Trajectory of Recovery in the Elderly (TORIE)
PI: Dr. Joshua Mincer
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Mount Sinai	Protocol Title:	Trajectory of Recovery in the Elderly	
	Principal Investigator Name/Contact Info:	Joshua Mincer, MD Joshua.mincer@mountsinai.org	
	Primary Contact Name/Contact Info	Mark Baxter mark.baxter@mountsinai.org Monique.pierre@mountsinai.org	
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MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

1) Objectives:

Research Question:

Specific Aims 1: To assess cognitive recovery in a group of adults by undertaking baseline and follow-up testing after the administration of general anesthesia in healthy volunteers, 40–80 years old.

Specific Aims 2: To evaluate alterations in resting state and activity driven brain networks using fMRI, DTI, and ASL to characterize these same volunteers before and during recovery from the administration of general anesthesia.

2) Background

Long term outcomes from anesthesia and surgery have become an important focus of perioperative care. From a time during which mortality in the operating room was somewhat common, perioperative mortality has decreased sufficiently to make a focus on long term recovery an important undertaking. Recently, an international group has developed a multi-modality scale called the Postoperative Quality of Recovery Scale or (POSTOP-QRS) to assess recovery following anesthesia and surgery. The domains assessed include the physiology, nociception, emotional, activities of daily living, cognitive and the overall perspective of the

patient. The POSTOP-QRS has been validated in a number of environments and for a variety of surgeries.

The cognitive domain has been the focus of extensive research and seems to be primarily a concern of the elderly. Our research group has been involved in cognitive function for many years starting with the International Study of Postoperative Cognitive Dysfunction (ISPOCD) in 1994. In the first large ISPOCD study, 25% of elderly patients were found to have measurable deterioration at 1 week following surgery and approximately 10% had measureable dysfunction at 3 months. The cause of this deterioration remains unknown. Amongst the major candidate etiologies are changes in cerebral oxygenation, perioperative stress of various sorts and direct anesthetic toxicity. The role of anesthesia appears to be minimal. First, multiple studies that have compared general anesthesia to regional anesthesia have failed to show any difference. Regional anesthesia (spinal and epidural anesthesia) involve blocking nerve conduction at the level of the spinal cord and do not involve major pharmacologic interventions that result in unconsciousness. Large studies, including a large study by the ISPOCD group, have failed to show any difference between regional and general anesthesia. A large meta-analysis including this study and 23 others also indicated that there is no advantage to regional anesthesia. A recent large retrospective review of data from an Alzheimer's disease research center showed no difference between surgery, medical illness and a control group in the incidence of dementia. A recently submitted review (reviewed for publication by the PI of this study) found that the patients in the ISPOCD did not progress to dementia faster than controls. There is fairly extensive evidence, primarily from animal studies, that inflammatory cascades are involved in the pathophysiology of delirium and POCD. This is strong evidence that general anesthesia is not the cause of POCD.

Nonetheless, the process of disrupting cognition with anesthetic drugs provides an important confounder in attempts to understand the etiology POCD. While many studies have evaluated how rapidly patients recover consciousness (i.e. wake up) from anesthesia, there have been no studies of cognitive recovery from general anesthesia. In addition, there is no data regarding the imaging correlates of general anesthesia and recovery from anesthesia.

3) Setting of the Human Research

76 volunteers will be given general anesthesia in the research imaging unit. Cognitive testing will occur prior to the administration of anesthesia and at intervals until complete cognitive recovery occurs. Cognitive

testing will also occur at 1, 7 and 30 days after the initial administration of anesthesia. The POSTOP-QRS will be conducted over the phone or in person at baseline and during recovery (while in the recovery room) and 1 day, 3 days,7 days and 30 days and after the initial MRI with anesthesia. A POSTOP-QRS will be repeated at 6 and 12 months after your initial procedure for safety purposes.

4) Resources Available to Conduct the Human Research

The neurocognitive anesthesia group consists of experienced physicians with multiple years of experience administering anesthesia in various settings, including MRI suites. There is also extensive experience in the administration and interpretation of neurocognitive tests. The group includes research coordinators who have been trained in a variety of neurocognitive assessments and other postoperative evaluations.

The neuroimaging group includes individuals with years of experience in the conduct of magnetic resonance imaging and its interpretation.

