PART B

STUDY DESCRIPTION

Title of Protocol	**P**erioperative multimodal general **A**nes**TH**esia **F**ocuss**IN**g on specific CNS targets in patients undergoing car**D**iac surg**ER**ies - The **PATHFINDER** II study
Principal Investigator	Dr. Balachundhar Subramaniam MD, MPH, FASA

B1. PURPOSE OF PROTOCOL

In the PATHFINDER 2 trial, we will test our intraoperative EEG-guided multimodal general anesthesia (MMGA) management strategy in combination with a postoperative protocolized analgesic approach to:

1.) reduce the incidence of perioperative neurocognitive dysfunction in cardiac surgical patients
2.) ensure hemodynamic stability and decrease use of vasopressors in the operating rooms
3.) reduce pain and opioid consumption postoperatively

Specific Aims:

In this randomized (1:1) study on 70 patients (age ≥ 60 years) undergoing cardiac surgery, we aim to:

1.) Demonstrate that the perioperative EEG-guided MMGA bundle reduces the postoperative increase in plasma levels of Interleukin -6 and Neurofilament light

2.) Demonstrate that the perioperative EEG-guided MMGA bundle reduces concurrent EEG burst suppression and cerebral desaturation events by 20% from the baseline/ standard of care group.
3.) Develop an EEG-guided MMGA curriculum for cardiac anesthesiology with preexisting online modules from Dr. Brown's lab supplemented with common clinical scenarios during a cardiac surgical case and establishing education and training for anesthesiologists and postoperative ICU nurses

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Multimodal General Anesthesia (MMGA) and inflammation

General anesthesia is a drug-induced reversible state consisting of unconsciousness, amnesia, antinociception, and immobility while maintaining physiological stability[1]. The primary objective of general anesthesia is to eliminate pain during surgery and invasive diagnostic procedures. The state of general anesthesia eliminates pain by preventing both nociception (the transmission of noxious neural sensory signals) and conscious perception of nociception. The current practice of balanced anesthesia typically uses opioids for antinociception, intravenous propofol to induce and inhaled ethers to sustain unconsciousness and produce amnesia, and muscle relaxers for immobility[1, 2]. However, recent advances in understanding specific neural circuits involved in antinociceptive and arousal pathways allows for the synergistic use of medications to create the state of general anesthesia while reducing total anesthetic agent exposure[3]. As described in *Brown et al.,* multimodal general anesthesia (MMGA) uses a combination of medications to control nociception, each targeting a different component of the nociceptive system. These medications also decrease arousal. Hence, less hypnotic agent is required to achieve unconsciousness. MMGA will utilize two or more drugs providing anesthesia from multiple brain circuits (e.g. Propofol, Dexmedetomidine, and Ketamine) and for analgesia (Dexmedetomidine, Ketamine, Remifentanil, Hydromorphone, and local anesthetic block) and muscle relaxants. By simultaneously targeting different neural circuits in low doses guided by EEG, clinicians can thereby maximize the therapeutic benefit while minimizing drug exposure and concomitant side effects. Rationally designed MMGA regimens have the potential to drastically benefit anesthesiology practice, particularly for surgeries where anesthetic dosing may interfere with surgical outcomes.

Common occurrence of cognitive disturbances after surgery and anesthesia has initiated studies trying to understand the mechanism underlying the disturbances. Factors such as hypoxemia, hypotension, Cardiopulmonary Bypass management, hypothermia, anticoagulation, cerebral blood flow have been studied[4]. Inflammation triggered by the perioperative stress also has been proposed to be a factor involved in perioperative cognitive decline[5,6]. The mechanism behind this is that the stress can cause a systemic inflammatory response leading to release of inflammatory cytokines like Interleukin (IL-6) and lipocalin-2, which in turn leads to neuroinflammation. In response to this, neuronal injury happens leading to release of neuronal proteins into the plasma. Measuring the rise of the inflammatory cytokines and neuronal components can indicate the magnitude of neuroinflammation. Neurofilament light is a neuronal cytoplasmic protein highly expressed in large caliber myelinated axons and has been seen to proportionally increase to the extent of neuronal damage[7].

Apart from reducing the amount of drugs administered during anesthesia, MMGA titrated by EEG also can potentially reduce the incidence of perturbations to perioperative brain health. This eventually can reduce the neuroinflammation and thereby the perioperative cognitive disturbances.
Nociception is the propagation of noxious stimuli through the sensory system, whereas pain is the conscious perception of nociceptive information.[8] Nociception due to the injury and inflammation of tissue with surgery is the main reason for providing general anesthesia. Opioids are the commonly used antinociceptive agents during the perioperative period. Despite all the advantages, they can cause respiratory depression, nausea, vomiting, urinary retention, constipation, ileus, and pruritus.[9] Moreover, increased dependence on opioids have resulted in an opioid epidemic in the United States.[10]

Considering the disadvantages associated with opioids, the current strategy for balanced anesthesia uses multiple agents in addition or without opioids to achieve the anesthetic state. This approach defined as multimodal general anesthesia includes agents that have specific central nervous system targets. Moreover using more drugs at minimal doses could maximize the advantages and minimize the adverse effects.[11]

Nociceptive pathways
Understanding nociceptive pathways becomes vital in formulating a successful strategy. The nociceptive system consists of nociceptors, ascending pathways, and descending pathways. Nociceptors are free nerve endings seen in peripheral tissue and viscera that initiates nociception or pain. Ascending pathways transmit nociceptive stimuli from the periphery to the spinal cord, brainstem (medulla and midbrain), amygdala, thalamus, relaying with the sensory cortex. Descending pathways begin in the sensory cortex and project to the hypothalamus and amygdala. These projections then synapse with periaqueductal gray in the midbrain and the nucleus of the tracts solitarius and projects to the spinal cord primarily through the rostral ventral medulla. These pathways are activated immediately by the ascending pathways and modulate nociception. Moreover, descending pathways are strongly connected with the arousal pathways, which explains the decrease in arousal effect caused by antinociceptive agents. Simultaneously focus on multiple targets in the nociceptive system is the key concept underlying the design of multimodal general anesthesia.

Opioids and nociception
Opioids act on receptors located on periaqueductal gray, spinal cord, amygdala, rostral ventral medulla, and cortex. These agents, a) block afferent nociceptive inputs into the spinal cord, b) enhance descending inhibition of nociceptive inputs, c) decrease nociceptive perception and the emotional effect of pain stimulation, d) decrease arousal through their inhibitory actions on brainstem cholinergic circuits, e) enhance cholinergic action on sinoatrial node (bradycardia) and reduces sympathetic responses with nociception

Ketamine and nociception
Ketamine targets N-methyl-d-aspartate (NMDA) glutamate receptors on peripheral afferent nociceptive neurons synapsing with the dorsal horn of the spinal cord. Its action on cortex and arousal system results in antinociceptive and decreased arousal. Glutamatergic projections from the parabrachial nucleus and medial pontine reticular formation are the target region for altering arousal. At higher ketamine doses, inactivation of these arousal pathways leads to unconsciousness with distinct electroencephalogram patterns (alternating slow-delta with gamma).

Dexmedetomidine

Dexmedetomidine causes inhibition of descending nociceptive transmission by activating inhibitory interneurons synapsing at the dorsal horn of the spinal cord. It also exerts an antinociceptive effect by decreasing arousal. It acts on presynaptic receptors and decreases the release of norepinephrine from locus ceruleus neurons projecting to the basal forebrain, intralaminar nucleus of the thalamus, preoptic area of the hypothalamus, and diffusely to the cortex. Consequently, this results in decreased arousal and the EEG shows spindle and slow-delta oscillations at low-to-moderate doses, and only slow-delta oscillations at a higher dose.

Propofol & Sevoflurane

These agents have no direct action on nociceptive pathways but decrease the perception by rendering the patient unconscious. They act on $GABA_A$ receptor synapses of inhibitory neurons to pyramidal neurons in the cortex, thalamus, brainstem, striatum, and spinal cord. Moreover, inhaled agents also block potassium channels, cyclic nucleotide-gated channels, and NMDA receptors. EEG shows characteristic slow-delta and alpha oscillations. Above 1 MAC (minimal alveolar concentration), inhaled anesthetics show a decrease in the alpha power and an increase in the delta that gives the appearance of a theta oscillation.

Monitoring for unconsciousness and antinociception

There is evidence that intraoperative EEG monitoring reduces anesthetic dose and recovery time.[12] Few studies suggest there may be a lower incidence of postoperative delirium (POD), as well as postoperative cognitive dysfunction (POCD) with processed electroencephalogram-monitored care. United Kingdom's National Institute for Health and Care Excellence published 2012 guidelines recommending the use of processed EEG monitoring, especially in "high-risk" patients to improve cognitive outcomes.[13]

In a recent study, EEG-guided anesthetic administration was not found to decrease the incidence of postoperative delirium as compared to the standard care.[14] However, the authors found a significant decrease in mortality up to 30 days after surgery in patients who received EEG guided anesthetic. They computed EEG suppression ratio and Bispectral Index (BSI) as exposure measures and multimodal anesthesia was not used.

