Official Title: Intraoperative Monitoring and Management Protocol to Reduce Strokes (IMMPRES): Pilot Study

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Study Protocol

If the patient is eligible, interested, and provides consent, they will complete initial preoperative baseline surveys and assessments. These assessments include: Medical History, Medications, Neurological Exam, NIH stroke Scale, Questionnaire for Verifying Stroke-Free Status (QVSFS), Delirium Screen, Modified Rankin Scale, Barthel Index, Digit Symbol Substitution Test (Cognitive Assessment), Trail Making Test part B (TMT-B) (Cognitive Assessment), and Montreal Cognitive Assessment (MoCA) (Cognitive Assessment), Depression Scale, and Quality of Life scale. General history, risk factor profile and physical examination (H&P) will be performed prior to entering the study. Neurological examinations, NIHSS, Modified Rankin Scale and Barthel Index will be performed by study neurologist. A Questionnaire for Verifying Stroke-Free Status (revised Questionnaire for Verifying Stroke-Free Status (QVSFS)), QOL assessment, Delirium and Cognitive assessment will be administered to each potentially eligible patient by a research coordinator. Subjects of child bearing age will complete a pregnancy test.

Baseline surveys and assessment will collected during a pre-operative session, either in conjunction with a pre-op clinic visit in-person prior to surgery during their surgical admission. This will allow maximum flexibility in timing, without interfering with clinical care.

Clinically collected data will be abstracted from the electronic medical record (EMR) for research purposes. We will review the patients preoperative medical records to screen patients for the use of intraoperative monitoring. This is currently a standard clinical practice. After enrollment, the subject will be randomized into the control or intervention group. Subjects will be computer randomized to condition 1:1. It will take approximately a half an hour to complete surveys and study procedures. On the day of surgery, EEG and somatosensory evoked potentials assessments will be performed preoperatively. The study team will code data to distinguish remote from in person assessment on the individual instruments.

Procedure: The cardiac surgeons who will be performing surgery will be informed by the principal investigator. The medical management of patients before, during, and after the procedure will be continued as routine medical care in standard medical therapy group. In the intervention group, standard medical therapy with intraoperative monitoring and management protocol will be done. Our IMMP will be a) intraoperative monitoring with SSEP and EEG during surgery and continued for 4 hours after; b) management protocol will be treating patients based on a SSEP and/or EEG changes. In patients with bilateral SSEP and/or EEG changes, we will aim for a MAP target of the greater of 20% above the patient's preoperative baseline or an absolute threshold of 80 mmHg. In patients with persistent unilateral SSEP and/or EEG changes, the higher MAP target will be maintained followed by immediate post-operative evaluation for stroke.
In the control group, the patient will receive standard of care.

Post-Procedure/Pre-Discharge: Brief history and physical examination daily while patient is in hospital. Neurological examination performed by study Neurologist. Delirium screen will be performed. NIH Stroke Scale (NIHSS) performed by study neurologist 18 to 54 hours post procedure. MRI will be performed before discharge. The MRI will be completed at the MRI Research Center. This trial will include 1.5 T MRI scanners.
All subjects will have continuous monitoring with a pulse-oximeter. MR technologists will monitor pulse-oximeter. They will terminate the scan, and call an investigator to evaluate the subject, if pulse-oximeter data goes below/above some defined threshold (sustained heart rate over 100 bpm, oxygen saturation below 90%). The responsible investigator for each study scan when scheduled and who will available to respond if necessary will be selected on a case-by-case basis in REDCap "MRI Completion" instruments. The Digit Symbol Substitution Test (Cognitive Assessment), Trail Making Test part B (TMT-B) (Cognitive Assessment), and and Montreal Cognitive Assessment (MoCA) (Cognitive Assessment) will be performed.

Follow-up: At 30 days post-op: Modified Rankin Scale, Barthel Index, Questionnaire for Verifying Stroke-Free Status (QVSFS), Quality of Life Assessment, Digit Symbol Substitution Test (Cognitive Assessment), Trail Making Test part B (TMT-B) (Cognitive Assessment), and Montreal Cognitive Assessment (MoCA) (Cognitive Assessment) will be performed. The Cognitive Assessments (DSST, TMT-B, & MoCA) & Neurological Assessments (MRS & The Barthel Index) through mail and telemedicine/Microsoft Teams.