5) Study Design

a) Recruitment Methods

Participants will be recruited through local contacts and IRB approved advertisements in local media.

A copy of the study advertisements will be sent to the IRB for approval

The study team is requesting the following 2 approvals:

(1) The use of ResearchMatch.org as a recruitment tool for this research study/protocol ("recruitment access")

(2) To send the attached study recruitment message to potential study volunteers through ResearchMatch.org.

The study team would like to employ the following recruitment methods:

Distribution of brochures

Advertisement in the Mount Sinai Broadcast Communications- The Mount Sinai Update- a weekly e-mail sent to members of the Mount Sinai community.

Team4Cure

Signs on Bus Sheds

Radio advertisements (script will be sent to IRB for approval)

b) Inclusion and Exclusion Criteria

Inclusion criteria

- 40-80 years old (children and young adults rarely have POCD or PD)
- American Society of Anesthesiologists (ASA) Physical Status I or II (i.e. Individuals with minimal disease burden)
- Capable and willing to consent

Exclusion criteria

- Airway assessment as potentially difficult (Mallampati III of greater)
- Allergies or hypersensitivity to drug or class
- Chronic Inflammatory conditions such a lupus or system rheumatoid arthritis (arthritis limited to 1 or 2 joints will be acceptable)
- Patients with diabetes mellitus
- Patients with a recent illness (within the last 2 weeks)
- Patients with severe visual or auditory disorder/handicaps
- English illiteracy
- Pregnancy (Urine pregnancy test will be performed)
- Participants not expected to be able to complete the postoperative tests
- malignant hyperthermia
- - nursing mothers
- - BMI ≥ 30
- - patients with significant metal implants in their body
- - anything noted in medical history that would suggest that the subject has a health condition. (Note: elevated cholesterol without history of coronary artery disease will not be used to exclude potential participants)
- Current use of cocaine or opiates (Urine toxicology screen performed)
- Current smokers

c) Number of Subjects

Seventy Six Participants will be recruited.

d) Study Timelines

Volunteers who agree to participate will have a history and physical and undergo an assessment using the Postoperative Quality of Recovery Scale (POSTOP-QRS), NIH Toolbox and paper and pen cognitive tests. The baseline assessment is carried out prior to the anesthesia/MRI study described below. The POSTOP-QRS assesses six domains of recovery which are delineated in the table labeled table 2 (copied from the original reference).

The NIH Toolbox is a multidimensional set of brief measures assessing cognitive (as well as emotional, motor and sensory) function from ages 3-85. By using multiple constructs of each domain, the NIH Toolbox monitors neurological and behavioral function over times. This facilitates the study of functional changes across the lifespan.

The paper and pen cognitive tests (See Manual of Procedures page 13) are cognitive tests which have been validated to measure change when taken repeatedly within a short time span. These tests will be used in conjunction with the NIH Toolbox to assess cognitive changes in study participants.

The location of the testing will either be in the clinical research unit (CRU), anesthesia research area or a private area in the MRI research suite.

On the day of anesthesia, the anesthesia staff will confirm the participant's eligibility and document a preanesthesia evaluation. A urine drug screen for cocaine and opiate use will be administered. A positive test will exclude participation. A twenty gauge intravenous catheter will be inserted in a peripheral vein. A complete anesthesia setup will be available, including an MRI compatible anesthesia machine and a set of vital sign monitors (blood pressure, ECG, oximetry, end-tidal CO2 and gas analysis.) Following the pre-anesthesia scans, the MRI bed will be moved out of the scanner and the anesthesia will be induced using propofol (approximately 2 mg/kg) followed by the insertion of a laryngeal mask airway (LMA). Anesthesia will be maintained using sevoflurane. The anesthetic depth will be adjusted to be between 40-60 using a Bispectral Index Monitor (Covidien, MA, USA) which must

be removed for subsequent scans. Respirators will be controlled by the anesthesia machine. This induction sequence lasts about 15 minutes. The subject is then moved back into the scanner under anesthesia for about 2 hours. After the last scan, the subjects will emerge from the anesthetic and the LMA will be removed. After we determine that they are sufficiently conscious to perform another N-back task, (this took about 15 minutes on average during the preliminary study) the scanner bed is moved back into the scanner bore for another resting state fMRI followed by an N-back scan similar to the one before the anesthesia. Participants will be reassessed using the POSTOP-QRS battery and transported to a postanesthesia care unit (PACU). T+40 POSTOP-QRS information will be acquired in the PACU. The follow up scan on the next day and day 7 (+/-2 days) will be performed without anesthesia. The Confusion Assessment Method (CAM) will be used on postop day 1 and 7 (+/-2 days) to assess for delirium.

