications associated with immobility, and increasing access to post-ICU rehabilitative care.

6 ASSESSMENT OF SAFETY

6.1 DEFINITION OF ADVERSE EVENTS (AES)

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). In the current IND an AE may include, but is not limited to:

- Sustained hypertension = SBP > 200 mmHg or DBP > 120 mmHg for > 30 min, refractory to medical therapy, or
- Sustained tachycardia = HR > 120 bpm for > 30 min, refractory to medical therapy, or
- Sustained intracranial hypertension = ICP > 25 mmHg for > 5 min, refractory to medical therapy

6.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of the investigator or the Independent Medical Monitor, it results in any of the following outcomes:

- Death not related to withdrawal of life-sustaining therapy
- A life-threatening adverse event
- Prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Important medical events that may not result in death, be life-threatening, or require prolonged hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

Neurologic

- Seizure
- Neuro-worsening = decline in Glasgow Coma Scale (GCS) score of ≥ 2 points and/or loss of pupillary reactivity and/or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention

Cardiovascular

- Acute coronary syndrome

Renal

- Acute renal failure

Pulmonary

- Acute respiratory distress syndrome (ARDS)

Any event that the Principal Investigator or the Independent Medical Monitor judges to impose a significant hazard, contraindication, side effect or precaution.

Of note, the clinical criteria for the aforementioned events will be based upon event definitions published in a recent study of medical and neurological ICU complications by Muehlschlegel and colleagues.[63] Also of note, all AEs and SAEs will be classified according to the SNOMED Clinical Trials criteria (https://browser.ihtsdotools.org/?)

6.3 CLASSIFICATION OF AN ADVERSE EVENT

6.3.1 SEVERITY OF EVENT

The Principal Investigator and Independent Medical Monitor will classify each AE using the following grading system:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

6.3.2 RELATIONSHIP TO STUDY AGENT

All AE's will have their relationship to IV MPH intervention assessed by the Principal Investigator and Independent Medical Monitor based on temporal relationship and clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Related** – The AE is known to occur with IV MPH, there is a reasonable possibility that IV MPH caused the AE, or there is a temporal relationship between IV MPH administration and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between IV MPH administration and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of IV MPH caused the event, there is no temporal relationship between administration of IV MPH and event onset, or an alternate etiology has been established.

6.3.3 EXPECTEDNESS

Expectedness will be determined by the Principal Investigator and Independent Medical Monitor with reference to the package insert for oral Ritalin (see IND #113736). An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

6.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution, discharge from the hospital or death.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be provided for AEs characterized as intermittent.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until for 7.5 hours (approximately five half-lives of IV MPH) after the last dose is administered. AE's will be followed until resolution or stabilization.

Any Clinical Oversight Committee member shall have the discretion and responsibility to recommend that the study be terminated.

6.5 REPORTING PROCEDURES

6.5.1 ADVERSE EVENT REPORTING

All anticipated and unanticipated AE's will be recorded in the REDCap data collection system throughout the study.

The Clinical Oversight Committee, including the Independent Medical monitor will meet quarterly (four times per year) unless no patients are enrolled in a prior quarter.

In accordance with IND, IRB and FDA requirements, AE's will be reported on an annual basis by way of inclusion in the annual report and in the annual AE summary, which will be provided to the Independent Medical Monitor. The Clinical Oversight Committee will review all AEs.

The following disease-related events common to patients with DoC caused by severe brain injuries (e.g. expected), will not be reported per the standard process for reporting, unless the Principal Investigator or the Independent Medical Monitor believes that the event is related to the study drug: hyperglycemia, fever, systemic inflammatory response syndrome, hypotension, pneumonia, anemia, hyponatremia, urinary tract infection, pulmonary edema, and venous thromboembolism. Clinical criteria for these events are defined in a recent paper by Muehlschlegel and colleagues.[63] Events that are part of the natural history of recovery from TBI and are key features of the post-traumatic confusional state (PTCS)[65], such as agitation, insomnia and restlessness, will be recorded as events of clinical interest. Consistent with the operational definition of insomnia[66], insomnia will only be reported as an adverse event if it is self-reported by the pariticpant. When a patient emerges from MCS into a confusional state, basic communication abilities often return, making it possible to assess for insomnia based on self-report.

6.5.2 SERIOUS ADVERSE EVENT REPORTING

SAEs that are unanticipated and possibly related to the study intervention (i.e. a single occurrence of an event that is uncommon and known to be strongly associated with IV MPH exposure or one or more occurrences of an event that is not commonly associated with IV MPH, but is otherwise uncommon in patients diagnosed with DoC caused by severe brain injuries) will be reported to the Independent Medical Monitor, IRB, and FDA in accordance with published guidelines.