Components of Multimodal General Anesthesia

COMPONENT	DRUGS
Antinociception	Ketamine, Remifentanil, Dexmedetomidine, Acetaminophen
Unconsciousness (amnesia)	Propofol, Sevoflurane
Immobility	Atracurium, Rocuronium, Succinylcholine

Elderly patients undergoing cardiac surgery are at a high risk for adverse consequences in the perioperative period including comparatively higher rates of morbidity, mortality, complication rates, repeat hospital admissions, and healthcare utilization[15,16,17]. Cardiac anesthesiology is challenging due to the high-risk nature of bypass and valve procedures, distinct mean arterial pressure (MAP) goals at different phases of surgery, and repeated nociceptive stimuli. Interference of the surgical procedure with the typical signs used to titrate anesthetic agents further complicate cardiac anesthesiology, as blood pressure and heart rate no longer provide insight into nociception during cardiac bypass. Intraoperative hemodynamic instability and postoperative cognitive dysfunction are also more common in elderly cardiac surgical patients due to factors such as limited cardiac and autonomic reserve, decreased cognitive reserve, and increased susceptibility to deeper anesthetic states[18,19,20]. While EEG-guided anesthesia has not previously shown clear improvement in perioperative outcomes[21,22], the lack of traditional nociceptive signaling during cardiac bypass necessitates a role for direct brain monitoring via EEG in cardiac surgery to enable personalized anesthesia care and reduce incidence of hypotension, morbidity, mortality, and complications in the postoperative period.

There is a compelling association between increased postoperative myocardial and renal dysfunction with increasing duration of intraoperative hypotension[23] (hypotension threshold defined as MAP < 65 mm of Hg) in non-cardiac surgical patients. However, targeting higher MAP during cardiopulmonary bypass can likewise increase adverse events[24]. Reduction of anesthetic dosing could potentially reduce

anesthetic-induced myocardial depression and vasodilation, therefore providing better hemodynamic stability with less vasopressor support.

Pilot Studies:

We have performed prior studies to test the relationship between vasopressor use, hemodynamic stability, and postoperative complications[23,25,26]. We have also performed pilot studies to determine the effects of multimodal pain management strategies on postoperative cognitive dysfunction[23, 24]. Finally, we have performed a feasibility study to determine the safety and efficacy of rationally designed EEG-guided MMGA in a small cohort of patients undergoing cardiac surgery.

In a retrospective analysis of 6000 cardiac surgical patients, increased use of vasopressors was associated with increased postoperative complications[23] (manuscript under review). In an ongoing retrospective study, we have found that an increased duration of hypotension was associated with increased mortality, renal failure, and stroke. Our multivariate logistic regression model showed that there is a significant association of a composite outcome of stroke, renal failure, and death with the fourth quartile of duration of hypotension with MAP < 65 mmHg and total vasopressor dose in mg[16] [2.09 with 95% CI = 1.35 - 2.38 and 1.65 with 95% CI 1.08 - 2.56, respectively]. At a different institution, in a randomized clinical trial of 239 patients undergoing elective cardiac surgery the use of processed EEG using a visible Narcotrend (NT) monitor significantly reduced the intraoperative vasopressor (noepinephrine) dose[29]. After adjusting for type of surgery, intraoperative norepinephrine application was reduced in visible-NT (n=120, mean of cumulative dose 4.71 µg/kg bodyweight) compared to blinded-NT patients (n=119, 6.14 µg/kg bodyweight) with an adjusted robust mean difference of 1.71, with 95% CI 0.33 – 3.10 µg/kg bodyweight.

In the PATHFINDER pilot study[30] (NCT04016740), we used an EEG-guided MMGA strategy for elderly patients (age ≥ 60 years) undergoing cardiac surgery with cardiopulmonary bypass. We successfully implemented our non-randomized prospective observational feasibility trial in the operating rooms and intensive care unit at the Beth-Israel Deaconess Medical Center (Boston, MA) from July 2019 to January 2020 and did not find any adverse effects associated with MMGA. Thus, we are prepared to compare MMGA in cardiac surgery with standard of care. We found similar intraoperative hemodynamic stability (intraoperative hypotension, coefficient of variation), reduced intraoperative midazolam use, and a trend towards reduced postoperative delirium (17%, 3/17 PATHFINDER MMGA subjects with one excluded for an unrelated postoperative complication) when comparing our EEG-guided MMGA to historic controls from our postoperative acetaminophen DEXACET trial[28] (29%, 17/59 DEXACET subjects).

Though our postoperative acetaminophen trial showed a small reduction in postoperative pain intensity and analgesic use, when intraoperative MMGA and postoperative acetaminophen are used as a bundle to manage nociception they could have additive or synergistic analgesic effects.

We propose to randomize (1:1) 70 patients undergoing cardiac surgery to our perioperative EEG-guided MMGA bundle (described in full below) or standard-of-care management based primarily on the use of sevoflurane for unconsciousness and intermittent doses of fentanyl and hydromorphone for antinociception.

We will test our intraoperative EEG-guided MMGA management strategy in combination with a postoperative protocolized analgesic approach to ensure hemodynamic stability and decreased use of vasopressors in the operating rooms and reduce pain and opioid consumption postoperatively. We will also investigate whether EEG-guided MMGA strategy reduces the incidence of perioperative neurocognitive dysfunction in cardiac surgical patients. This approach will further individualize care and minimize the use of intraoperative vasopressor-inotropic dose, dose of anesthetic medications, and postoperative opioids given to each patient potentially preventing hemodynamic complications and post-operative cognitive dysfunction after surgery.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design:
This is a randomized control trial. Study enrollment will consist of 70 patients (1:1 allocation, 35 controls, 35 experimental) (age ≥ 60 years) undergoing coronary artery bypass grafting (CABG) and/or valve or aortic cardiac surgery procedures with cardiopulmonary bypass (CPB) who are eligible for fast tracking (early extubation within 6 hours achieved with time directed protocols and low dose opioid anesthesia) in the intensive care unit at Beth Israel Deaconess Medical Center. Patients meeting inclusion criteria with no exclusions will be approached by a research team member and PI to obtain written informed consent.

Enrollment:
Study subjects will be identified from the perioperative information management system (PIMS), surgical consult lists, cardiac surgical clinic visit schedules and pre-admission testing (PAT) clinic visit schedules. We have requested a waiver of authorization for pre-screening purposes. After confirming eligibility, the patient will be approached by an IRB approved research team member to discuss the study in detail. Written informed consent will be obtained research team member and PI before initiation of any study procedure.

Allocation of patients:
70 patients will be enrolled in this study and randomized by 1:1 allocation. 35 patients will be randomized to the perioperative EEG-guided MMGA bundle and 35 patients will receive standard-of-care management based primarily on the use of sevoflurane for unconsciousness and intermittent doses of fentanyl and hydromorphone for antinociception.

Study Procedures:
Preoperative
Assessment by an anesthesiologist, including detailed patient education about:

i. Multimodal general anesthesia and
ii. Postoperative pain management
iii. Standardized education training to train clinical anesthesiologists involved in the intervention
    1. Short YouTube modules published by Prof. Emery Brown's lab
    2. IARS (International Anesthesia Research Society) tutorials and certification (paperwork will be stored in our REDCap database)
    3. Instruction in Management Strategy: Creation of standard scenarios requiring drug administration changes in the intraoperative period

Intraoperative
The anesthesiologists involved in this study will be taught using a combination of online resources and in-person training to infer differences in anti-nociception, unconsciousness, movement, and changes during other perioperative events by monitoring the EEG. They will also be trained in titrating hypnotic medications and antinociceptive medications based on changes in heart rate, blood pressure, specific surgical time-points, and the EEG waveforms.

i. Routine anesthetic induction

Standard practice of induction using 250mcg (3-5 mcg/kg) of IV fentanyl, 50-200mg of Propofol or 10-20mg of Etomidate and endotracheal intubation will be facilitated by 50-100mg of IV rocuronium.

ii. Bilateral Pecto-intercostal fascial block (PIFB) block

Intervention patients will receive a bilateral PIFB block will be administered by trained anesthesiologists after induction and before incision using 20 ml of 0.2% Ropivacaine on both sides (total of 40 ml). Trained anesthesiologists will use ultrasound guidance to administer the PIFB in the plane between the external intercostal and the pectoralis major muscles.

iii. Medications

Drug	Dose	Dose changes based on
Ketamine	0.1 to 0.2 mg/kg/hr	EEG monitoring Patient responses/nociception Hemodynamic stability
Remifentanil	0.05 to 0.4 mcg/kg/min	
Dexmedetomidine	0.2 to 0.5 mcg/kg/hr	
Propofol	15 to 200 mcg/kg/min	
Sevoflurane	Inhaled as needed	
Rocuronium	Boluses	Train of Four (TOF) monitoring and clinical status

iv. EEG monitoring (level of unconsciousness and titration of drugs) : EEG stickers attached and connected to the Sedline monitor (described below in perioperative EEG and Cerebral Oximetry (CO) monitoring) at least 5 minutes prior to start of induction.

v. CO monitoring : CO stickers attached, connected to the Sedline monitor and data collected passively (no titration of drugs).

