PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

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PROTOCOL TITLE

Neuroimaging Study of Dexmedetomidine-Induced Anesthesia

FUNDING

MGH DACCPM Department SUNDRY Funds

VERSION DATE

3/29/2023

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

AIM 1: Characterize the effect of dexmedetomidine on noradrenergic arousal circuitry

Hypothesis 1.1. Compared to baseline, dexmedetomidine-anesthesia will lead to activation between locus coeruleus and various brainstem arousal nuclei, and decreased thalamo-cortical connectivity.

Hypothesis 1.2. Compared to dexmedetomidine-anesthesia, recovery from dexmedetomidine-anesthesia will lead to decreased connectivity between brainstem arousal nuclei and increased thalamo-cortical connectivity.

AIM 2: Characterize the effect of dexmedetomidine on cerebrospinal fluid flow

Hypothesis. Compared to baseline, dexmedetomidine-anesthesia will be associated with increased cerebrospinal fluid flow

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

From a scientific standpoint, a concise definition of consciousness is elusive. Experimentally, consciousness can be studied using natural sleep or anesthesia paradigms to induce altered levels of arousal, ranging from a light state of unconsciousness during sleep to deep levels of unconsciousness during general anesthesia. Previous research in humans has highlighted the role of the locus coeruleus in arousal modulation as well as the thalamus and cortex in consciousness.

Detailed studies of noradrenergic circuitry are expected to provide valuable insights into the mechanisms underlying functional arousal, and even consciousness. These insights will have implications for disorders of consciousness including coma and vegetative states as well as for anesthesia practice.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site

restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

We will enroll 20 subject subjects (male and female) between the ages of 18-45 years. Informed consent for this protocol will be obtained during the screening visit, after which the study team will allocate a study identification number to the potential subject. All subjects who provide informed consent but later decline participation in the study will not be subject to any study-related follow-up or intervention.

Primary inclusion criteria: (1) between the ages of 18 to 45; (2) normal body weight and habitus, BMI ≤ 30; (3) non-smoker; (4) American Society of Anesthesiologists (ASA) physical status classification P1 or P2, (5) active health insurance coverage, (6) fully vaccinated against COVID-19.

Primary exclusion criteria include but are not limited to (A) the following conditions: (1) Cardiovascular: hypertension; (2) Endocrine: diabetes; (3) Allergies: dexmedetomidine, ondansetron, glycopyrrolate, phenylephrine **and (B) the following conditions, if they are not stable and controlled:** (1) Cardiovascular: myocardial infarction, coronary artery disease, peripheral vascular disease, arrhythmia, congestive heart failure, valvular disease, hypertension; (2) Respiratory: bronchitis, chronic obstructive pulmonary disease, smoking, shortness of breath, sleep apnea; (3) Hepatic: hepatitis, jaundice, ascites; (4) Neurologic: seizure, stroke, positive neurologic findings on neurologic examination, multiple sclerosis, Meniere's disease, Parkinson's disease; (5) Gastrointestinal: esophageal reflux, hiatal hernia, ulcer; (6) Endocrine: diabetes, thyroid disease; (7) Renal: acute or chronic severe renal insufficiency; (8) Hematologic: blood dyscrasias, anemia, coagulopathies, on anticoagulant therapy; (9) Musculoskeletal: prior surgery or trauma to head neck or face, arthritis, personal or family history of malignant hyperthermia; (10) Psychiatric: history or treatment for an active psychiatric problem, depression; (11) Reproductive: pregnancy, breast-feeding; (12) Medications: regular use of prescription and non-prescription medications expected to affect CNS function; St. John's Wort (13) Allergies: ondansetron, glycopyrrolate, dexmedetomidine, phenylephrine; (13) Dermatologic: ulcerative skin conditions or other dermatologic conditions which could interfere with blood pressure cuff placement; (14) Contraindications to MRI: history of head trauma, surgical aneurysm clips, cardiac pacemaker, prosthetic heart valve, neurostimulator, implanted pumps, cochlear implants, metal rods/plates/screws, intrauterine device, hearing aid, dentures, metal injury to eyes, and metallic tattoos; (15) lifetime history of substance abuse.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

We will pursue our study aims using a single-arm study design.

Screening Visit: All subjects will complete a screening visit. Study subjects will undergo a review of systems and a physical examination to ensure that they meet the basic inclusion and exclusion criteria for the study. Particular attention will be paid to the subject's airway anatomy and neurologic function. Abnormal findings on physical examination may result in exclusion from the study. Abnormal findings will be reported to the subject, and recommendations for medical follow-up will be given as needed. Study staff will also discuss current patient medications. Many medications other than birth control, over the counter medications, and multivitamins are not permitted. Only medications that are not expected to affect central nervous system function are permitted. All further questions will be explained as needed. A urine hCG pregnancy test will be performed. Only subjects with negative tests will be enrolled. Each subject will sign informed consent. The clinician obtaining consent will explain in detail the protocol of the study, its purpose

and potential benefits to society. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time.