IND Safety reports will be submitted electronically in the common technical document (eCTD) format based on the following time-table:

- 7-day IND Safety Report (unexpected fatal or life-threatening AEs related to the intervention); a copy of the report sent to the Independent Medical Monitor within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to the intervention); a copy of the report submitted to the FDA will be submitted to the Independent Medical Monitor within 24 hours of FDA notification.

All SAEs will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the participant is stable.

The following disease-related medical events common to patients with DoC caused by severe brain injuries (e.g. expected), will not be reported per the standard process for reporting, unless the Principal Investigator or the Independent Medical Monitor believes that the event is related to the study drug: sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure, acute liver failure, and rhabdomyolysis.

Similarly, the following disease-related neurological events common to patients with DoC caused by severe brain injuries (e.g. expected), will not be reported per the standard process for reporting, unless the PI or the Independent Medical Monitor believes that the event is related to the study drug: ICP crisis, herniation, rebleed (e.g. contusion expansion or subdural hemorrhage expansion), brain edema requiring osmotherapy, seizure, ischemic stroke, CNS infection. Clinical criteria for these medical and neurological events are defined in a recent paper by Muehlschlegel and colleagues.[63]

6.5.3 REPORTING EVENTS TO PARTICIPANTS

The Principal Investigator will inform the participant's clinical team on all AE's and incidental findings. The clinical team and/or Principal Investigator will discuss findings with the participant's surrogate (and the participant if he/she has regained the capacity for assent or consent) and recommend follow-up as needed.

6.5.4 REPORTING OF PREGNANCY

Females who are pregnant will not be enrolled in this study.

7 UNANTICIPATED PROBLEMS

7.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The Principal Investigator and Independent Medical Monitor will be responsible for determining whether an AE is anticipated or unanticipated.

7.1.1 UNANTICIPATED PROBLEM REPORTING

The Principal Investigator will report unanticipated problems to the reviewing IRB, the Independent Medical Monitor, and the FDA via MedWatch (https://www.fda.gov/safety/medwatch/). The unanticipated problems report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are SAEs will be reported to the IRB and to the Independent Medical Monitor within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problems will be reported to the IRB and to the Independent Medical Monitor within 7 days of the investigator becoming aware of the problem.
- All unanticipated problems will be reported to appropriate institutional officials (as required by Partners Human Research Committee written reporting procedures) and the OHRP within 7 days of the IRB's receipt of the report of the problem from the investigator, in accordance with IRB policy.
- Unanticipated problems will be reported to the FDA via MedWatch in a time frame consistent with FDA requirements.

7.1.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The Principal Investigator will inform the participant's surrogate (and the participant if he/she has regained the capacity for assent or consent) of all unanticipated problems related to increased risk to subjects.

8 MONITORING AND QUALITY ASSURANCE

Safety oversight will be under the direction of the Clinical Oversight Committee composed of individuals with the appropriate expertise. The Principal Investigator and Independent Medical

Monitor are both board-certified neurointensivist physicians. The Clinical Oversight Committee also includes a neuro-ethicist with extensive experience working with patients with DoC caused by severe brain injuries.[64] There are also experts in electrophysiology, neuroimaging, behavioral assessment, and statistics. The members of the Clinical Oversight Committee are free from conflict of interest. The Clinical Oversight Committee will meet at least quarterly (four times per year) to assess safety and biomarker data, unless no data are acquired in the prior quarter.

Monitoring the validity and integrity of the data and adherence to the IRB-approved protocol will be the primary responsibility of the Principal Investigator. For each subject, he will confirm that written informed consent has been properly obtained, and that all data are appropriately recorded and maintained. The Principal Investigator will guarantee strict adherence to the IRB-approved protocol, and will monitor the integrity of the data collected. Should an AE need to be reported, the Principal Investigator will be responsible for reporting it in a timely manner according to the IRB regulations. All data collected during the study will be recorded and stored in a de-identified form for offline analysis.

8.1 DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Plan will be executed by the Independent Medical Monitor who will, on a quarterly basis, review all AEs and unanticipated problems, distinguish SAEs from non-serious AEs, and provide attributions regarding causality and severity. Parameters for AEs and SAEs and subsequent action are described above.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial. If the Independent Medical Monitor judges that risks to subjects outweighs the potential benefits, the Independent Medical Monitor shall have the discretion and responsibility to recommend that the study be terminated.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 INSTITUTIONAL REVIEW BOARD

This protocol and the informed consent document (see section 4a) and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study.

