Optimizing Cerebral Autoregulation During Surgery

Study Protocol and Statistical Analysis Plan

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Feasibility of Autoregulation Targeting (FEAT) Study

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FEAT Study Protocol

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STUDY TEAM ROSTER

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1 STUDY OBJECTIVES

To conduct a pilot trial to determine the feasibility, safety, and potential efficacy of targeting MAP within the limits of cerebral autoregulation during hip, knee, or lung surgery compared with usual care.

2 BACKGROUND AND RATIONALE

Surgery for hip fracture in particular can be devastating for older adults, with complications that include delirium, [1] inability to walk unaided, [2] and 1-year mortality >20%.[3] Other types of major surgery in older adults, including other major orthopedic surgery and lung surgery can also have a high incidence of delirium that ranges up to 20%. During many types of surgery, extreme variations in blood pressure are common in older adults due to age-associated vascular and autonomic dysfunction. [4] However, there is no standard of care as to what constitutes adequate blood pressure in individual patients during surgery to avoid cerebral ischemia, with over 80 empiric definitions of hypotension in the literature. [5]

Our group has championed a more precise method for defining optimal blood pressure in individual patients than the current practice of empiric targets. Through the process of cerebral autoregulation, the brain is exquisitely regulated to maintain a constant cerebral blood flow across a wide range of mean arterial pressures (MAP). [6] However, when MAP declines below the lower limit of autoregulation (LLA) or rises above the upper limit of autoregulation (ULA), compensatory mechanisms fail and cerebral hypo- or hyperperfusion can occur. We have developed validated methods to identify the LLA and ULA in real-time in individual patients, and using these methods during cardiac surgery, we have found several key results. First, the MAPs at the LLA and ULA varied tremendously among individuals, implying that "one size fits all" blood pressure targets are inadequate. [7] Second, the extent that MAP varied above and below the limits of cerebral autoregulation was associated with postoperative delirium[8] and kidney injury, [9] implying that hypo- or hyperperfusion may lead to organ dysfunction.

Finally, and most importantly, an intervention to maintain MAP during cardiac surgery within a patient's limits of cerebral autoregulation reduced delirium compared with usual care (in pilot data from a trial conducted by my mentor).

However, the results of this trial in cardiac surgery may not apply in other surgeries due to differences in patients and surgical insult. It is also unclear if MAP can be effectively targeted in the other surgery populations. To address this gap in knowledge, we plan to determine the feasibility, safety, and potential efficacy of targeting MAP within the limits of cerebral autoregulation during a more generalizable group of surgeries, including hip or knee surgery (fracture or periprosthetic revision) or lung surgery compared with usual standard of care.

3 STUDY DESIGN

3.1 Study Design Overview

We will conduct a randomized, double-masked controlled trial. We will enroll 25 patients with usable data. Randomization will be 2:1 in intervention vs. standard arm with stratification by orthopedic vs. lung surgery in permuted blocks of 3 or 6 (i.e. each surgical strata will have the opportunity for 17 intervention patients and 8 control patients to be enrolled).
Patients randomized to the intervention arm will have their MAP targeted within the limits of cerebral autoregulation during surgery. Patients randomized to the standard arm will receive observational monitoring.

3.2 Perioperative Care

All anesthetic care will be according to usual practice, except the targeting of mean arterial pressure in the intervention group. This trial will not specify general or regional anesthesia, and this decision will be left up to the clinical team. Generally, this is as follows: for general anesthesia, induction with propofol (1-2mg/kg) or etomidate (0.1-0.3 mg/kg); maintenance with volatile anesthetic titrated to 0.5-1.0 MAC; and pain control with fentanyl (2-5 mcg/kg) or dilaudid (10-20 mcg/kg). An epidural may be used as appropriate. Depth of sedation may be titrated using a BIS monitor to 40-60. For patients who receive spinal anesthesia, the protocol may be: spinal anesthesia with isobaric bupivacaine, propofol (1-2 mcg/kg/min) for sedation, and fentanyl (1-3 mcg/kg) as needed for pain. Sedation may be titrated to a level consistent with arousability to voice. Surgical technique will be based on usual clinical practice for patients enrolled.