Follow-up: At 3 months: Neurological exam, Modified Rankin Scale, Barthel Index, TIA/Stroke Questionnaire, Quality of Life Assessment, Digit Symbol Substitution Test (Cognitive Assessment), Trail Making Test part B (TMT-B) (Cognitive Assessment), and Montreal Cognitive Assessment (MoCA) (Cognitive Assessment) will be performed. The Cognitive Assessments (DSST, TMT-B, & MoCA) & Neurological Assessments (MRS & The Barthel Index) through mail and telemedicine/Microsoft Teams.

Follow-up: At 1 year: Neurological exam, Modified Rankin Scale, Barthel Index, TIA/Stroke Questionnaire, Quality of Life Assessment, Digit Symbol Substitution Test (Cognitive Assessment), Trail Making Test part B (TMT-B) (Cognitive Assessment), and Montreal Cognitive Assessment (MoCA) (Cognitive Assessment) will be performed. The Cognitive Assessments (DSST, TMT-B, & MoCA) & Neurological Assessments (MRS & The Barthel Index) through mail and telemedicine/Microsoft Teams.

Assessments and Questionnaires:
1. NIH Stroke Scale (NIHSS): The NIHSS was specifically designed for assessment of interventions in clinical trials. Rather than measuring function specifically, the NIHSS operates a 15-item ordinal, non-linear, neurological impairment scale covering consciousness, ocular movement, vision, coordination, speech and language, sensory function, upper and lower limb strength, facial muscle function, and hemi-neglect61. NIHSS became the gold standard for stroke severity rating after the first successful trial in acute stroke therapy62.
2. Stroke/TIA Questionnaire: The Questionnaire for Verifying Stroke-Free Status

(QVSFS) 50is an 8-item structured interview designed to identify stroke-free individuals. The QVSFS has negative predictive value of the QVSFS was 0.96, with positive predictive value of 0.71. The QVSFS can effectively identify stroke-free individuals with a high degree of accuracy, even in a population with a large proportion of patients with prior stroke or TIA.

3. Cognitive Assessment: The Montreal Cognitive Assessment (MoCA), a widely used test will be used measure to assess cognitive decline. It has shown to be superior to the Mini-Mental State Exam (MMSE) in evaluation of executive, visuo-spatial and language skills after stroke63,64. The MoCA instrument assesses multiple cognitive domains65: visuospatial abilities, executive functions, short-term memory recall, attention, concentration, working memory, language, and orientation to time and space and we feel this will provide a thorough assessment of the impact of acute perioperative covert stroke. MoCA scores range from 0 to 30 with higher a higher score indicating superior cognitive function. A decrease of 2 points or more in MoCA score is perceived to be important to patients, and has been used as a cut-off for important cognitive decline.21,66 The Digit Symbol Substitution Test (DSST) is a widely used sensitive test to evaluate cognitive decline across a wide range of clinical populations. DSST evaluates cognitive speed, attention, and executive functions by requiring participants to match symbols to numbers within a 120 second time limit using a key.67 Scores range from 0 to a maximum of 133 with a higher score indicating superior cognitive ability. We will utilize a decrease of 5 or more points on the DSST is considered clinically meaningful cognitive decline on the basis of differences in score observed between patients aged 70 and 75 years old in the Cardiovascular Health Study68,69 The Trail Making Test part B (TMT-B) is the widely used test for cognitive decline after cardiac procedures.56 The TMT-B measures cognitive domains of processing speed, sequencing and mental flexibility by measuring the time (in seconds) to connect numbers and letters
randomly placed on a page in an alphanumerical order, alternating between numbers and letters. Completion times between 78 and 128 seconds are considered average for adults aged 75 to 98 years of age. We will use a threshold of an increase of 10% or more in TMT-B completion time has been considered meaningful cognitive decline in a recent sub study of the HOPE-3 trail.

4. Modified Ranking Scale(mRS). The Modified Rankin Scale (MRS) is a brief physical function assessment, which covers the entire range of functional outcomes from no symptoms to death, has demonstrated validity with measures of stroke pathology (eg, infarct volumes) and agreement with other stroke scales. It is widely used in clinical trials72 and has demarcated effective and ineffective acute stroke therapies in trials with appropriately powered sample sizes73.