A complete blood count, blood glucose level, liver function tests (LFTs), blood urea nitrogen (BUN) and creatinine (Cr) level panel may be obtained at the initial screening visit. If the subject has had these tests performed within the last thirty days at a Partners affiliated institution with satisfactory results we may not perform these tests at their screening visit. For inclusion into the study protocol, each subject will be required to have values within the range of normal with the following exceptions: (1) AST, ALT and bilirubin levels within 1.5 times the upper limit of normal; (2) Alkaline phosphatase ≤ 130; (3) WBC ≥ 3.5; (4) Platelet count ≥ 120; (5) BUN and creatinine within 1.5 times the upper limit of normal, (6) any of RBC, Hemoglobin, Hematocrit, MCH, and MCHC within 10% of the lower or upper limit of normal. A 12-lead EKG will be performed.

Subjects may undergo a QST battery, using a validated cuff pain device (Hokanson Rapid Cuff Inflator).[28-30] With the cuff wrapped comfortably around the gastrocnemius muscle, we may assess cuff pain thresholds and individually determine the tailored pressures necessary to produce mild/low pain (10-20/100), moderate pain (40-50/100), and high pain (70-80/100). Patients may be tested with the array of cuff stimuli that may be applied in the subsequent study visit.

Study Visit: During the study, a board-certified anesthesiologist will be present whose sole responsibility will be to monitor (check) your safety. The sequence of this study visit will be as follows: arrival (approximately 30 minutes), baseline (approximately 40 minutes), monitored anesthetic care (approximately 40 minutes), recovery (approximately 40 minutes), and discharge (approximately 30 minutes). We anticipate the study to last approximately 3 hours.

A. Arrival:
Upon arrival, confirmation of the study subjects' fasting status (minimum 8 hours) will be made. A urine sample will be obtained for pregnancy testing in all female subjects. Standard MRI compatible monitors for anesthesia care monitoring including blood pressure (cuff), electrocardiogram, capnography and pulse oximetry will be placed on the subject. An intravenous line will be placed for drug administration. The sequence of study visits will be as follows: baseline, monitored anesthetic care, and recovery (post-analgesia). We anticipate that the brain imaging portion of the study will last approximately 90-120 minutes. Board-certified anesthesiologists will be responsible for administering all medications and for monitoring potential side effects throughout the course of the study visit, including patient airway management. The board-certified anesthesiologists will always monitor and care for the subject according to the standards for delivery of anesthesia at the Massachusetts General Hospital.

Subjects may undergo a QST battery, using a validated cuff pain device (Hokanson Rapid Cuff Inflator).[28-30] With the cuff wrapped comfortably around the gastrocnemius muscle, we may assess cuff pain thresholds and individually determine the tailored pressures necessary to produce mild/low pain (10-20/100), moderate pain (40-50/100), and high pain (70-80/100). Patients may be tested with the array of cuff stimuli that may be applied following the fMRI scans. We have pioneered the adaptation of cuff pain stimulation to the fMRI environment, and have safely and effectively used these procedures in numerous studies.[31,32]

B. Baseline
We will obtain BOLD fMRI as well as run a localizer scan, locus coeruleus mapping sequences, cerebrospinal fluid flow scans and a MR spectroscopy sequence. Approximately 6 minutes of resting fMRI data (REST) will be collected with subjects resting comfortably, eyes open, in the scanner before monitored anesthetic care.

C. Monitored Anesthetic Care

Drug administration will be performed as follows: 1.0 mcg/kg bolus of dexmedetomidine up to a maximum of 75 mcgs will be infused (Medfusion pump) gradually over 10 minutes and an infusion of up to 0.5 mcg/kg/min will be maintained for approximately 20-30 minutes. The drowsy state associated with dexmedetomidine may be similar to falling into light sleep. Immediately preceding and following drug administration, resting BOLD fMRI as in the baseline portion will be obtained. Patients will be verbally stimulated at the end of the anesthesia portion. We will also conduct structural and cerebrospinal fluid scans as well as a MR spectroscopy sequence. Verbal cueing at the end of the anesthesia portion will allow the study team to confirm patients are awake and alert before continuing to the post anesthesia portion of the study.

