Preoperative Cognitive Screening in Older Spinal Surgical Patients
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Detailed Protocol with Statistical Analysis Plan

Protocol Title: Preoperative Cognitive Screening in Older Thoracic and Spinal Surgical Patients: Feasibility and Utility for Predicting Morbidity

Background and Significance:

Approximately 1 of every 3 surgical procedures nationally is performed on a patient ≥ 65 years of age yet this demographic represents only 13% of the population.[1-3] At our institution, a tertiary care center, 40% of elective, non-cardiac surgery is performed on seniors (see Feasibility Data). This proportion will grow, as seniors (defined here and throughout as persons ≥ 65 years) are a fast-growing segment of the population. Making matters worse, geriatric surgical patients often do poorly.[2,4-7] Thirty-day mortality for community dwelling Medicare enrollees is a remarkable 4.5% for appendectomy and 18% for colectomy and double this for nursing home residents, and even survivors frequently experience sustained functional decline.[1,2,4] This places enormous emotional and economic burdens on geriatric patients, their families, and the healthcare system. The challenge therefore is to identify risk factors for poor outcomes preoperatively so that the vital organ function can be improved or accommodated in the planning and execution of surgical, anesthetic, and postoperative care. Preoperative assessment of vital organs—heart, lungs, kidney, liver, blood—has been a staple of preparation for surgery for decades, and established algorithms address how to evaluate and manage a wide range of conditions perioperatively. Oddly, the brain is not among the vital organs that get formally evaluated preoperatively.[8] For geriatric surgical patients, this is a major and likely costly omission because brain dysfunction is common in seniors. Five-10% of Americans over age 65 and 25-40% of those over 85 have dementia; including MCI (mild cognitive impairment), the prevalence of cognitive impairment is 35-50% in those ≥ 65 (depending on the age structure of the population and the definition and assessment methods used) and higher still in those ≥ 85.[9-11] Therefore, it is reasonable to assume that many seniors scheduled for elective surgery have cognitive impairment that goes unrecognized. Our preliminary data support that hypothesis. We preoperatively screened 289 geriatric elective surgical patients with the MiniCog, a brief and well-validated test of visuospatial representation, recall, and executive function,[12-17] and found, using standard cutoffs, that 24% overall and 33% of those ≥ 75 years of age scored in a range that suggests functionally meaningful impairment. Yet, the intake nurse classified all but one as being cognitively intact, including 3 of 4 who had a MiniCog of 0. These results are consistent with published data from smaller studies that used similar tools to

screen patients ≥ 65 years presenting to an emergency department or having surgery with planned admission to the ICU which, depending upon the type of cognitive testing and age, show 20% to 63% are cognitively impaired.[18-21] Thus, there is evidently a problem that goes undetected without screening.

But does it matter? We contend the answer is 'yes'[8] and conceptualize cognitive impairment as a form of brain failure that, like heart failure, arises from multiple causes but leads independently to poor outcomes. Evidence supports this reasoning. First, cognitive dysfunction is a risk factor for adverse life events.[22] At a minimum, therefore, cognitive screening may help identify those least likely to benefit from the surgery. Second, routine clinical interactions, whether in primary care or hospital settings, are insensitive for detecting cognitive impairment or even frank dementia,[13,17,23] an observation we confirmed in our pilot study (Preliminary Data). Failure to recognize the problem could lead to suboptimal outcomes in a surgical setting if patients cannot recall what is expected of them postoperatively in terms of activity restrictions, wound care, medication regimens, and rehabilitation. Third, many seniors experience subtle and long-lasting executive dysfunction postoperatively that is independent of the specific anesthetic or surgical procedure, suggesting the patient's preoperative cognitive function is a predisposing factor.[24-26] Fourth, some evidence indicates poor cognitive status increases complication risk, undermines the chance of a good outcome, and adds to the cost of care. In hospital delirium is a prime example, as it occurs in 15-80% of older surgical patients and contributes to poor outcomes.[27-30] Although pre-existing cognitive impairment is an established risk factor for delirium, we seldom know a patient's cognitive status preoperatively because it is not currently assessed. Pre-existing cognitive impairment may also be a risk factor for serious non-cognitive morbidity[31,32] or mortality in geriatric patients having major elective operations[19-21] but data on non-cognitive outcomes are limited and no such association has been tested in a naturalistic, real-world setting (i.e. screening by regular preoperative evaluation center staff) such as we propose. Nonetheless, it is noteworthy that brief screening tests like the MiniCog were sufficient to detect such relationships and that guidelines issued jointly by the American College of Surgeons (ACS) and the American Geriatrics Society (AGS) strongly recommend routine preoperative cognitive assessment and specifically mention the MiniCog, detailed history, and informant questionnaire[3]—precisely the tools we propose to use. Still, perhaps because the data justifying the recommendation are sparse, it has not been widely adopted.