The data collection schedule is below:

	Pre-Procedure	Day of Procedure	T+15	T+40	T+1d	T+3d	T+7d	T+30d	T+6mth
H&P	X								
PostOp -QRS	X	X	X	X	X	X	X	X	X
NIH Toolbox/paper and pencil cognitive tests	X				X		X	X	
MRI		XXX			X		X		
Anesthesia		X							
Blood collection		XX							

e) Study Endpoints

The primary endpoint is return to baseline cognitive function.

f) Procedures Involved in the Human Research

Cognitive testing, administration and monitoring of anesthesia, MRI

As the participants in the study are volunteers, we will be in touch with their PMD if they have one. Upon discharge from the hospital, subjects will be provided with a card that will remind them of their next appointment as well as who to contact in case of emergency related to this study.

g) Specimen Banking

Blood specimens will be drawn for biomarker analysis. The specific biomarkers will be the subject of another grant submission.

"Specimens will be stored for no more than 5 years. The specimens will only be accessed based on a specifically approved IRB protocol. Participants will be allowed to have their specimens either de-indentified or destroyed."

h) Data Management and Confidentiality

Data will be maintained either on paper forms or within database secured behind the MSSM firewall

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Provisions to monitor the data to ensure the safety of subjects is undertaken by at least three means.

1) The patients will be highly selected and subsequently monitored during the procedure

2) We have designed a format for focused enrollment to support an early safety assessment after 10 subjects between 70-80 have completed their assessments

3) Although not a clinical trial, a Data and Safety Monitoring Board has been approved by the National Institute on Aging to monitor this study and will undertake their first evaluation after 10 patients have completed the protocol.

To ensure the feasibility of the study and as a further safety precaution, we will first enroll 10 persons in the 70-80 year old range and follow the study protocol. These results will be closely monitored for any adverse events. Should any participant not return to their baseline POSTOP-QRS by 30 days the DSMB will be notified. This design ensures that we will demonstrate that it is feasible to recruit in this age range and that volunteers are able to conduct all steps of the protocol safely.

Patients who are enrolled in the protocol will have an initial anatomical MRI. The clinical neuroradiologist on this study (Dr. Delman) will review this anatomical scan prior to the initiation of anesthesia. Any lesion or finding that would indicate additional risk to proceeding will cause the protocol to cease. Any incidental findings on MRI will be reported to the participant as per the standard incidental finding procedures in place for all imaging studies at Mount Sinai. Briefly, in the presence of incidental finding the preference is to present the information to the participant in collaboration with their primary care physician. In the absence of a

primary care physician, we will arrange a consultation with the neuroradiologist and provide a primary care referral.

The principle methodology to minimize the risk of drug administration will be to monitor the patient within the MRI suite by a team of at least two trained anesthesia personnel. To minimize the risks we have obtained a state-of-the-art MRI compatible anesthesia monitor which provides ECG, pulse oximetry, automated blood pressure, continuous capnography and gas concentration evaluation. As the research MRI suite is at some distance from the regular operating rooms, our protocol requires the presence of least two anesthesiologists at each session. Vital signs are assessed and recorded at a minimum of every 5 minutes. Research personnel familiar with all aspects of the protocol will be involved in the anesthetic and PACU care of all participants.

Dosing of all anesthetics is altered in an age appropriate manner. For propofol, the standard induction dose is 2.5 mg/kg. For elderly patients, the accepted range is 1.5-1.8 mg/kg. Furthermore, as the point of the current use of induction agent is merely to have a rapid induction for the insertion of the laryngeal airway, the dose is titrated to effect to achieve the needed state with the minimum amount of medication.