3.3 Intraoperative Monitoring of Cerebral Autoregulation

For monitoring of cerebral autoregulation, we will obtain digital signals from at least one or as many as three of the following monitors that are non-invasive and low-risk. First, the near infrared spectroscopy (NIRS) monitor measures regional oxygen saturation in the brain using two adhesive pads placed on the patient's forehead. The NIRS monitor will always be used. These monitors are FDA-approved and are standard of care during cardiac surgery at Johns Hopkins. Second, the Clearsight monitor is a non-invasive measure of real-time arterial blood pressure using a finger cuff. This device is FDA-approved and routinely used in operating rooms. If the patient has an arterial line, the arterial waveform will be extracted directly from the anesthesia monitor. Third, the Bispectral Index (BIS) is a non-invasive FDA-approved device also used in operating rooms to measure the depth of anesthesia using two adhesive pads that are placed on the patient's forehead.

The waveforms obtained from the NIRS, Clearsight or arterial line, and BIS monitors will be analyzed using dedicated software. In this paragraph, we describe how the data inputs from these three monitors are processed to calculate key measures of the adequacy of cerebral autoregulation and organ perfusion. NIRS measures regional cerebral oxygen saturation (rScO2) and is weighted toward venous blood, thus indicating the adequacy of O2 supply versus demand. Our group has demonstrated that rScO2 provides a clinically acceptable surrogate of CBF for clinical autoregulation monitoring.11,15 Arterial pressure waveforms are obtained from the Clearsight monitor or arterial line. Both of these signals will be sampled with an analog-to-digital converter using ICM+ software (the University of Cambridge, Cambridge, UK) at 60 Hz. These signals will then be time-integrated as non-overlapping 10-second mean values, which is equivalent to applying a moving average filter with a 10-second time window and re-sampling at 0.1 Hz. This operation eliminates high frequency noise from the respiratory and pulse frequencies, according to the Nyquist theorem, allowing detection of oscillations and transients that occur below 0.05 Hz. A continuous, moving Pearson's correlation coefficient will be performed between the mean arterial pressure (MAP) and rScO2, rendering the variable COx (cerebral oximetry index). Consecutive, paired, 10-second averaged values from 300-second duration will be used for each calculation, incorporating 30 data points for each index. This methodology has been previously validated. The MAP at the lower and upper limits of autoregulation will be indicated by the MAP at which COx transitions from approximately <0.3 to >0.3.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Patients

Specific **inclusion criteria** are:

- Planned hip or knee surgery (either for fracture or periprosthetic revision), or lung surgery
- Age ≥60
- Ambulatory at baseline.

- Expected duration of surgery > 90 minutes

Specific **exclusion criteria**

- Planned concurrent surgery
- Allergy to adhesive tape
- Short Blessed Test score >20
- Clinical diagnosis of dementia
- Opinion of either the anesthesiologist or surgeon that the patient is not appropriate.

Because of the age of these patients, it is anticipated that they will suffer from chronic diseases common in the elderly. However, each patient will be healthy enough to undergo the proposed operation, as judged by both the surgical and anesthesia services according to usual clinical practice.

4.2 Study Enrollment Procedures

Patients will be approached for enrollment in this study prior to surgery. Some patients may be called by research staff to describe the study and assess their willingness to participate if time allows based on the surgery schedule. The consent process will be conducted with the patient by an IRB-approved consent designee that is also a physician or a mid-level provider prior to surgery. As part of the consent process, the investigator or study team members will have 1) informed each patient accordingly and allowed sufficient time to decide whether or not to participate in the study; and 2) given the opportunity to inquire about details of the study and to answer any questions regarding the study. Patients are free to withdraw consent for participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may be discontinued at any time at the discretion of the PI.

If the patient is not signing consent for surgery and has a medical decision maker doing so, then it will be determined that this patient lacks the capacity to give written consent for this project. Of note, we are excluding patients with known dementia. We will identify the legally authorized representative in accordance with the Maryland law applicable to surrogate decision-making for health care to sign written consent. If the patient regains the capacity to consent, signs their own consents, and no longer requires a medical decision maker, then we will discuss this project with them and confirm their willingness to participate. We will attempt to discuss the study with patients who do not sign their own consents due to lack of capacity. However, we anticipate that the cognitive capacity of these patients will be low and they may not be able to understand. Thus, we will not obtain formal assent.