With national geriatric surgery volume large and growing and morbidity high, better understanding of preoperative cognition as a predictor / mediator of outcome has the potential to yield huge clinical and economic dividends. Assuming identification of a problem is the first step in solving it and that cognitive impairment is a form of brain failure, the lack of routine preoperative cognitive screening is presumably a major barrier to improving geriatric surgical care. Having demonstrated already in 289 patients that MiniCog testing is feasible in a preoperative evaluation center and that even non-medical personnel can administer and score it reliably (Preliminary Data), we are optimistic such screening can be implemented broadly. Unclear, however, is whether it is worth doing in terms of providing information about cognitive function that is unavailable from standard sources (patient/informant inquiry, focused chart review) and whether, like dysfunction of other vital organs, preoperative brain dysfunction is relevant to the surgical outcome of seniors.

Because of our success in screening older surgical patient undergoing elective surgical procedures we are now investigating whether the baseline peripheral immune status as measured by inflammatory cytokines in the plasma and white blood cell response to an ex-vivo immune challenge is predicted by the patient's baseline cognitive screening score. This will allow us to determine whether an exaggerated immune response to the surgery is predictive of adverse outcomes in aging patients.

The results of this work will lay the foundation for future studies that treat preoperative cognitive impairment as a risk factor and test interventions to improve geriatric surgical care and outcomes based on it. Examples might include discussion about the appropriateness or timing of surgery, preoperative consultation by a geriatrician, more careful titration of depth of general anesthesia (recently shown to reduce the risk of delirium),[33,34] or triage to a specialized geriatric care unit postoperatively.[31,35] Given the prevalence of likely cognitive impairment in our pilot study, preoperative cognitive screening promises to be an excellent low-cost, patient centered, high impact proposition for enhancing surgical outcomes in seniors.

Objectives:

Our overriding hypothesis is that preoperative cognitive impairment is a risk factor for poor surgical outcomes in seniors and that preoperative screening is superior to standard or systematic clinical processes for identifying at-risk patients.

Objective 1. Assess the marginal benefit of structured preoperative cognitive screening relative to standard or systematic preoperative evaluation for identifying seniors with likely cognitive impairment.

Objective 2. Determine whether preoperative cognitive impairment predicts postoperative outcome.

Objective 3. Determine whether other preoperative variables (mood, social support, history of depression, pain, and health and functional status) predict postoperative outcome.

Subject Selection: This project is designed as a prospective, single-center observational study. The cohort will consist of 500 consenting subjects ≥ 70 years of age who present to the BWH Weiner Center for Preoperative Evaluation (CPE) prior to elective thoracic surgery (specifically, thoracoscopic lung resection, lobectomy, thoracotomy, or esophegectomy) or to neurological anterior, posterior cervical, thoraco, or lumbar spine surgery performed by neurosurgeons or orthopedic spine surgeons. 250 subjects undergoing thoracic surgery will be recruited and 500 subjects undergoing spine surgery will be recruited. These ages are chosen as significant clinical data demonstrate increased cognitive impairment in community dwelling elders. Eligibility criteria include: patients ≥ 70 years of age with an ASA physical status of I-III presenting for elective thoracic, or orthopedic anterior or posterior cervical, thoraco, or lumbar spine surgery. Exclusion criteria will include history of stroke (not including TIAs) or brain tumor, uncorrected vision or hearing impairment (unable to see pictures or read or hear instructions); limited use of the dominant hand (limited ability to draw); and or inability to speak, read, or understand English.

An additional cohort of 50 patients aged 45-60 undergoing elective neurological posterior thoracolumbar spine surgery or orthopedic spine surgery with an ASA physical status of I-III will be recruited through the BWH Weiner Center for Preoperative Evaluation (CPE). Eligibility and exclusion criteria will be the same as the aged 70 and older cohort, barring age. The purpose of enrolling this small younger subject population is to compare biomarkers between the two groups.

In addition to the 750 older (aged 70 and above) subjects undergoing elective surgery and 250 younger (aged 45-60) elective spine surgery patients, 10 young, healthy control subjects will be also be recruited. These participants will complete the memory testing, and undergo the blood draw procedure, to act as a comparison to the older surgical population. This gives a combined study total of 250 recruited patients.