9.2 INFORMED CONSENT PROCESS

9.2.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A signed consent form will be obtained from the patient's surrogate. A copy of the consent form will be given to the surrogate.

9.2.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be obtained from the patient's surrogate. The investigator obtaining consent will explain in detail the protocol of the study, its purpose and potential benefits to society. The surrogate will be informed of all risks related to IV MPH and about the minimal risks of routine EEG and MRI. The surrogate will also be informed about the small space within the MRI scanner and noises made by switching gradients. The surrogate will be informed that his/her refusal to consent to the study or choosing to terminate it at some point will have no effect on care and treatment received by the participant at any Partners institution now or in future. The surrogate will be informed that the participant's personal information will be protected as per the HIPAA guidelines. Surrogates will have as much time as they wish to consider consenting to the study.

The surrogate will also provide screening information about the subject for MRI compatibility. Informed consent clearly states that the subject and surrogate may choose to terminate the study at any time.

9.3 PARTICIPANT AND DATA CONFIDENTIALITY

Participant and data confidentiality will be maintained through routine precautions. We assign a series of letters and numbers to the research data preventing the identity of the subject to be viewed. We keep any paper records of procedures and scans in a locked closet. In addition, all electronic clinical and imaging datasets will be de-identified using a code whose translation key will be stored on a password-protected network drive that is behind the institutional firewall and is securely backed up nightly. Electronic data will be stored in one of two secured locations: 1) on a password-protected network drive that is behind the institutional firewall and is securely backed up nightly; or 2) in a secured, password-protected, web-based REDCap database. Of note, REDCap was designed to comply with HIPAA regulations. It utilizes "Secure Sockets Layer (SSL)" encryption, and it is the database tool that is currently recommended by Harvard Catalyst (see http://catalyst.harvard.edu/services/redcap/).

Only authorized personnel will have access to these data. The Principal Investigator shall be responsible for the confidentiality of the data and access to the data. We will take every precaution to preserve the rights of the research subject.

9.3.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be

done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, or the OHRP.

10 DATA HANDLING AND RECORD KEEPING

10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection and accurate documentation will be the responsibility of CITI-certified study staff under the supervision of the Principal Investigator. All source documents and reports will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and AE's will be reviewed by the Principal Investigator.

10.2 STUDY RECORDS RETENTION

In compliance with local IRB policies, all study records will be maintained in an electronic regulatory REDCap binder. All individual subject-specific data will be stored in a separate file. Access to study documents will be restricted to study staff. Physical (paper) records will be stored in a secure locked office. Electronic records will be stored on Partners HealthCare compliant computers or mobile devices or other internally hosted services. Research records will be retained for at least seven years from the time the study is completed.

10.3 PROTOCOL DEVIATIONS

All protocol deviations will be reported to the local IRB in accordance with institutional policies. Minor protocol deviations, which do not have the potential to negatively impact subject safety or integrity of study data, or affect the subject's willingness to participate will be recorded in a log and submitted with the annual IRB Continuing Review application. Major protocol deviations, alterations, or modification to the IRB-approved research that has the potential to negatively impact subject safety or integrity of study data, or subject willingness to participate, will be reported to the IRB within five working days of the date the investigator becomes aware of the unapproved deviation.

11 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Independent Medical Monitor**
Brian L. Edlow, M.D.	Thomas P. Bleck, M.D.
Massachusetts General Hospital	Rush University

12 LIST OF ABBREVIATIONS

AAN	Ascending Arousal network
AE	Adverse Event
BP	Blood Pressure
CRF	Case Report Form
CRS-R	Coma Recovery Scale- Revised
DMN	Default Mode Network
DoC	Disorders of Consciousness
EEG	Electroencephalography
EVD	External Ventricular Drain
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
HARDI	High Angular Resolution Diffusion Imaging
HR	Heart Rate
IRB	Institutional Review Board
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IV	Intravenous
MCS	Minimally Conscious State
MGH	Massachusetts General Hospital
MPH	Methylphenidate
MRI	Magnetic Resonance Imaging
OHRP	Office for Human Research Protections
PTCS	Post-traumatic Confusional State
Rs-fMRI	Resting State Functional Magnetic Resonance Imaging
SAE	Serious Adverse Event
$T_{1/2}$	Half life
TBI	Traumatic Brain Injury
T_{MAX}	Time to Maximum Concentration
VS	Vegetative State
VTA	Ventral Tegmental Area

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