5. STUDY PROCEDURES

5.1. Schedule of Evaluations

	HOSPITALIZATION PHASE								FOLLOW-UP PHASE (± 30 days)		
Name	Screening	Baseline	Day of Surgery	Intraop monitoring	POD 1	POD 2	POD 3	Post Discharge	Day 60	Day 180	Day 365
Demography	✓										
Registration and Contact		✓									
Short Blessed Test		✓									
AD8 (patient or proxy)		✓									
Eligibility Confirmation		✓									
Baseline Exam (Pain scales, OTMT, WHO-DAS 2.0, IADL, BRS, 3D-CAM)		✓									
NIRS Monitoring			✓	✓							
Clearsight or arterial monitoring			✓	✓							
BIS monitoring			✓	✓							
Randomization and Intervention			✓	✓							
Surgery Data Collection								✓			
Postoperative Assessment (3D-CAM, Pain, Adverse Events)					✓	✓	✓				
Discharge Contact Info							✓				
Postoperative Events (Pain, Discharge contact)								✓			
Follow-up (Patient or Proxy) (60, 180, 365 days)									✓	✓	✓
AD8 (Patient or Proxy; 365 days)											✓
Adverse Events			✓		✓	✓	✓	✓	✓	✓	✓
End of Study											✓

[1]WHODAS or WHODAS-Proxy to be used as appropriate.

5.2 Description of Evaluations

5.2.1 Screening Evaluation

Screening Procedure

The OR schedules of eligible surgeons will be reviewed daily for potential participants. If the patient is ≥ 60 years of age and is undergoing traumatic hip fracture surgery or revision hip or knee replacement surgery or lung surgery, the patient is eligible for further screening and will be placed on the screening log.

Patients will then be assessed for meeting inclusion/exclusion criteria. Assessment will be done using the patient chart. If they meet all criteria, and staff are available to monitor the patient in the OR, they are then eligible for enrollment into the study and will be approached.

A screening log will be kept on the accm-charlesbrownstudies$ [redacted] drive in the CerebralAutoregulationHipSurgery folder.

There is a separate document describing the protocol for the screening log.

Enrollment will be conducted as described in Section 4.2.

Consent designees

- Charles Brown
- Laeben Lester

5.2.2 Enrollment

Prior to the start of surgery, the patient will be enrolled in the study. At this time, the patient will be assigned a study number. During the study patients will be identified by their first and last initial and a unique study number.

Patients who are excluded based on the secondary screen (Short Blessed Test) or for other reasons (e.g. cancelled surgery) will retain a study number but will be noted to be excluded or withdrawn, as appropriate, prior to randomization.

Study numbers will be assigned sequentially, starting with 3001.

5.2.3 Baseline Data

The following data will be collected onto case report forms (CRFs)

- Participant ID/Screening
- Registration and Contact Information
- Eligibility Confirmation
- Baseline Exam
- Baseline Pain Assessment
- 3D CAM
- Short Blessed Test
- Oral Trail Making Test
- AD8 (patient or proxy)
- WHODAS (or WHODAS Proxy)
- Instrumental Activities of Daily Living
- Brief Resilience Scale

5.2.4 Intraoperative Data

Surgical and anesthesia characteristics will be extracted from EPIC and/or the anesthesia monitor.

All subjects may be monitored during surgery using the following devices:

- **Near Infra-red Spectroscopy** is an FDA noninvasive device that is routinely used to monitor cerebral oxygen saturation during cardiac surgery. It is applied as adhesive pads to the forehead and is routinely used in cardiac surgery.
- The **Clearsight monitor** is FDA noninvasive device that is used to monitor arterial blood pressure waveforms during surgery. It is applied as a device around the finger.
- The **Bispectral Index** is an FDA noninvasive processed EEG that is used in clinical care to measure depth of anesthesia. It is applied as an adhesive patch to the forehead.

5.2.5 Postoperative Data

The following assessments will be performed and entered in CRFs

Post-op Day #1

- 3D CAM (CAM-ICU for intubated patients)
- Post-op Assessment
- Pain Scales – Post-op
- Adverse Events

Post-op Day #2

- 3D CAM (CAM-ICU for intubated patients)
- Post-op Assessment
- Pain Scales – Post-op
- Adverse Events

Post-op Day #3

- 3D CAM (CAM-ICU for intubated patients)
- Post-op Assessment
- Pain Scales – Post-op
- Adverse Events

Discharge

- Surgery Data Collection
- Postoperative Events
- Adverse Events
- Acute Pain Management
- Discharge Contact Information

Day 60

- Ambulation
- Adverse events
- Pain
- Short Blessed Test
- Oral Trail Making Test
- WHODAS (or WHODAS Proxy)
- Instrumental Activities of Daily Living

Day 180
- Ambulation
- Adverse events
- Pain
- Short Blessed Test
- Oral Trail Making Test
- WHODAS (or WHODAS Proxy)
- Instrumental Activities of Daily Living

Day 365
- Ambulation
- Adverse events
- Pain
- Short Blessed Test
- Oral Trail Making Test
- AD8 (patient or proxy)
- WHODAS (or WHODAS Proxy)
- Instrumental Activities of Daily Living

End of Study
- The End of Study form will be filled out at the time the participant completes the study or ends participation early.