For sevoflurane, the age adjusted minimal alveolar concentration of MAC (volatile equivalent of an ED50) decreased with age. For the current study, the participants are all administered sevoflurane to a processed EEG level of 40-60. This ensures a similar level of anesthetic depth in all participants and, based on extensive experience, the amount of anesthetic needed to achieve these levels will be similar to the age adjusted MAC." During the resting state scan the anesthesiologist will manage the sevoflurane as follows: 15 min 1MAC (baseline), 15 min 1.5 MAC (increased), 1 MAC (return to baseline), deviation from this protocol for the safety of the individual will be determined by the anesthesiologist during the procedure.

Volunteers who undergo the complete protocol, including the anesthesia, will be brought to a (PACU) where their recovery will be supervised by regular PACU nursing staff. PACU nurses will be in-serviced to assure familiarity with the protocol. Discharge from the PACU is determined by an algorithm that was modified from the Aldrete criteria. In addition, volunteers are required by hospital policy to have a competent adult to accompany them from the hospital back to their home.

The PACU discharge criteria in use for this study are the same criteria used for discharging all standard surgical patients. In essence, these are a modification of the Aldrete criteria (see below). This system is employed by the PACU nurses, who make the determination of when patients are ready to proceed to either second stage recovery or home.

Respiration

2= Able to take deep breath and cough

1= Dyspnea/shallow breathing

0= Apnea

O2 Saturation

2= Maintains >92% on room air

1= Needs O2 inhalation to maintain O2 saturation >90%

0= Saturation < 90% even with supplemental oxygen

Consciousness

2= Fully awake

1= Arousable on calling

0= Not responding

Circulation

2= BP+ 20mm HG pre op

1= BP+ 20- 50 mm HG pre op

0= BP+ 50mm HG pre op

Activity

2= Able to move 4 extremities

1= Able to move 2 extremities

0= Able to move 0 extremities

The total score is 10. Patients scoring > 8 (and/or are returned to similar pre op status) are considered fit for transition to Phase II recovery"

If a patient has persistent issues, we will continue to follow the patient. If there is any concern regarding change in cognitive function, we have the ability to refer the patient into formal assessment by the ADRC."

Risks associated with the neuropsychological testing will be minimized by extensive training of the research assistants, with particular focus on sensitivity to the patient's condition. Confidentiality and privacy will be maintained by initial and continuing education of the research staff, as well as proper design of all procedures.

Although this is not a clinical trial, we will have a Data and Safety Monitoring Board that will meet via teleconference after the first 10 volunteers aged 70 to 80 years old and at a minimum of twice per year. The DSMB will evaluate all unanticipated events and safety if volunteers are not found to return to baseline POSTOP-QRS function by 30 days.. All adverse and unanticipated events will be reported to the IRB as well as to the DSMB.

All of our databases are kept on the research drive which is maintained by IT and is behind Sinai's firewall. The coordinators and the anesthesia investigators will have access to the full information. As the data are behind the fire wall, they will contain identifying information. That is necessary because we have to find the participant at intervals to follow up on the testing scheme. The data will be stored for 6 years after the study is complete.

Drs. McCormick and Baxter will be the Mount Sinai Principal monitors.

j) Withdrawal of Subjects

Participants may withdraw at any time. Standard procedure for all anesthetics is to perform a postoperative evaluation, usually by phone, within 48 hours. If a participant decides to drop out, we will inquire as to whether we can maintain their information that we have to date. If they say no, we will destroy their information.

6) Risks to Subjects

The risks directly attributed to the administration of general anesthesia have decreased markedly with provision of intensive continuous monitoring. Direct anesthetic morbidity and mortality is estimated at less than 1 in 450,000 cases. We believe that, in the absence of surgical stress that there is an extremely low risk of cognitive dysfunction. Both our experience in which cognitive dysfunction is transient and recent animal data suggest that there is more than adequate clinical equipoise to justify the proposed study.

There are minor risks associated with the placement of the intravenous catheter, placement of the airway device and conduct of the cognitive

tests. There is a risk of reaction to the enclosed space of the MRI machine.

Once patients are anesthetized, a laryngeal mask airway (LMA) will be placed in the back of their mouth to allow them to breathe on their own during the two hour general anesthetic. This device will be placed by an experienced anesthesiologist. The LMA is very safe, but has risks associated with it. The estimated rate of critical incidents associated with the LMA is 15 in 10,000 anesthetics (0.15%). Risks of the LMA when used for general anesthesia include:

- Aspiration (entry into your lungs) of stomach contents
- Pressure-related injury of your mouth and throat
- Laryngospasm (temporary closure of your vocal chords)

Risks to privacy and confidentiality for this small pilot study are very low. All data will be guarded as for any study involving human subjects.