Postoperative

i. Standard pain management protocol (both control and intervention groups)
   - IV Acetaminophen 1gm x 4 doses at 6 hourly intervals starting from 1 hour after ICU arrival
   - IV Hydromorphone/fentanyl boluses as needed per current practice for rescue analgesia
   - Other oral pain medications as per standard of care (Oxycodone etc.)

ii. Dexmedetomidine infusion 0.4-1.4 mcg/kg/hr (EEG guided for intervention group)

iii. Dexmedetomidine infusion will be continued till extubation and dose will be titrated based on patient response, hemodynamic stability and EEG monitoring.

iv. Propofol infusion may be added/used for sedation based on the treating physician's discretion

v. Parasternal block (PIFB or Transversus Thoracic Plane Block) on Postoperative day 0 – currently incorporated into standard pain management after surgery based on physician discretion (for control groups)

vi. PIFB on postoperative day 1 (provided they are extubated or getting ready to be extubated) to help with mobilization (for intervention group)

vii. Passive collection of CO data will be continued postoperatively

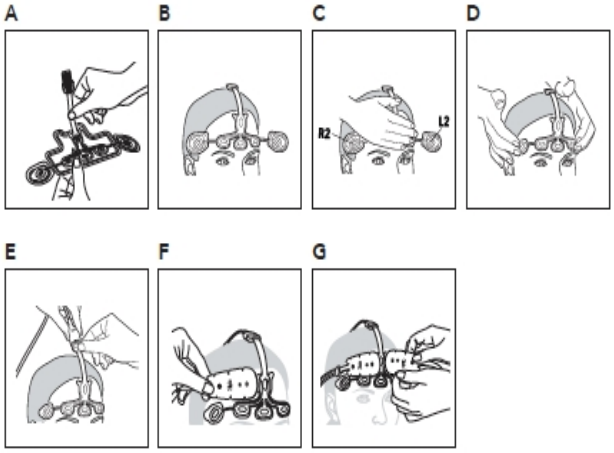
Data will be collected in order to determine whether there is a difference in opioid consumption or pain scores following surgery. Subjects will be followed postoperatively to assess their pain and cognitive function daily until discharge. Subjects will also undergo repeat neurocognitive assessments at one month and six months with T-MOCA postoperatively, via telephone.

Two 30 minute training sessions will also be conducted by the study PI, educating nurses on what to look for in an EEG, and how to read and interpret the monitor. These sessions will utilize online training videos for guiding the sedation in patients of the intervention group in the ICU/during postoperative care.

The anesthesia research team will also be available to assist during the postoperative period.

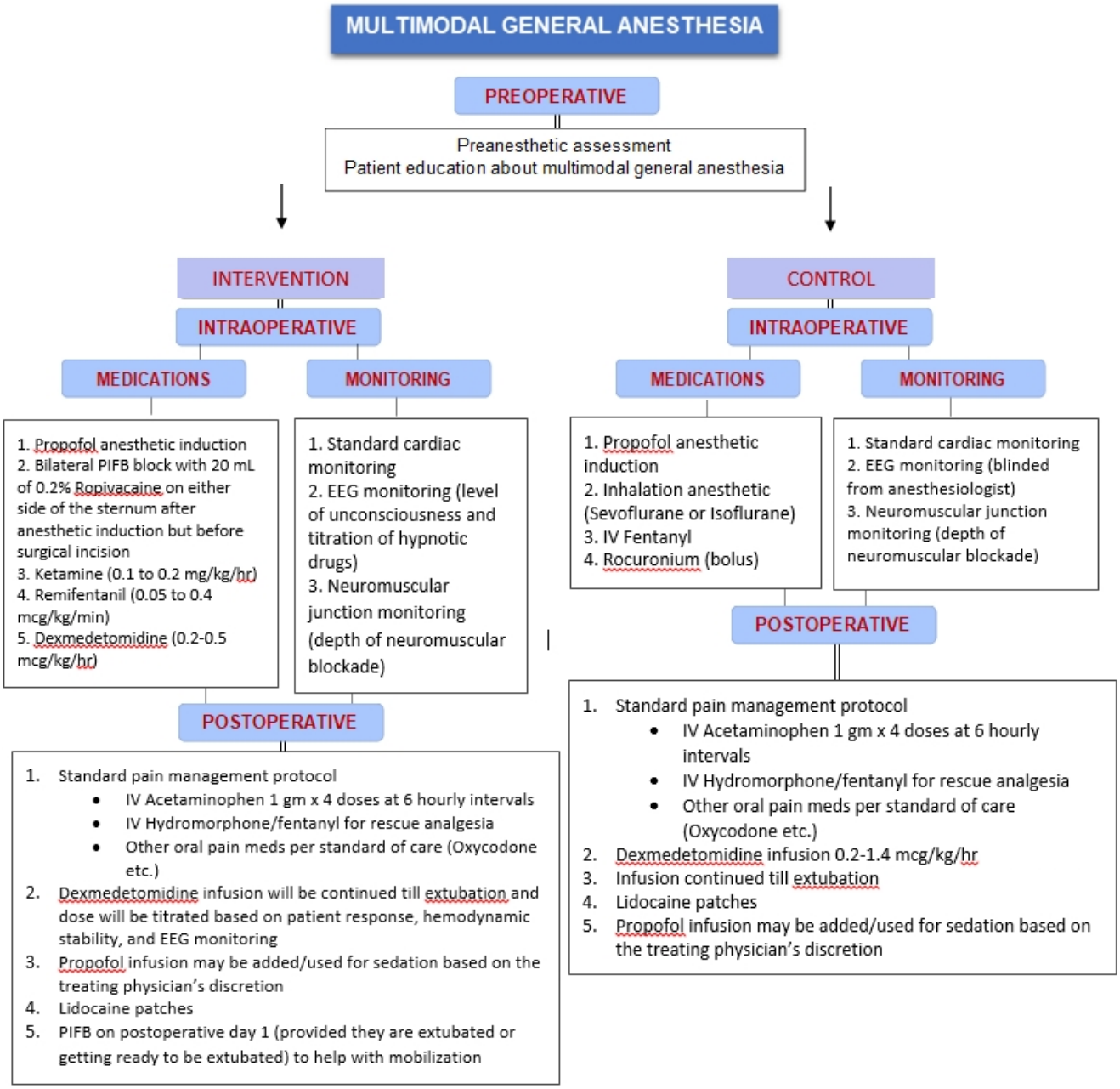
Perioperative EEG and CO monitoring

All patients will undergo EEG and CO monitoring during intraoperative and postoperative period (up through 24 hours/till extubation whichever occurs earlier). Electroencephalograms and CO will be recorded using the SedLine monitor (Masimo Corporation, Irvine California).[OBJ] SedLine is a FDA approved, patient-connected, 4-channel processed electroencephalograph EEG and Cerebral oximetry monitor designed specifically for intraoperative or intensive care use. It displays electrode status, EEG waveformsDensity Spectral Array (DSA) and bilateral regional cerebral oxygen saturation.