5.3 Randomization

Randomization will be 2:1 in intervention vs. standard arm with stratification by orthopedic vs. lung surgery in permuted blocks of 3 or 6 (i.e. each surgical strata will have the opportunity for 17 intervention patients and 8 control patients to be enrolled). A patient will be considered to be randomized when they enter the operating room and the anesthesiologist is handed a sealed opaque envelope indicating the study allocation.

5.4 Description of Intervention and Control

The critical difference will be blood pressure targets during surgery. Cerebral autoregulation monitoring will begin prior to anesthesia induction, with the LLA and/or ULA anticipated to be available within 30 minutes. The methods are described in the subsequent section “Intraoperative Monitoring of Cerebral Autoregulation.” These values will be used to establish blood pressure targets.

In the intervention group, at 30 minutes after the start of monitoring, Dr. Brown will visualize the autoregulation curves. Upon confirmation of an adequate curve, a blood pressure target will be provided to the anesthesiologist. Dr. Brown will visualize the autoregulation curves every 30-60 minutes to update the blood pressure target as necessary. The lower limit of autoregulation will not be <55 mm Hg. or >90 mm Hg.

In the intervention arm, the anesthesia provider will target MAP>LLA with the following strategy: reduce anesthetic agent while maintaining adequate anesthetic depth as clinically determined, IV fluid administration, and vasopressor infusion (likely dopamine or levophed, but at the discretion of the anesthesiologist). MAP<ULA will be targeted with the following strategy: vasodilator infusion (likely nicardipine or nitroglycerine, but at the discretion of the anesthesiologist) or other clinical approaches as decided by the anesthesiologist. If the treating anesthesiologist or surgeon feels that the blood pressure target is too high or too low for clinical reasons, then they will request a different target, and this request will take priority. In the control arm, the anesthesia provider will use usual care guidelines, which is generally systolic blood pressure >90 mm Hg.

Patients will be allowed to be enrolled in other studies. Adherence will be assessed as part of the feasibility outcomes.

6 SAFETY ASSESSMENTS

6.1 Adverse Events and Serious Adverse Events

Adverse events (AE) encountered during or after surgery are recorded on the appropriate AE section of the CRF. Adverse events are defined as any untoward or unfavorable medical occurrence in a human study, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to the participant's participation in the research.

Serious adverse events (SAE) are a subset of AE that meet one of the following criteria:

- Results in death
- Is life threatening
- Places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization substantially
- Causes persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards

Severity Classification

Classifications of adverse events include the following:

- ***Mild:*** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
- ***Severe:*** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Expectedness of Adverse Events

AEs will be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol, investigator brochure, product insert, or label. Categories are:

- ***Unexpected -*** nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure.
- ***Expected -*** event is known to be associated with the intervention or condition under study.

Relatedness of Adverse Events

The potential event relationship to the study intervention and/or participation is assessed by the site investigator. A comprehensive scale in common use to categorize an event is:

- ***Definitely Related***: The adverse event is clearly related to the investigational agent/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is

confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- ***Possibly Related****:* An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- ***Not Related****:* The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

6.2 Reporting Procedures

All adverse events are evaluated by Dr. Brown and two other Johns Hopkins faculty with respect to intensity, frequency, relationship to study, and outcome.