Because dexmedetomidine may cause a decrease in the heart rate and blood pressure, an anesthesiologist may be required to administer intravenous glycopyrrolate 0.2 to 0.4 mg IV push over approximately 2 minutes for heart rate less than 50 beats per minute sustained over 30 seconds. Also, an anesthesiologist may be required to administer phenylephrine for blood pressure readings less than 80/60. Blood pressure readings will be obtained 3-5 minutes apart. An anesthesiologist may be required to stop dexmedetomidine infusion in response to systolic blood pressure readings below 90 mmHg or heart rate less than 60 beats per minute.

D. Recovery (Post Analgesia)
After recovery, we will run a brief localizer scan (20-30 seconds). We will obtain resting state BOLD fMRI in addition to structural, cerebrospinal fluid flow, and MR spectroscopy sequences as discussed previously. We may also conduct a locus coeruleus mapping sequence.

Following recovery and subject removal from the scanner, we may repeat the QST battery, as discussed previously. If conducted, the QST battery will take place outside of the MRI scanning environment. With the cuff wrapped comfortably around the gastrocnemius muscle, patients may be tested with the array of cuff stimuli that were be applied earlier in the study visit.

E. Discharge
If medically stable, as deemed by a board-certified anesthesiologist, the intravenous line and physiological monitoring devices will be discontinued, and subjects will be discharged home with a responsible family member or other adult caretaker. Discharge home will be based on criteria established by the Massachusetts General Hospital Department of Anesthesia practices for discharge from the hospital following ambulatory surgery. The subject must have stable vital signs, be able to respond appropriately to normal commands, be free from any nausea and vomiting, and able to walk unassisted and have an accompanying adult to escort them home. Subjects will be advised against returning to work and driving or operating heavy equipment for 24 hours. If subjects experience adverse events at home, they will be referred for evaluation at the nearest emergency department.

The study investigator will contact all study participants 24 hours after the administration of dexmedetomidine to address any concerns.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

All procedures related to administering anesthetic drugs and physiological monitoring will follow MGH Department of Anesthesia, Critical Care and Pain Medicine standard of care, and the American Society of Anesthesiologists practice guidelines.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The preparation of dexmedetomidine will be done by the MGH Research Pharmacy. The study anesthesiologist will monitor the patient continuously for the duration of the dexmedetomidine infusion, and after the infusion has been stopped to ensure normal physiology. This is in accordance with MGH Department of Anesthesia, Critical Care and Pain Medicine standards for monitoring anesthetized patients at an out-of-operating room location and the standards for monitoring in the post-anesthesia care unit.

These studies will take place at the Biomedical Imaging Core at Charlestown Navy Yard. Imaging will be performed on one of the Martinos Center's 7T MRI scanners (Magnex Scientific/ Siemens, Oxford, UK; Siemens MAGNETOM, Erlangen, Germany). Our research laboratory is equipped with MRI compatible equipment for monitoring of physiologic data (i.e., blood pressure, pulse oximetry, heart rate, CO2). The CNY MRI environs is equipped with code carts. These code carts are strategically located in the MRI environs for the treatment of allergic reactions (i.e. contrast).

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

In addition to the study team comprising of a post-doctoral fellow and two clinical research coordinators, safety monitoring includes the presence of a board-certified anesthesiologist at all times whose primary responsibility is to ensure subject safety.

Nursing (currently or intending to breast feed baby) and/or pregnant subjects will be excluded from the study (pregnancy test x2 for female). We will ensure NPO status if at least 8 hours and pre-emptively administered anti-emetics to all study subjects.

We do not anticipate respiratory depression during the conduct of this study. This is because dexmedetomidine at the dose being studied is associated with an arousable brain state with maintained ventilation and oxygenation. However, the study team will have laryngeal mask airways (weight appropriate) and ambu-bags readily available during all study visits. In the event that subjects react unfavorably to the anesthetic or in the event of an emergency, we will call 911 and he/she will be transported to the MGH emergency room for continued monitoring.

Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any events that are fatal event, immediately life-threatening events, permanently or substantially disabling events, or events requiring or prolonging inpatient hospitalization. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect or precaution. Reporting to the IRB will be done within 24 hours of the SAE.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Data risks: Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on Partners approved devices/portals.

However, there is a small risk that people outside of this study may be exposed to information about study subjects.

Dexmedetomidine risks: The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in patients with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. As such, study subject hemodynamic parameters will be continuously monitored to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes.

Glycopyrrolate risks: Risks involved in the administration of glycopyrrolate include hypertension and tachycardia.

Ondansetron risks: Risks involved in the administration of ondansetron include headache and hypoxia.

Phenylephrine risks: Risks involved in the administration of phenylephrine include hypertension and bradycardia.

Cuff pain stimuli risks: Risks of cuff pain include mild transient bruising associated with inflation of the cuff. Our previous experience has also demonstrated that pain ratings go down to nil within several seconds of stimulus termination. A button press rapidly deflates the cuff, ensuring subject safety.