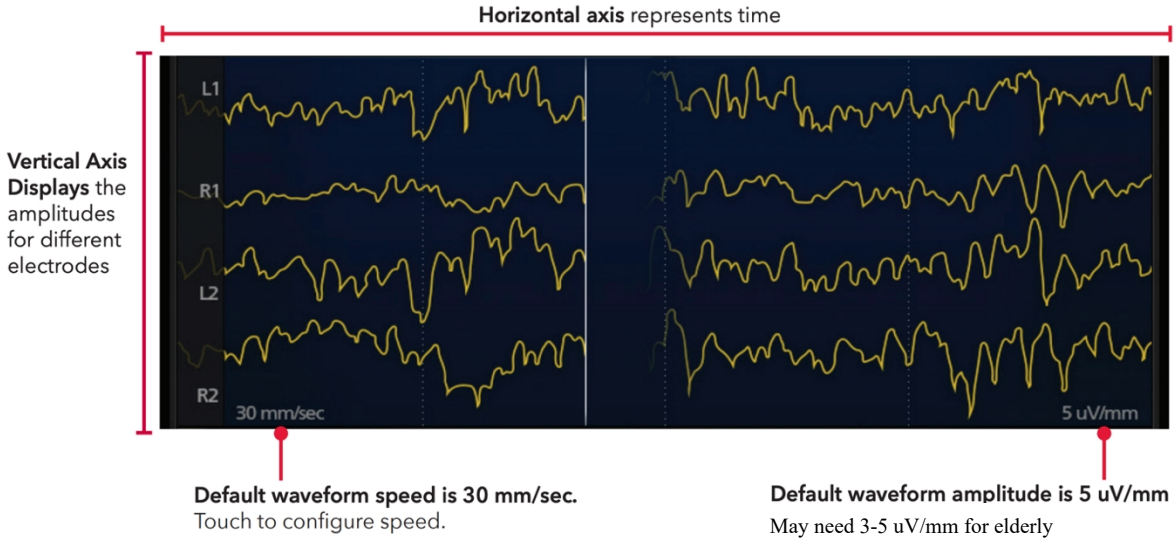
The Sedline EEG electrode (Images A-E) array records approximately at positions Fp1, Fp2, F7, and F8, with reference approximately 1 cm above Fpz and ground at Fpz. The spectrograms will be computed using the Multitaper method from the unprocessed EEG signals recorded at a sampling frequency of 250 Hz. Individual spectra will be computed in 3-sec windows with 0.5 sec overlap between adjacent windows.[OBJ] Multitaper spectral estimates have near optimal statistical properties that substantially improve the clarity of spectral features.

The CO sensors (Images F and G) are applied on the forehead as shown in images F and G.


MULTIMODAL GENERAL ANESTHESIA
PREOPERATIVE
Preanesthetic assessment
Patient education about multimodal general anesthesia
INTERVENTION
INTRAOPERATIVE
MEDICATIONS
MONITORING
1. Propofol anesthetic induction
2. Bilateral PIFB block with 20 mL of 0.2% Ropivacaine on either side of the sternum after anesthetic induction but before surgical incision
3. Ketamine (0.1 to 0.2 mg/kg/hr)
4. Remifentanil (0.05 to 0.4 mcg/kg/min)
5. Dexmedetomidine (0.2-0.5 mcg/kg/hr)
1. Standard cardiac monitoring
2. EEG monitoring (level of unconsciousness and titration of hypnotic drugs)
3. Neuromuscular junction monitoring (depth of neuromuscular blockade)
POSTOPERATIVE
1. Standard pain management protocol
• IV Acetaminophen 1 gm x 4 doses at 6 hourly intervals
• IV Hydromorphone/fentanyl for rescue analgesia
• Other oral pain meds per standard of care (Oxycodone etc.)
2. Dexmedetomidine infusion will be continued till extubation and dose will be titrated based on patient response, hemodynamic stability, and EEG monitoring
3. Propofol infusion may be added/used for sedation based on the treating physician's discretion
4. Lidocaine patches
5. PIFB on postoperative day 1 (provided they are extubated or getting ready to be extubated) to help with mobilization
CONTROL
INTRAOPERATIVE
MEDICATIONS
MONITORING
1. Propofol anesthetic induction
2. Inhalation anesthetic (Sevoflurane or Isoflurane)
3. IV Fentanyl
4. Rocuronium (bolus)
1. Standard cardiac monitoring
2. EEG monitoring (blinded from anesthesiologist)
3. Neuromuscular junction monitoring (depth of neuromuscular blockade)
POSTOPERATIVE
1. Standard pain management protocol
• IV Acetaminophen 1 gm x 4 doses at 6 hourly intervals
• IV Hydromorphone/fentanyl for rescue analgesia
• Other oral pain meds per standard of care (Oxycodone etc.)
2. Dexmedetomidine infusion 0.2-1.4 mcg/kg/hr
3. Infusion continued till extubation
4. Lidocaine patches
5. Propofol infusion may be added/used for sedation based on the treating physician's discretion

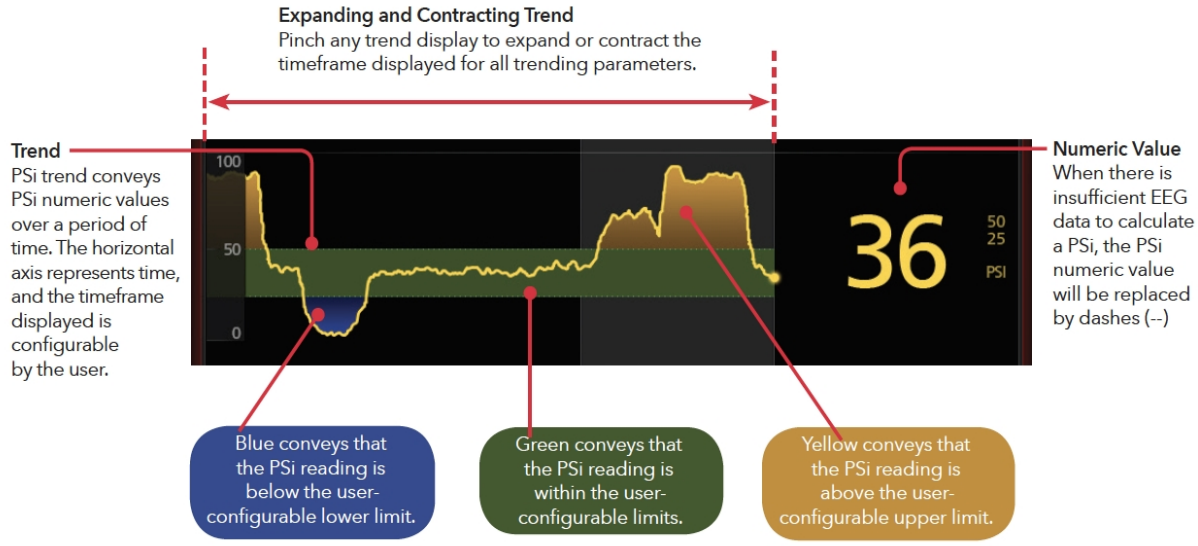
EEG Display

The EEG waveforms reflect electrical activity mostly from the front of the brain. The display is configured to contain 4 data input sources, acquired from the 4 sensor electrodes: L1, R1, L2, and R2.



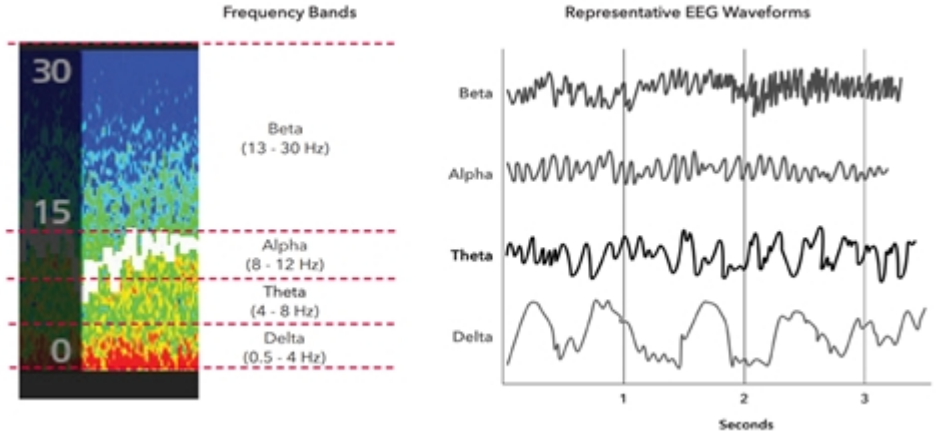
Patient State Index (PSi)[31,32]

The PSi is a processed EEG parameter that is related to the effect of anesthetic agents, and takes into consideration, among other factors:
(1) changes in power in various EEG frequency bands
(2) changes in symmetry and synchronization between critical brain regions
(3) the inhibition of regions of the frontal cortex.



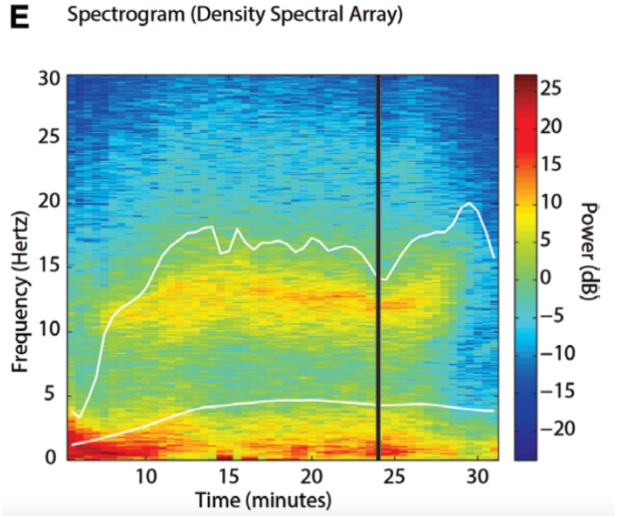
Density Spectral Array (DSA)[31,32]

The DSA contains left and right spectrograms representing the power of the EEG on both sides of the brain.