Subject Enrollment: The Brigham and Women's Hospital is the only study site.

Study staff will use the CPE computerized scheduling system, which is updated continuously in real time and captures relevant information such as age and procedure, to identify potential subjects. When patients check in with the receptionist in the CPE for their appointment they will be notified that they may be eligible to participate in a study in the CPE involving patients over the age of 70, or between the ages of 45 and 60. The receptionist will then provide them with a brochure (Attachment- Brochure) about the study that includes information about the purpose of the study, the risks to the patient, and the potential benefits to society. The patient will then be asked if they are willing to speak with one of the study investigators and only those patients that agree to speak with a study investigator will be approached. The staff member will then describe the goals and risks of the study in a quiet room in the PATC and ask the patient if they choose to participate; the staff member will also briefly and verbally screen for eligibility, asking the patient if he or she has a history of stroke, brain tumor, etc. After all questions have been answered and the patient has the opportunity to read the consent form, written consent will be obtained by one of the study investigators.

Control subjects will be recruited from the community, and will be eligible if they are over the age of 18 and not scheduled for any elective surgeries. All eligible controls must be able to read and understand English, and be able to use their dominant hand.

Study Procedures:

After obtaining consent, study staff will gain information about the patient's age and years of education. Study staff will administer standard instruments to assess mood (Geriatric Depression Scale-Short [GDS], a 15-item self-report questionnaire, and the Beck Anxiety Inventory [BAI]), The Amsterdam Preoperative Anxiety and Information Scale [APAIS], a brief, 6-item self-report questionnaire), social support (MOS Social Support Survey, a 12-item self-report questionnaire), pain (the Brief Pain Inventory Short-Form), frailty (the FRAIL scale assessing fatigue, resistance, ambulation, illness, and loss of weight), a risk assessment prior to surgery (MEDIA) measuring previous difficulties with memory, episodes of confusion, and cognitive enhancing medications, physical activity (the International Physical Activity Questionnaire – Short Form), and health and functional status (basic and instrumental activities of daily living [ADLs and IADLs, RAND 36-SF, and the WHODAS respectively]). The World Health Organization Disability Assessment Schedule 2.0 (WHODAS) is an alternative to the SF36 to measure physical health and disability. Past diagnosis of

depression and pain noted on the patient's preoperative evaluation form will be recorded, as well as past history of delirium or other post-anesthetic complications, use of hearing and/or hearing aids, and medical comorbidites. In addition, patients will be asked if they've had a fall within the last 6 months, whether they've been evaluated for a change in memory or thinking, who accompanied them to their appointment, their employment status and their living situation (alone, institutionalized, living with family members) in a patient survey. The study staff will also administer the MiniCog, a simple cognitive screening tool that takes just 2-4 min to complete and has little or no education, language, or race bias. In addition, the Animal Fluency test will be administered, which is a short cognitive screen that takes one minute to complete. Patients will also complete the self-report cognitive assessment CANTAB Insight Cognitive Exam, using an iPad developed by Cambridge Cognition. This 10 minute assessment measures cognitive health on five axes: executive function, processing speed, attention, working memory, and episodic memory through three cognitive tests: Matching Patterns, Working Memory, and Pairs Associates Learning Tests. Other measures of cognitive impairment will be obtained by study staff through: documentation on the patient's standard preoperative form, patient or informant report of diagnosis or evaluation for cognitive impairment or memory concerns, and systematic medical record review. Each enrolled patient will receive a business card listing the investigators' contact information and be advised to expect a follow up telephone call 6 months and 1 year after surgery to verify data elements and reassess functional outcome.

During their routine preoperative blood draw the phlebotomist will be provided with one 10mL heparinized blood tube, one 5mL heparinized blood tube and one 5mL non heparinized blood tube labeled with only the patient's study ID number that will be returned to the investigative team and processed within 30 minutes of the blood draw. If the phlebotomist is not able to obtain a sample during the patient's preoperative appointment, a sample will be drawn by a study staff member trained by one of the anesthesiologists, or a nursing or physician member of the anesthesiology team prior to incision instead. 200 uL of this sample will be sent to a Partner's Core Facility for analysis of the APOE gene, specifically for the e4 allele which has been shown to be linked in the development of late-onset Alzheimer's and delirium. The presence of the E4 allele will be included in our multivariate analysis for the development of postoperative delirium. Genetic results will not be shared with participants, nor entered into the medical record. 20mL of blood will also be obtained on postoperative days 1-3 by a study staff member trained by one of the

anesthesiologists, or a nursing or physician member of the anesthesiology team. Total, the proposed collection is 80mL.