5. Barthel’s index: The BI operates according to a 10-item scale in which patients are judged upon degree of assistance required when carrying out a range of basic activities of daily living (ADL). The assessment is a validated questionnaire comprising a total score of 100 for the 10 items of the scale. The patient’s answers on each item are scored based upon actual ability (preferably observed by the assessor). The usual scoring for each item is 0 points for “no ability” to do the item independently, 5 points for “moderate help” with the item, and 10 points for being able to manage the item independently. The BI has emerged as the second most popular tool for assessment of

post-stroke outcome in clinical stroke trials74.
6. Delirium Assessment: We will utilize modified Confusion Assessment Method (CAM)52, 3D CAM59 for hospitalized patients and ICU CAM75 for patients in the ICU to evaluate for delirium. 3D CAM, a 3-minute structured assessment has a sensitivity of 95% [84%, 99%] and specificity of 94% [90%, 97%] to identify delirium in the hospital76. In a large systematic review, ICU CAM to diagnose delirium had a pooled sensitivity of the CAM-ICU was 80.0% (95% confidence interval (CI): 77.1 to 82.6%), and pooled specificity of 95.9% (95% CI: 94.8 to 96.8%). Delirium after cardiac surgery can be high (41%) and an Independent Predictor of Functional Decline.
7. Quality of Life assessments: We will utilize EuroQol 5-dimension (EQ-5D) questionnaire to assess the patients' health-related quality of life. EQ-5D is a self reported questionnaire designed to measure the health status and can be collection by phone or video interview. The EQ-5D questionnaire consists of two parts. The first part contains the EQ-5D descriptive system, comprising of 5 questions regarding mobility, selfcare, usual activities, pain, and depression (scores range from 0 to 1). The second part is a vertical, visual analogue scale with the end-points of "best imaginable health state" and "worst imaginable health state" (scores range from 0 to 100). EQ-5D has been used as a measure of health-related quality of life in patients who have suffered an clinical stroke7879, covert stroke21, and in those undergoing cardiac surgery.
8. Assessment of Depression: Depression after stroke affects approximately one third of stroke survivors in the first year after stroke, with a cumulative incidence of 55%.81,82 We will use the 9 – item Patient Health Questionnaire to measure the incidence of depression. The 9-item Patient Health Questionnaire (PHQ-9) (sensitivity: 0.86; 95% CI, 0.70–0.94; specificity: 0.79; 95% CI, 0.60– 0.90) appeared to be the optimal measures for screening and was suggested to be more pragmatic 83.

Intraoperative Neurophysiological Monitoring: Blood
pressure management will be institutional standard of care as determined by the Anesthesiologist per standard of care. Electroencephalography (EEG): EEG recording and analysis during carotid surgery has as previously described by the group18. Electrode placement on the scalp is based on the international 10-20 EEG system. EEG recording will start after anesthesia had been successfully induced and continue throughout the procedure. We will record 16 channel EEG system The EEG recording parameters are as follows: notch filter 60 Hz, the band pass filter for 1-70 Hz; sensitivity will vary between 5-7 microvolts/div and a time base of 30 mm/sec. Significant EEG changes, will be defined as a loss of in the amplitude of fast frequency and /or increase of delta activity by more than two fold15. A raw digital and quantitative EEG will be processed using software provided by the Natus Medical ® Pleasanton, CA.
Somatosensory evoked potentials (SSEP): SSEP recording and analysis during cardiac surgery will be performed as previously described by the group18. We will independently stimulate the bilateral median nerve at the wrist using adhesive sticky pad electrodes. Scalp electrodes will be placed at P4/Fz and P3/Fz will be placed per the international 10–20 system. A cervical electrode is localized at the CV2, and peripheral electrodes are placed at the erb's point bilaterally (EPs and EPd). Three channels of data will be collected for each median nerve SSEP: FZ-P4/P3 to record the cortical potential, FZ-CV2 to record the cervical potential, and EPs-EPd to record the

erb’s point potential. Stimulation frequency will be set to 2.33-2.41 Hz with duration of 0.2-0.3 milliseconds. Band pass filters are set at 10-300 Hz for the cortical channel, 30-1,000 Hz for the cervical channel, and 100Hz- 1 kHz for the erb’s point channel. The analysis time is 100 milliseconds. Significant SSEP changes, a variable of interest will be defined as greater than 50% decrease in the amplitude N20-P30 in SSEP in the Fz-P4/P3 channel 14any time during.