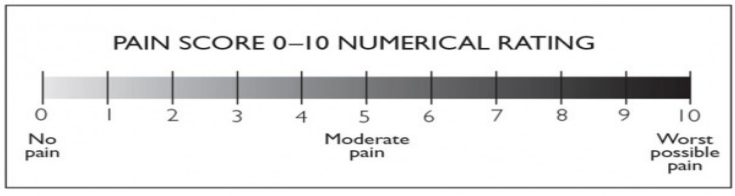


Multitaper DSA[32]

When using a Multitaper DSA, EEG data are transformed into the frequency domain, which may provide a better display of EEG features.



Postoperative pain assessment



Postoperative pain will be assessed with a standard 11-point scale and by pain medication intake. Pain scores will be obtained by asking the subject and also collected from the medical record when documented clinically. Pain medication intake will be extracted from the medical record.

Delirium and cognition assessment

Once consent is obtained, a trained research team member will proceed with baseline preoperative and postoperative cognitive, delirium, and depression assessments.

Baseline assessment

This will include the assessment of cognitive function using the:

1) Montreal Cognitive Assessment (MoCA), supplemented with
2) Days of the week (DOW) & Months of the year (MOY) for additional attention testing
3) Delirium Symptom Interview (DSI) to capture symptoms of delirium
4) Confusion Assessment Method (CAM): Using data from the cognitive testing and DSI, the researcher will complete the long CAM which includes the diagnosis of delirium using the CAM diagnostic algorithm.

These detailed assessments will take no more than 45 minutes.
If this baseline assessment shows a MoCA score <10, the subject will be excluded from the study.

Postoperative assessment

On each postoperative day during the hospital stay a research team member will administer a

1) Standard cognitive assessment, including DOW, MOY, CAM, and DSI. These daily assessments will take approximately 10-15 minutes.
2) If a subject is intubated postoperatively, a CAM-ICU will be performed instead of a CAM assessment.
3) If a participant declines to complete a daily standard cognitive assessment, trial staff will offer the 3D-CAM as a shorter alternative. If the participant refuses both the daily standard cognitive assessments and the 3D-CAM, trial staff will use the CAM Only, a conversation based method to score the CAM.
4) If daily assessments have plateaued for 3 consecutive days (CAM negative each day), they will then only need to be completed every other day, as long as the subject remains CAM negative, until the date of discharge.
5) In addition, medical charts will be reviewed every day until discharge or day 30 (whichever occurs first) to identify delirium. Any events related to delirium during the hospital stay and at the follow-up time points (1 month and 6 months) will be recorded on REDCap eCRF. Events such as trying to get out of bed, verbal abuse, falls, pulling tubes, inappropriate behavior during the hospital stay as noted in the medical charts will be recorded. At phone follow-up : prolonged rehabilitation, cognitive decline will be recorded.

Remote assessments

After the patient consents to participate in the study and opts in for phone call assessments, the study team may use the t-MoCA as a substitute to the MoCA for remote assessment of baseline cognition. The standard cognitive assessment forms used for daily, in-hospital assessment in the postoperative period may be administered remotely as well. For the discharge assessment, we may use the a-MoCA or the t-MoCA as a substitute to the MoCA if inability to in-person visits arise. The study team may conduct substitution assessments via phone or HIPAA approved telemedicine video conferencing platform. The a-MoCA and the t-MoCA are identical assessments but differ in naming, where the term “a-MoCA” is used for in-person assessments, and the term “t-MoCA” is used for assessments conducted via phone. Both assessments exclude the visuoconstructional tests of alternating trails, drawing of cube and clock, and animal naming.

Discharge assessment

On the day of discharge, the MoCA, with DOW and MOY, the CAM, and the DSI will be completed. (If the discharge assessment was performed in anticipation of discharge on a specific day but the discharge was delayed (i.e. logistical reasons, clinical reasons), this will not be considered a protocol deviation.)

Follow-up assessment

Follow-up assessments will be administered at 1 month (+14 days /- 7 days) and 6 months (+/- 30 days) after the date of surgery. These will be completed by a research team member via telephone and will include a telephone version of the MoCA (t-MoCA), with DOW and MOY, the CAM, and the DSI. These assessments will be done at the patient's convenience and ability to finish the evaluations.

Assessments	Baseline	Daily	Discharge	1 month	6 months
Montreal Cognitive Assessment (MoCA)	X		X		
Days of the Week (DOW)	X	X	X	X	X
Months of the Year (MOY)	X	X	X	X	X
Delirium Symptom Interview (DSI)	X	X	X	X	X
Confusion Assessment Method (CAM or CAM-ICU) (3D CAM/CAM Only if participant not compliant)	X	X	X	X	X
Standard Cognitive Assessment (Registration and Memory Recall, Digit Span, and Orientation)		X			
Charted Delirium		X	X		
Pain Score / Pain Medication Intake		X	X		
Telephone Montreal Cognitive Assessment (t-MoCA)				X	X

Standard Therapy (Usual Care)

All study participants (*n* = 70) will receive standard pain management during postoperative period that comprises of nurse-administered boluses of IV opioids (intravenous morphine/ hydromorphone/ fentanyl) or oral opioids such as oxycodone or IV Acetaminophen titrated to pain relief. However, the study participants receiving MMGA (*n* = 35) will receive EEG guided Dexmedetomidine and Propofol infusion in addition to the above mentioned pain management postoperatively. They will also receive bilateral PIFB (similar to what they received in the intra-operative period) with 20 ml of 0.2 % Ropivacaine on both sides (total of 40 ml) on postoperative day 1. The block will be administered by trained anesthesiologists using ultrasound guidance for placement of the local anesthetic in the plane between the external intercostal and the pectoralis major muscles.

Delirium treatment

The delirium research assessments will not be provided to the treating clinicians. Treating clinicians will assess and treat delirium per the standard of care.

Data Collection, Outcomes and their Measurement

Patient related information such as baseline characteristics including, comorbid conditions, medications, surgical and anesthetic data will be obtained from Society of Thoracic Surgery database, Anesthesia Information Management Systems and patient's medical record. EEG changes, waveforms and other related data will be recorded from the monitor. Additionally, to track other important factors related to outcome and protocol adherence, we may extract clinical data from the medical record including, but not limited to:

1) Anthropometric data (e.g. age, height, weight, race/ethnicity)
2) Admission type
3) Medications
4) Pain scores

5) Respiratory physiological data
6) Hemodynamic data (e.g. heart rate, blood pressure)
7) Laboratory data
8) Complications data
9) Hospitalization-related time data (e.g. admitting diagnosis, hospital and ICU length of stay)
10) Vital status

These data will be merged with subject cognitive assessment data. All data will be stored on password-protected computers, in locked file cabinets and/or offices, or REDCap. We are working with a collaborator on the study, Emery Brown MD PhD, at Massachusetts General Hospital (MGH). Dr. Brown's group will assist in the analysis of the EEG and hemodynamic data collected during the study. There is at present no plan to exchange intellectual property. Dr. Subramanian and his research group will be responsible for conducting and collecting data from this study.

BIDMC will provide MGH EEG data and data on the intraoperative anesthetic management to analyze. No PHI will be shared between institutions as all data will be fully de-identified before secure transfer to MGH.

Biospecimens

Collection: To better understand how the perioperative bundle impacts nociception[35], whole blood specimens will be collected at five time points: Baseline (time of the pre-operative study assessments or on day of surgery),end of bypass (in the OR) , end of surgery (in the OR) , POD 1 (in the ICU), and on POD 2 (in the ICU). One purple top EDTA tube (10 cc) will be collected at each time point, for a total of 50 cc's of blood collected per patient. Blood samples will be collected by nursing staff or by a study team member trained in phlebotomy. All efforts will be made to use existing catheters (e.g. arterial lines) or harmonize with clinical blood collection to reduce patient discomfort.

Processing & Storage: All samples will be centrifuged within 30 min of collection at 25 °C at 2300 × g for 10 minutes and plasma and buffy will be aliquoted into smaller vials and stored at –80 °C in the locked Anesthesia research lab space of DANA 7. All samples are logged into a centralized sample tracking system to provide efficient storage, retrieval and chain of custody information. The specimens will be analyzed in batches at the end of the trial using commercially available ELISA assays. These results will be integrated with the other data collected within the study and used to test a number of post-hoc hypotheses.

Data related to specimen collection, including documentation of signed consent for collection will be stored in REDCap or on password-protected computers on BIDMC secure servers only, which will ensure privacy of subjects and protection of confidentiality. Specimens will be labeled with subject ID and timepoint of collection and no other identifiable information. Both data and specimen will only be accessible by CCI approved study team members listed on the study protocol and RSF.