However, the additional 60mL blood sample on post-op days 1-3 will only be collected if the Hematocrit level is 0.25 or higher. Briefly, half of the sample would be spun down and plasma harvested and stored at -80 degrees C and when an adequate sample size obtained used to measure inflammatory cytokines by ELISA. From the whole blood, we will isolate and purify monocytes using magnetic activated cell sorting (MACS), and then further isolate total RNA from the monocytes, which will be analyzed using RNA-seq. This analysis will capture the complexity of monocytes at different stages of the perioperative state by providing a comprehensive, genome-wide sampling of cell types. The remainder of the sample will be divided into 1-ml aliquots and incubated at 37°C for 15 min with phosphate-buffered saline (PBS) (control), 100 ng/ml interleukin (IL)-6, 100 ng/ml IL-10, or a combination of 100 ng/mlIL-2 and 2 ng/ml granulocyte macrophage colony-stimulating factor, or 1g/ml lipopolysaccharide. Blood samples will be resuspended in 1.4 ml stabilizing buffer and incubated for 10 min at room temperature for fixation in PFA, cooled to 4C, and stored at 80C until further processing for flow cytometry to determine the immune response of the white blood cells to a ex-vivo immune challenge and whether these correlate with Mini-Cog score or the development of delirium.
We will be sending de-identified (containing only subject ID and whether they were in the young or old cohort) blood samples from the proposed research to the Broad Institute and OLINK for RNA-seq analysis and protein analysis, respectively. We have fee-for-service agreements with both services. All samples and data collected for this research will be obtained with IRB approval and informed consent of study participants to sharing de-identified data. We will transfer de-identified blood samples of the patients enrolled in the study. We will then receive analyses in the form of raw data through PI-controlled password encrypted data files. The identities of research participants will not be disclosed to the repository. We will take appropriate steps to de-identify datasets according to the HIPAA privacy law. https://privacyruleandresearch.nih.gov/pr_08.asp. The raw data collected from the Broad Institute and OLINK will then be further analyzed by research staff listed on this protocol.

Delirium will be assessed prospectively twice per day (early afternoon, early afternoon) on postoperative days 1, 2, and 3 by a trained study team member using the Confusion Assessment Method [CAM-3D] and the 4AT. Delirium is most common on postoperative days 1-3 and both the CAM and the 4AT are well-validated measures of delirium in surgical patients. For patients that are in the Intensive

Care Unit (ICU) postoperatively, the Confusion Assessment Method for the ICU (CAM-ICU) will be administered prospectively twice per day on postoperative days 1, 2, and 3 by a trained study team member (Attachment-CAM-ICU). For functional status, the WHODAS will be administered 6-12 months postoperatively either by personnel in the surgeon's office as part of routine follow up or by study staff or by telephone. We will also collect information on secondary outcomes including duration of PATC visit, presence of an advanced directive, whether they had surgical procedure, time to PACU discharge, discharge to place other than home (rehabilitation, skilled nursing facility), hospital length of stay (LOS), in hospital complications, perioperative variables including drugs administered, pain scores and pain medication administration, BIS, estimated blood loss, blood transfusions, fluid administered, blood pressure, oxygen saturation, 30-day reoperation or readmission rate, and 30-day and 1-year mortality. These outcomes are recorded in the medical record, the BWH Balanced Scorecard, an electronic database of all hospitalized patients that tabulates 31 elements of the hospital event, or the BWH Research Patient Database Enhanced Query. Data will also be confirmed by a follow up telephone interview. Thirty day and 1 year mortality will be recorded.

Controls will be asked to complete the MiniCog, as well as a blood sample comprising of one 10mL heparinized blood tube, one 5mL heparinized blood tube and one 5mL non heparinized blood tube.