The protocol for the FEAT trial for reporting AE is the following:

- All AE are recorded on an AE form.
    a. The AE may be identified from a list of pre-defined complications or from informal review of the electronic medical record by research staff.
    b. Serious AE will be further recorded on a separate form.
    c. A panel of three faculty at Johns Hopkins (including Dr. Brown) will adjudicate expectedness and relatedness of each AE.
- Serious AE (SAE)
    a. If **unexpected,** SAE will be reported to the NIA, IRB, and the independent safety officer within 48 hours.
    b. If **expected**, then SAE will be reported using the SAE form within 14 days of discovery.
    c. An SAE will be considered expected if it is listed in the DSMP and/or the adjudication committee considers it expected (with consideration that events with <5% incidence should be considered unexpected).
- Non-serious AE that are unexpected, possibly related, and may place participants at greater harm than originally recognized will be reported to the IRB, NIH, and the independent safety officer within 14 days.
- All other adverse events will be maintained in the study database and reported to the IRB during continuing review and to the safety officer every **6 months.**

7. STATISTICAL CONSIDERATIONS

7.1. Outcomes:

Primary outcome variables

Feasibility outcomes will be recruitment >60%, enrollment of at least 3 patients per month, available lower limit of autoregulation target in >65% of all patients, at least 1 delirium assessment in >95%, and at least 1 cognitive and functional assessment in >90%.

Safety outcomes will be increased operative bleeding and significant organ ischemia (myocardial infarction, as judged by treating physicians).

Secondary clinical outcome variables

Extent of mean arterial pressure outside the limits of cerebral autoregulation (after the establishment of the MAP target) will be assessed based on intraoperative monitoring data.

Delirium will be assessed in the hospital using the 3D-CAM (CAM-ICU for intubated patients).

Cognitive and functional outcomes will be assessed by telephone at postoperative days 60 and 180, and in-person or by telephone at 1-year follow-up.

a. Cognitive outcomes are: Short Blessed Test score, Oral Trail Making Test Score, AD8 score
b. Functional outcomes are: inability to walk ≥10 feet without human assistance, WHO-DAS 2.0 score, Instrumental Activities of Daily Living, and institutionalization

7.2. Analytic Plan:

We will examine whether targeting MAP based on the limits of cerebral autoregulation during surgery is feasible and safe, and we will explore whether it can reduce delirium, improve cognition, and improve function. The primary goal is to assess feasibility and safety of the intervention. We will monitor success in implementing each aspect of the protocol, and performance and safety metrics will be compared against pre-specified criteria as defined in the primary outcome section.

We will then assess potential efficacy of the intervention to optimize blood pressure management, reduce delirium, improve SBT score, and improve functional status. The first analysis will be by intention-to-treat by randomization status with primary outcomes of extent of mean arterial pressure outside the limits of autoregulation after establishment of a target, frequency of delirium, change in Short Blessed Test score, and change in WHO-DAS score. We will calculate the mean or frequency of each outcome and between group differences, each with associated 95% confidence intervals. The former will provide estimates of variability in outcomes needed in power calculations for a definitive trial, and the latter will provide a benchmark by which pursuit of a further trial can be evaluated. We will then examine differences in characteristics between groups and in multivariable regression models adjusted for surgery type and age. Finally, we will examine secondary outcomes, including change in OTMT, conversion to dementia, and inability to walk 10-feet. Together, these analyses will inform selection and measurement of primary and secondary outcomes, as well as confounding variables, for a future trial powered for efficacy.

7.3. Sample Size:

Based on the experience of the investigative team, a sample size of 25 patients would allow determination of whether feasibility outcomes had been met and assessment of safety events. Such information would be critically important to support a future trial.

We also calculated a formal sample size to have adequate precision for estimating the primary outcome of delirium. We estimate that a sample size of n=25 would provide the precision to estimate the incidence of delirium to within 16 percentage points using a 95% CI.

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1 Data Collection Forms

The study administrators will be responsible for obtaining and recording data.

8.2 Data Management

Patient information will be collected and recorded on a case report form (CRF) for this study by authorized staff. Data will be transferred from the CRF to a study database, devoid of any patient identifying

information and will be stored electronically on a server that is password protected. All patient information will be kept confidential. All patient binders will be housed in the study administrator's office at Johns Hopkins behind two locked doors. Additionally, the screening log will be password-protected and housed on a server that only study staff will have access to.

8.3 Quality Assurance

Because our group has been conducting an observational study using similar assessments and monitoring over the past several years, study coordinators are experienced in the administration of the patient assessments, autoregulation monitoring, and data abstraction. and will train research staff. The study coordinator will train any additional research staff, including co-evaluating patients, oversight of patient interactions after independence, and periodic audit of data collection. The study team will meet weekly to discuss all aspects of the study.

9 PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

9.2 Informed Consent

Patients will sign informed consent prior to any study activities.

9.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

9.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.