Study Outcomes:

Primary Outcomes

Surgical and delirium markers: Increase in plasma levels of IL-6 and neurofilament light from baseline to postoperative days 1 and 2 will be compared between the groups. Blood samples will be collected, stored, and analyzed at five time points through the perioperative course. Plasma levels of these markers will be quantified at baseline, postoperative day 1, and postoperative day 2.

Secondary Outcomes

1.) Concurrent EEG burst suppression and cerebral desaturation: Incidence and cumulative duration of episodes of concurrent burst suppression and cerebral desaturation will be extracted and quantified from the monitors.
2.) Opioid consumption and postoperative pain control: Total postoperative opioid dose, opioid consumption and pain scores will be quantified and compared between the two groups.

Total dose of opioids consumed by all the study patients in the 48 hours post-operative period will be obtained from the medical records. This will be converted to morphine equivalents for standardization of the outcome and for ease of analysis. Pain will be assessed postoperatively by nursing staff every 4-8 hours and data will be collected form patient's electronic medical records

3.) Duration of Burst suppression will be extracted and quantified from the EEG record and compared between both the groups.
4.) Incidence of Postoperative Delirium (POD): POD will be diagnosed by our trained research members based on the Confusion Assessment Method (CAM) algorithm postoperatively until discharge.
5.) Cognitive function: Postoperative cognitive dysfunction at 1- and 6- months will be assessed with telephone version of the Montreal Cognitive Assessment (t-MoCA)
6.) Hemodynamic stability: metrics of total vasopressor dose in norepinephrine equivalents, time above/ below 90-130 mmHg systolic blood pressure, area under the 65 mmHg mean arterial blood pressure curve, and coefficient of variation of mean arterial blood pressure will be collected from the intraoperative record and medical records to be quantified and compared.
7.) Other Surgical and delirium markers: Plasma cortisol will be quantified at baseline, end of bypass, and end of surgery. Lipocalin will be quantified at baseline, postoperative day 1 and postoperative day 2.

Pain is routinely assessed in the postoperative period by nurses on an 11-point scale (i.e. patients are asked to rate their pain on a scale of 0 to 10). This is typically assessed every 4-8 hours by nursing staff and is readily available on the patient's electronic medical records. The total dose of opioids consumed in the 48 hours post-operative period will be obtained from the patient's medical records. This will be converted to morphine equivalents for standardization of the outcome and for ease of analysis. Data will be collected and stored REDCap or on password-protected computers. Any data collected on paper will be stored in locked study offices or file cabinets.

Cohort Retention

To maximize retention of the trial cohort throughout the 6-month follow-up period, trial staff will send reminder letters to participants one month before the 6 month phone call. Staff will collect up to three contact methods from each participant, as well as contact information for a designated secondary contact. Additionally if the participant opts in, trial staff may align the 1 month follow-up survey with the participant's 1 month post-surgery follow-up appointment to conduct the assessment in-person.

Multiple phone calls may be required to reach patients; If participants cannot be reached by phone for the follow-up surveys after three attempts, trial staff may 1) mail them the survey materials with a self-addressed, stamped envelope to return at their convenience or 2) email the survey questions via email through a secure REDCap link. The mailed and online version of the survey will not include the t-MOCA questionnaire as this needs to be administered verbally rather than self-administered.If we do not receive any response, a request letter will be mailed to the patient's address. Furthermore, for participants who are out of window, trial staff will cross-check with participant's provider to verify whether participant's contact information is up to date.

Adverse Event Reporting

We will follow the current CCI reporting policy with regard to adverse event reporting. Subjects will be monitored daily during their hospital stay, for up to four post-operative days. This time window is selected based on the half-life of the medications used for MMGA. All serious or related events will be reported to the CCI within the required time frame.

In addition, we will collect data on clinical events unrelated to the study intervention such as arrhythmias, hypertension, respiratory depression, infection, hypotension, hematoma, and local anesthetic systemic toxicity

B. Statistical Considerations

Sample Size Justification:

In this study, we are looking to test our intraoperative EEG-guided management strategy in combination with a postoperative protocolized analgesic approach to compare to the standard of care approach among cardiac surgical patients. For this randomized control trial, we plan to enroll and analyze 70 patients (1:1 allocation 35 in intervention group, 35 in control group).

We performed sample size estimation power analysis for the ANOVA repeated measure within factors using the data on IL-6 collected as part of a published randomized clinical trial we conducted[36]. The IL-6 data which is yet to be published showed a mean increase of 226 pg/mL from baseline to postoperative day 2. We hypothesized that patients in the intervention group will have a 30% lesser change i.e. mean increase of 158.2 pg/mL. Using the information above, we require a sample size of 58 for analysis using the following scenario; effect size Cohen's f = 0.17, 0.05 level of significance, 80% power, and three measurements per patient to show the statistically significant difference between the two groups. We require total participants of 62 (31 per group) considering a 5% attrition rate.

From a previous study on the changes in plasma neurofilament light levels with anesthesia and surgery, a mean increase of 12.8 pg/mL from baseline to 48 hours was observed[37]. Using a 0.05 level of significance and a power of 80%, expecting a 30% reduction in the increase, we would need a sample of 33 patients per group based on power analysis for the ANOVA repeated measure within factors. Considering 5% attrition (2 per group), we would require total of 70 patients (35 per group).

Concurrent EEG burst suppression and cerebral desaturation: Data from our ongoing multisite RCT (NCT04093219) shows mean bypass period of 88 minutes and mean of 8.0 minutes of both burst suppression and cerebral desaturation. We assume there would be a 25% reduction in the intervention group. Based on power analysis for the Poisson regression, a sample size of 35 per group will have 80% power to detect this difference accounting for 5% attrition.

EEG Burst Suppression. In our pathfinder 1 trial, we observed burst suppression duration 9[6] mins in MMGA patients. If we take this as a 33% reduction, we assume that in control group this would be 15 minutes (our two control patients showed an average of 20[10] minutes). A sample size of 20 patients per group will have more than 90% power to detect this difference.

Exploratory Aims. Our exploratory aims are considered as such either due to low statistical power for capturing effects or lack of data enabling estimation of effect. Detecting the expected change in postoperative delirium (17% vs. 33%, alpha=0.05, 80% power using Fisher's exact test) would require 125 patients per group. Detecting a 25% reduction in mean vasopressor dose would likewise require >100 patients per group. We have yet to develop a metric for anesthetist effort aside from total vasopressor dose or bolus count. Likewise, we do not have baseline expectations for cortisol at each timepoint. Thus, we seek to explore these outcomes in this intermediate-size trial. We plan, upon successful completion of this trial, to expand to a multicenter clinical trial where we can study these metrics with the appropriate statistical power.

Data Analysis:
Analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) or later. The Shapiro-Wilk test will be used to assess normality. Descriptive statistics of the data will be performed. Continuous data (age, pain scores, and opioid consumption) will be represented using median (interquartile range), and frequencies and percentages will be used to summarize categorical variables. Descriptive statistics will be reported for time to extubation, as well as secondary outcomes. Electronic data will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. All data from the study will be stored on password protected computers or locked cabinets. Data will be analyzed by a statistician at BIDMC. Data sharing will be allowed between studies to facilitate use of patient-level data.

Primary Outcome: The primary outcome of the proposed study is total increase in Interleukin-6 and neurofilament light levels from baseline to day 1 and day 2, which will be quantified and compared between the two study groups. The differences in increase will be compared using Repeated measure two way ANOVA.The primary analysis will be conducted on a modified intention-to-treat (ITT) basis, which includes all patients who received at least one dose of the study drug. Given the randomized trial design, results of the unadjusted analysis will be reported.

Secondary Outcomes: Concurrent burst suppression and cerebral desaturation events will be quantified as cumulative duration and compared between the groups using Poisson Regression . Total postoperative opioid dose, opioid consumption and pain scores will be quantified and compared between the two study groups. This value will be reported as overall morphine equivalents and assessed between treatment groups. Differences morphine equivalents, will be compared using parametric or non-parametric t-tests, as appropriate. Duration of delirium, defined as the total number of in-hospital postoperative days in which delirium is present, and severity of delirium, evaluated both as the peak (highest) and sum CAM-S score over all hospital days, will be assessed between groups using a t-test or non-parametric equivalent. Interrater reliability testing will be performed, with percent agreement, kappa, and weighted kappa reported for all CAM variables. Further, a hierarchical linear regression model will be used to characterize the trajectory of t-MoCA, scores over time. This framework was chosen because of its flexibility with the timing of patient interviews and the repeated observations in each patient over time. This will include data from patients at discharge, one and six months postoperatively. Differences in burst suppression duration during surgery, overall hospital and ICU length of stay will be compared using parametric or non-parametric t-tests, as appropriate.