Data Analysis: As in our pilot study, we will define "likely cognitive impairment" as a score ≤ 2 on the MiniCog; while we are aware it is by no means a gold standard, it is based on a well validated cutoff that serves our purpose of identifying patients who may need special approaches during the perioperative period. All analyses will be repeated in the subset of individuals with the greatest degree of cognitive impairment based upon a MiniCog score of (0-1) in order to understand why these individuals were not identified as cognitively impaired. We will first test the sensitivity of standard procedures compared to systematic procedures with MiniCog defined impairment or severe impairment. We will also compare sensitivity and specificity of the standard vs. systematic approach, and vs. the published sensitivity of 75% in comparable populations. As a secondary outcome, we will try to understand the full relationship among our four assessments, for instance whether systematic chart review and patient/informant reports detect individuals not detected by standard MiniCog cutoffs, as such individuals would be important to include as part of a broad "impairment" outcome for Aim 2 and consider in

subsequent work for special care in the perioperative period. Similarly, if we see patients who have received a formal evaluation of cognitive status in a memory clinic, by a primary care physician, or neuropsychological testing, we will try to understand qualitatively how MiniCog scores compare to such evaluations. Another secondary outcome will be how well patient/informant report can augment chart review when the patient does not have a primary care physician within our network. Differences between sensitivities and specificities will be compared using standard methods using confidence intervals.

We will use logistic regression with any delirium as the outcome and cognitive impairment as defined by the MiniCog cutoff (or level of cognitive function as defined by the ordinal MiniCog score, modeled as best fits the data) in univariate analyses and in multivariate models adjusting for demographics (age, gender, education), baseline functional and medical covariates (ASA functional status, METs, frailty). Analogous analyses for our secondary outcomes will use logistic, linear, or Cox proportional hazards models to assess the relationship of MiniCog scores to these outcomes. In univariate analyses, we will compare change in WHODAS in MiniCog-impaired vs. unimpaired patients using Wilcoxon U test and with ordinal MiniCog score using Spearman rank order correlation. Multivariate analyses will model change in WHODAS (ranked or transformed for best model fit) as a function of MiniCog impairment status (or ordinal value as above), controlling for age, gender, education, comorbidity index, and frailty. In exploratory analyses, patients with and without postoperative delirium will be analyzed separately and compared.

Assays performed using blood collected between from the current study will be analyzed in the grant Circulating Extracellular Vesicles as Biomarkers of Postoperative Delirium (grant submission number 1R21 AG061696-01). Co-investigator Gregory Crosby, MD, is the PI of the above grant; no changes to the current protocol will be made for this analysis.

Risks and Discomforts:

Overall, this study poses low risks for the subjects. The sources of risk are of two types in this study, 1) participation in the interviews and cognitive test and 2) the risk of breach of confidential information. The first "risk" of the study is the time necessary to participate in the study assessments. However, in our pilot study, patients viewed the interactions with the research staff as very positive and enjoyable. It is possible that some of the assessments may pose the risk of fatigue or emotional distress. Should a patient become tired or distraught, the interview will be halted. A related "risk" of participation is the potential breach of confidentiality and privacy of the Protected Health

Information. Methods to reduce this risk include all investigators undergoing extensive training in general principles of informed consent, confidentiality, and administering research instruments in a humane, reliable, and valid manner. All data will be deposited into REDCap, a secure, web-based application for research storage and used for research purposes. There will be no interventions as a result of this study. The data gathered will have no effect on the care that the patient is to receive. Both the CPE providers preoperatively evaluating the patient and the surgeon will not have access to the result of the baseline testing.

Potential Benefits:
This study is being performed to advance medical knowledge. There are no expected benefits to individual subjects participating in the study but it will help advance understanding of how preoperative cognitive performance affects perioperative outcomes in older patients. This study has the potential to aid and improve decision-making by physicians and older patients in the future if they reveal a relationship between poor preoperative cognitive status and adverse cognitive and functional postoperative outcomes in older patients.

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

The Principal Investigator or a member of the investigative team will monitor each subject at this single site, and will review the accuracy and completeness of all testing, source documents and informed consent.

There will be no Data Safety Monitoring Board as the results of these studies will have no impact on the care that patients receive. The outcomes of the study are intended to be published in a peer-reviewed manuscript to document whether preoperative cognitive screening is a risk factor for adverse postoperative outcomes and the feasibility and cost of preoperative cognitive stratification in the preadmission testing center. All adverse events will be reported to the Partners the Human Research Committee (HRC) in accordance HRC guidelines. A 24-hour/7-day telephone or pager number will be provided for contacting the licensed physician investigator for this purpose.

The research staff will monitor all subjects during the course of study involvement for evidence of any adverse events such as unexpected stress and the testing discontinued and the incident reported to Partners the Human Research Committee within 24 hours of local event awareness (but no later than the next business day). The report will include a complete description of the event, use of all concomitant medications, and the local investigator's assessment of causality of the adverse event. Follow-up evaluations will be done until there is resolution of the adverse events, which are unlikely as this protocol is non-invasive

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