MRI risks: MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped. Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

There are no direct benefits to the individual subjects involved in this study. The potential benefits of this study to society include a greater understanding of noradrenergic pain circuitry, which will

provide a principled framework for characterizing and treating pain and aid circuit-based development and validation of novel pain drugs. Results emanating from this study may also lend insights into non-noradrenergic pain circuitry as well as the neural circuitries underlying arousal and perceptual disturbances.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The subjects will be recruited from a cohort of subjects obtained from announcements on the Partners Public Affairs distribution list and the MGH Research Study Subject Program (RSVP). Prior to the study enrollment, each subject will sign informed consent. Within this population of subjects, every effort will be made to obtain a sample of study subjects that is representative of the population in the Greater Boston area with respect to race, ethnicity and gender. Study enrollment will not be permitted for any individual associated with the research group.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Native English speakers are required for language comprehension reasons.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

We will select 20 male and female subjects for this study between the ages of 18 and 45.

The subjects will be recruited using:

1. An announcement of the study distributed through the Partners Public Affairs
2. MGH Research Study Volunteer Program (RSVP).

We will call subjects to administer a study screening questionnaire. All subjects will be informed that allowing us to collect and record their names with their answers is a loss of confidentiality, and that we will take reasonable steps to protect the confidentiality of their information. Subjects will also be informed of the lack of security involved with sending unsecured mail prior to sending

medical information over email and will thus be encouraged to complete screening procedures over the phone.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

For successful completion of this protocol, subject remuneration will be $250. If the study subject is unable to complete the entire protocol, pro-rating of this remuneration will be as follows:

- Study subjects who complete the medical screening evaluation but do not begin the anesthesia portion of the study will receive $50.

Study subjects who complete all study portions will receive $250.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Prior to the beginning of the study, the subjects will give informed consent for screening visit assessments. The investigator will review and discuss the details of the research study with the potential subject using the informed consent document as a guide. This discussion will include all of the required elements of informed consent. After consent, the subject will receive their initial physical examination, and give a urine sample to ensure negative toxicity. Female subjects will also be given a pregnancy test to ensure they are not pregnant.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Safety monitoring will include the presence of an anesthesiologist to monitor the subject. The principal investigator and co-investigators will be responsible for monitoring and quality assurance of the study.

Weekly meetings will be held and documented. Current subjects in the study will be discussed at each meeting, and charts will be reviewed for completeness. The team will evaluate the progress of the study; verify that the rights and wellbeing of the subjects are protected; ensure that the reported study data are accurate, complete and verifiable from source documents; and assure the conduct of the study is in compliance with the approved protocol and amendments. We will repost all instances of follow-up medical care that occurs within a month after the study visit (i.e. seizure, prolonged hallucination) regardless of perceived relatedness to the study.

Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any events that are fatal events, immediately life-threatening events, permanently or substantially disabling events, or events requiring or prolonging inpatient hospitalization. This also includes post-discharge hospital visits, Emergency Department visits and psychiatric complications. Any event that a study investigator judges to impose a significant hazard, contraindication, side effect or precaution will be reported as such as well. SAEs will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC adverse events reported guidelines.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

After each section of the study is completed, we will review events and outcomes. Thus, we will be immediately aware of any adverse events or protocol violations, and will be able to review and report these events to the appropriate channels of the Partners Human Research Committee in a timely fashion. In addition, unanticipated problems involving risks to subjects or to others will be reviewed and reported to the appropriate channels of the Partners Human Research Committee.

If the subject experiences any kind of pain or discomfort during the study, study staff will attempt to alleviate or remove the source of the discomfort. If the discomfort is inherent to the study procedure, then study will be stopped, and the subject's participation will be terminated if they feel they do not want to continue with the study.

All outcome monitoring and adverse events will be reported through appropriate channels of the MGH Human Research Committee.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The principal investigator will review with the study staff the results of the pre-study assessment, and the clinical and technical overview of completed studies to confirm adherence to the IRB-approved protocol. Weekly meetings will be held and documented.

All MRI data and physiological measures will be stored for later off-line analysis. Any unanticipated problems involving risks to subjects or others, including adverse events will be reported to the PHRC as described by the PHRC Unanticipated Problems Including Adverse Events reporting guidelines.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All medical information produced by the study is secured in the investigator's file and is identified by a unique alphanumeric code. All data will be labeled with an alphanumeric code rather than with the subject's name, initials, medical record number, date of birth, or Social Security number. The key to the code which links subject's identity to the code will be kept in a secure location separate from the CRFs, subject data and documents.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No data or specimens will be sent outside of Partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A