Adjusted Analyses: Given the randomized nature of this trial, we do not anticipate differences between treatment groups at baseline. However, if baseline differences exist, we will fit a multivariable model adjusting for any potential confounders identified. We anticipate adherence to the randomization assignment to be high; however, it is possible that patients may not complete their course of the study drug. We will therefore perform a sensitivity analysis on a per-protocol basis, including only patients who were randomized and completed the appropriate treatment regime.

Effect Modification by Key Biological Variables: We will evaluate whether the effect of EEG-guided MMGA bundle differs across subsets of patients defined by few targeted factors, specifically sex, age groups, treating institution, sedation regimens, surgery type, preoperative cognitive dysfunction (MoCA < 23), history of alcohol abuse, and history of chronic opioid use. We will conduct a Cochran-Mantel-Haenzel analysis and test for effect modification using the Breslow-Day test.

Missing Data: The frequency and percentage of missing values for each variable will be collected, analyzed, and reported. For the proposed trial, we anticipate that the proportion of participants with missing primary endpoint values will be small (<1%). Further, in our previous study, from which much of the preliminary data was obtained, less than 6% of all data was missing. We therefore do not plan to

impute missing data. Anyone who received even a single dose of the study medication will be included in this modified ITT analysis

C. Subject Selection

Inclusion Criteria

1) Age ≥ 60 years
2) Undergoing any of the following types of surgery with cardiopulmonary bypass:
    - CABG with or without valve surgery (aortic and/or mitral)
    - Isolated valve surgery

Exclusion Criteria

1) Preoperative LVEF <30% (justification: hemodynamic compromise will be detrimental in these patients)
2) Emergent surgery (justification: insufficient time to initiate intervention)
3) Aortic surgeries
4) Non-English speaking (Justification: cognitive assessment instruments are not validated in a sufficient range of languages, and the research team lacks polylingual capabilities or the financial resources to hire interpreters for the duration of all proposed assessments.)
5) Cognitive impairment as defined by total MoCA score < 10 (justification: baseline cognitive dysfunction will confound primary outcome measure)
6) Currently enrolled in another interventional study that could impact the primary outcome, as determined by the PI (justification: confounding of primary outcome)
7) Significant visual impairment (justification: will be difficult for patients to draw individual components in MOCA score)
8) Chronic opioid use for chronic pain conditions with tolerance (total dose of an opioid at or more than 30 mg morphine equivalent for more than one month within the past year) (justification: these patients have different post-operative analgesic requirements, which will confound interpretation of secondary endpoints)
9) Hypersensitivity to any of the study medications (justification: safety concerns)
10) Active (in the past year) history of alcohol abuse (≥5 drinks/day for men or ≥4 drinks/day for women) as determined by reviewing medical record and history given by the patient (justification: altered drug metabolism could result in unpredictable effects)
11) Liver dysfunction (liver enzymes > 4 times the baseline, all patients will have a baseline liver function test evaluation), history and examination suggestive of jaundice. (justification: altered drug metabolism could result in unpredictable effects)

Drop-out Criteria

Prior to the continuation of any study medications in the postoperative period in ICU, the following criteria will be assessed. If the patient meets any of the following, the infusions will be discontinued.

1) Unable to meet the standard Fast Track Criteria postoperatively, as determined by the surgical and ICU Physician Assistants (justification: unstable/ patients with complications are not suitable for providing study medications)
2) Hemodynamically unstable (defined as HR > 120, SBP < 80, MAP < 50 within 30 minutes prior to drug administration) (justification: administering study medications will be detrimental to these patients)
3) Abnormal chest tube output (1000cc in 2 hours) (justification: administering study medications will be detrimental to these patients)
4) Oxygenation outside of normal limits (defined as PaO_2 < 60mmHg on an FiO_2 of 1.0 or SpO_2 < 85% within 30 minutes prior to drug administration deemed significant per clinical judgment – e.g. transient desaturation with repositioning will not disqualify the patient) (justification: administering study medications will be detrimental to these patients)
5) Received an infusion or bolus ≥ 0.05 mcg/kg/min of epinephrine (justification: administering study medications will be detrimental to these patients)

6) Received an infusion or bolus ≥ 0.50 mcg/kg/min of milrinone (justification: administering study medications will be detrimental to these patients)
7) Received an infusion or bolus ≥ 0.20 mcg/kg/min of norepinephrine (justification: administering study medications will be detrimental to these patients)
8) Significant clinician or nursing concern (justification: administering study medications and monitoring without treating clinician's or nursing cooperation will be impossible)

Subjects will not be recruited on the basis of race, ethnicity, or gender. However, it is not clear whether the final study sample will contain a representative spread of the BIDMC racial and gender makeup, as a result of the exclusion of non-English speaking patients. There is no reason to exclude pregnant women from this protocol. However, based on the study plan to recruit patients 60 years of age or older, presenting for cardiac surgery, we will be recruiting from a subject pool generally exclusive of pregnant women.

B4. POSSIBLE BENEFITS

There are no guaranteed health benefits to the patient being included in this study. This study will be more likely to be beneficial to future patients if these protocols get implemented among cardiac surgery patients with future trials. An improved understanding, and potentially information as to whether or not this MMGA strategy could improve outcomes after cardiac surgery for other patients in the future.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risk of the study drugs

Dexmedetomidine and Remifentanil
The drugs Dexmedetomidine and remifentanil are FDA approved for sedation and analgesic purposes. Bradycardia, hypotension and respiratory depression are less common side effects. In an intensively monitored setting of operating room and cardiac vascular intensive care unit, the risks of bradycardia, hypotension and respiratory depression if any can be managed effectively.

Ketamine
Ketamine is an FDA approved drug for perioperative analgesic and anesthetic purposes. Psychomimetic events (hallucinations, dreams, and diplopia), sedation, cardiac dysrhythmias and liver toxicity were some of the side effects reported. However, these side effects are almost never been reported with low dose infusions (IV infusion rate of less than 1.2 mg/kg/h and bolus dose less than 1 mg/kg).[26] Moreover, in an intensively monitored setting of operating room and cardiac vascular intensive care unit, these risks can be identified early and managed effectively.

Ropivacaine
Ropivacaine is an FDA approved medication for nerve blockade. Cardiotoxicity, which includes arrhythmias, hypotension, bradycardia and cardiac arrest, is less common when the doses used do

not exceed toxic limits. Although incidence of cardiotoxicity is extremely low, ropivicaine is intensively monitored in the setting of cardiac ICU, and any signs of impending cardiotoxicity can be identified early and managed effectively. Ropivacaine systemic toxicity can also manifest as seizures, which is less common in the doses used in the study. Further, other central nervous system reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors. Despite this, ropivacaine is effectively used in regional anesthetic techniques and the advantages of effective analgesia in terms of better patient recovery seem to outweigh the risks.

Risks Associated with Block Administration

PIFB is a relatively superficial block and is devoid of complications like pneumothorax, especially when performed under ultrasound guidance. Infection secondary to the invasive procedure is rare because of the sterile aseptic precautions used to administer the block. There is a minor risk of hematoma associated with any regional block but the pecto-intercostal fascial plane is a relatively avascular plane and the use of ultrasound guided visualization further reduces the risk of hematoma.

More Common [>5% occurrence]

- Propofol: Low blood pressure, decreased function of the muscles of the body, burning, stinging or pain at the injection site
- Dexmedetomidine: Low blood pressure, slow or increased heart rate, high blood pressure, slowed breathing, nausea, anxiety
- Ketamine: The following, collectively known as an 'emergence reaction': hallucinations (which may include flashbacks or floating sensation), vivid dreams, and nightmares, feeling ill at ease, confused, anxious and irrational behavior. Unusual eye movements, increased muscle tone and muscle twitches (which may resemble 'fits' or convulsions), double vision, increased blood pressure and pulse rate, breathing more quickly, nausea, vomiting.
- Remifentanil: Muscle stiffness, low blood pressure, feeling sick or being sick
- Ropivacaine: Constipation, nausea, vomiting

Less Common [>1% but <5% occurrence]

- Propofol: Nausea, vomiting, high blood pressure, slow or abnormal heart rate, decreased production of blood by heart, decreased respiratory function, mild itching or skin rash
- Dexmedetomidine: Decreased respiratory function, swelling in the legs, swelling, increased thirst or dry mouth, decreased urine output, decreased kidney function, shortness of breath, accumulation of fluid in chest or lung, respiratory failure
- Ketamine: Loss of appetite, feeling anxious, slowing of heart rate, changes in heart rhythm, lowering of blood pressure, breathing more slowly, narrowing of the voice-box leading to difficulty in breathing, pain, inflammation of the skin or rash at the injection site.
- Remifentanil: Breathing problems, constipation
- Ropivacaine: Abnormal nervous system function including excitation, depression, numbness, tingling sensation, seizures, drowsiness, unconsciousness, abnormal heart functions including abnormal rhythm, decreased heart rate, decreased blood pressure, or heart block.