7) Provisions for Research Related Injury

A physician will be responsible for the patient during their anesthesia and will immediately respond to all problems. As the majority of problems related to anesthesia (e.g. allergy) occur at that time, the anesthesiologists will be the physicians to manage the issues. Should the participants develop any other injury identified during follow up, they will be referred to an appropriate physician.

Should anyone have significant delirium/cognitive impairment or other medical complications from the study, they will be admitted, and the costs of the admission will be borne by the study."

8) Potential Benefits to Subjects

There is no benefit to participants in the study

9) Provisions to Protect the Privacy Interests of Subjects

The identity of all participants will be maintained confidential. No information will be shared outside of the medical center. All information will be maintained in secure form within Mount Sinai

10) Economic Impact on Subjects

There should be no economic impact on subjects

11) Payment to Subjects

Each participant will be given up to $600 for participating in the project. Reimbursement will be paid as follows; $300 for the initial day of anesthesia and MRI work, $300 after the 1 month post op assessment is completed.

Transportation to and from Mount Sinai will be provided for the participants at no cost to them for visits which require that they return to Mount Sinai.

12) Consent Process

Participants who contact the research group will be given an explanation of the project by one of the study investigators and provided with a copy of the consent form. If the potential participant desires, a time will be arranged for the participants to meet with the investigator and discuss the process. After all questions are answered, the participant will be asked if he or she wants to participate. If they believe that the project is right for them and that they understand the risks of the project, they will be asked to provide documentation of their consent by signing an IRB approved consent form

13) Process to Document Consent in Writing

We will use a standard IRB approved consent form and standard MSSM procedures for obtaining and documenting informed consent

14) Vulnerable Populations

Vulnerable populations will not be included in this pilot study

"It is extraordinarily important for safe conduct of this study that cognitively intact and healthy individuals are included in this protocol. To achieve these ends we:

1) Are including only volunteers. Our experience to date is that individuals who volunteer are cognitively intact although we did exclude potential participants in the pilot study for medical issues (asthma and hypertension) No surrogate consents are permitted.

2) The potential participants have to engage with our research group to go through the informed consent process. As in the pilot study, our coordinators, all of whom have extensive experience in delirium screening (under the supervision of Dr. Ben Lee, Liaison Psychiatry at Yale) and cognitive assessments (under the supervision of Margaret Sewell, PhD and Mary Sano, PhD), so they are extremely experienced with concepts of normal and abnormal. They are clearly aware of the need to have cognitively intact patients and will not pursue the consenting process for

anyone who is not 100% clear on the project. This is as opposed to previous studies in which we were specifically looking for patients who had Mild Cognitive Impairment, where the challenge was to be sure the patient understood enough to participate.

3) Once a volunteer clearly understands and agrees to participate, they undergo a series of cognitive tests (POSTOP-QRS, paper and pen cognitive test and NIH Toolbox). Inability to complete these tests or significantly impaired results on this test will be brought to the attention of the investigators who can recommend that the participant be excluded.

4) All participants will be examined by a board certified anesthesiologist who will discuss the patient's medical history, perform and examination and go over the requirements of the protocol. Any indication that the volunteer does not meet inclusion criteria will result in a determination for not proceed to imaging and anesthesia

5) Finally, if all of the above are consistent with the protocol, the participant will have their baseline MRI. The baseline MRI will be read by Dr. Bradly Delman before the protocol proceeds to the induction of anesthesia. Any signs of occult CNS disease will cause the protocol to be aborted.

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Participants will be offered the opportunity to discuss their test results if they desire. The testing battery employed in not particularly clinically relevant in the sense that it is not designed to diagnose cognitive problems, so the value is primarily for curiosity

18) IRB Review History

A pilot study was conducted prior to the submission of this project. This project is similar in nature.

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

Sevoflurance and propofol will be obtained from the standard sources. Sevoflurane is maintained by the anesthesia department in restricted but not secure areas (anesthesia workroom). Propofol is maintained by the pharmacy and will be obtained from through the research pharmacy.