Rare [<1% occurrence]

- Propofol: Decreased kidney, liver or lung function, heart failure

- Dexmedetomidine: Reduced heart function, swelling of the stomach, thirst, a condition where there is too much acid in the body, low albumin level in blood, shortness of breath, hallucinations
- Ketamine: Allergic symptoms ('anaphylaxis') such as breathing problems, swelling and rash, drifting in and out of consciousness (with feeling of confusion and hallucinations), flashbacks, feeling ill at ease, sleeplessness, feeling disorientated, effect on the reflexes which keep your airways clear, resulting in temporary inability to breathe, increase in salivation, inflammation of the bladder and/or pain when urinating ('cystitis').
- Remifentanil: Allergic reactions, heart function disorders
- Ropivacaine: Allergic reactions including hives, itching, redness, swelling, coughing, sneezing and breathing difficulty. Persistent numbness, tingling and weakness at the site of administration

Awareness
There is a slight risk of awareness as with any anesthesia technique where you might be aware of conversation, movement, pressure or discomfort during surgery which is rare. However, as we are monitoring the brain with EEG and giving the anesthetics, there is no increased risk of awareness in this study.

Ultrasound
Ultrasound is a very safe technology, and has no additional risks associated with it. There is also a minor risk of hematoma associated with the administration of any block; however use of ultrasound to guide administration of the block lessens the possibility of this risk.

EEG and CO
EEG and CO monitoring are FDA approved and are considered safe procedures. It has no discomfort and produces no sensation. In addition, there is no electric shock. The monitoring will be performed by trained doctors and nurses.

Risk associated with blood draw
There is a small risk of phlebotomy to obtain serum for the serum biomarker assays at 5 time points during the study. Wherever possible (and this will be for the majority of cases), the serum collection will be obtained at the same time as phlebotomy and other labs for routine clinical laboratory work, thereby eliminating an additional risk imposed by a separate phlebotomy for study purposes. However, in rare cases such (e.g. no arterial access, or pre-discharge sample collection) patients may require a separate lab draw. The risks of the phlebotomy procedure itself are minimal and are primarily related to pain or bruising at the needle puncture site. Due to the small volume requested for research (50 cc within a four-week span), the risks from anemia or blood loss are negligible.

Risk of Questionnaires
Patients will not be given the scores of their MoCA or CAM assessments, but if they were to become aware of a decline in their performance this could be stressful or disconcerting to the patient. Additional counseling regarding any psychological or emotional distress stemming from this will be provided by the principal investigator at the request of the patient or family.

Risk of a Confidentiality Breach
Any patient participating in a research study runs a small risk of breach of confidentiality. All study staff for this trial are well trained in HIPAA regulations and BIDMC confidentiality standards. Patient

data will be stored in locked cabinets and will be password-protected computers on BIDMC network secure servers or in REDCap directly. Data will be fully de-identified and transferred in a secure manner to MGH.

Risk/Benefit Ratio
The drugs used in this study are FDA approved for perioperative sedation, analgesia and anesthesia. When administered at recommended safe dosages and when monitored in the operating room and intensive care setting, the risks of complications associated with these drugs are far too small compared to the benefits of decreased pain and enhanced recovery following cardiac surgery.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment
Prescreening will be accomplished by reviewing the operating room schedule and surgical consult lists. Patient medical records will be reviewed for inclusion and exclusion criteria. All patients who meet inclusion criteria with no exclusions will be approached in the cardiac catheterization holding area, PAT clinic, cardiac surgery clinic, or in the preoperative holding area for full written informed consent. Besides the regular signature of the paper consent form, we will also offer the option of electronic consent signature (eConsent) through a secure platform. After confirming the eligibility from the medical records, we will send letters of recruitment (snail mails) to the eligible patients and if they respond expressing their interest, we will approach them via telephone for eConsent.

Consent
Written informed consent will be obtained from every subject prior to any study procedures. Well-trained study team members will introduce the study to gauge patient interest. For patients who express interest in learning more/joining the study, the study staff will contact appropriate study physician to join the conversation. At the time of consent, all study procedures will be explained in detail, including the associated risks and benefits. The subjects will have the opportunity to ask any and all questions and will be reminded that participation is voluntary. All subjects will be consented with in-person curtains drawn or the door closed, assuring patient privacy. They will also be consented at a time and location of their convenience via telephone call by the study staff after they express their interest to the letter of recruitment. Written informed consent will then be obtained prior to surgery and initiation of any research procedures. In all instances, the study physician will be sure to review the full consent with prospective participants. The subjects will have the opportunity to ask any and all questions, and are free to decline participation at any time. Written informed consent will be obtained and copies provided to the patient and filed in the medical record.
The research staff undergoes a rigorous consent training process. Within the Sadhguru Center for Conscious Planet (SCCP) at BIDMC, this training includes: didactic sessions, mandated attendance at CCI/HSPO seminars related to the informed consent process, shadowing of informed consent in a variety of contexts, trainee-led informed consent conversations with the aid of consenting checklists and accompanied by senior staff member and/or PI, robust feedback sessions, and clear communication when the team member is skilled enough to engage in informed consent discussions without direct supervision. All SCCP members, including non-physicians, undergo this training.

The consent process can now also be performed by delivering the Informed Consent Form to prospective study subjects remotely through a secure electronic-consent platform called “REDCap”. Subjects will receive an email with a link that will bring them to the electronic informed consent document. Utilizing a secure software platform, they will go through the electronic consent form with a study team member, in person. If they elect to consent to the trial, they will confirm with a study physician and sign and date the consent form electronically. The document will then also be signed by

the study physician who is conducting the e-consent process and the prospective patient's electronic consent and signature will be collected via photo, or email, and stored in their medical record.

Withdrawal: The patient has the authority to consent or decline all level of study activities. Should this occur during the active treatment phase of the study, investigators should request permission to contact the patient for follow-up and also to access the patient record for safety and outcomes data. Use of specimens collected to date should also be discussed.

Patients who experience unexpected surgical events may be withdrawn at the discretion of the local investigator. Enrolled patients who have open chest and / or circulatory assist device will be withdrawn. These subjects will not receive study drug, will not undergo research cognitive assessments, and will not have research labs drawn. These patients will be included in any intention to treat (ITT) analyses, but not in the primary modified intention to treat (mITT) analysis. Patients who withdraw before pharmacy confirmation on the day of surgery will not be included in the ITT analysis.

Subject Protection

Vulnerable subjects (employees, minors, pregnant women) or subjects potentially under undue influence are not anticipated to be study candidates. While the study does not specifically target patients with cognitive impairment, it is possible that some patients presenting for eligible surgical procedures may have mild preexisting cognitive decline. The study protocol does not exclude these patients, as this population is particularly in need of treatments for postoperative delirium. Instead, study staff will perform a careful capacity screen and ensure use of LARs as necessary. Patients will be informed that their decision to participate or not to participate will in no way affect their relationship with their health care provider. Patients have the ability to discontinue their participation at any time.

B7. STUDY LOCATION

Privacy

All efforts will be taken to ensure patient privacy. Patient interactions including consent will take place either in private clinical settings with curtains/doors closed so as to provide privacy and comfort. If the patients express their interest to the letter of recruitment, we will approach them via telephone at a time and setting that the patient is comfortable with. Throughout the study, only the minimum required information will be collected, assuring patient privacy during the study protocol as with usual patient care. Data collection from chart extraction will occur only on password-protected computers secured by the BIDMC firewall or in REDCap directly. Data collected will be limited to only the minimum necessary to accomplish the stated research purposes.

Physical Setting

All patients will be enrolled at BIDMC, or via telephone at a time that is convenient for the patient. Consent will be obtained from eligible participants in the cardiac catheterization lab holding area, PAT clinic, cardiac surgery clinic, or in the preoperative holding area or via telephone and e-consent. Study procedures, including administration of the PIFB will be performed in the operating room, the subject's inpatient room in the intensive care units, or in the ward at BIDMC. Data will be abstracted from the patients' chart and will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. All data collected on paper will be maintained in locked study offices accessible to only the study team. De-identified data analysis will take place at MGH only in a secure setting.

B8. DATA SECURITY

Data will be stored on password-protected computers behind the BIDMC firewall and entered into a computer database (REDCap). Computers and data collected on paper will be stored in locked rooms. For all analyses subjects will be identified only by their unique coded study ID number assigned for the sole purpose of this project. Limited information will be retained on patients who are prescreened and do not qualify, or who is approached and declined, for the purposes of generating a CONSORT diagram for the trial.

B9 Multi-Site Studies

N/A – Single Center Study

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Patients will be thanked for their time throughout the study. Because study results are likely to be published a few years after a given subject's participation, study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after study completion.

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